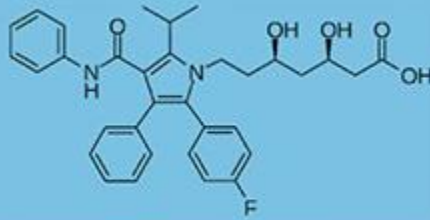


IAS STATIN
NEWSLETTER



INTERNATIONAL
ATHEROSCLEROSIS
SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 24, 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

Primary prevention – combining a genetic risk score with traditional RF evaluation

The optimal time to initiate statins in a primary prevention setting has been based on 10-year CVD risk estimates. This strategy does not reflect our current understanding of ASCVD, showing that the magnitude and duration of exposure to elevated LDL-c plasma levels will double our risk for each decade of exposure. Early intervention would result in tripling the benefits of lowering LDL-c compared to initiating treatment later. An alternative approach suggested by the authors is using a genetic risk score as an addition to the traditional risk calculators. This would allow the detection of high-risk individuals early in life and, combined

with the evaluation of traditional risk factors, provide patients with a bespoke type of risk assessment that would allow earlier intervention using statins or alternative approaches to reduce LDL-c and/or additional risk factors. In men, a genetic risk evaluation should be started in their second decade; women could have an evaluation in their thirties or forties. The genetic risk score suggested by the authors has been evaluated in over a million patients of European descent. Current initiatives are ongoing in different countries and ethnic populations, Hispanic, African Americans, and South-Asians. Using this approach would be a momentous paradigm shift from current primary prevention strategies and could improve chances of disease-free survival significantly.

Roberts R, Fair J. A Less than Provocative Approach for the Primary Prevention of CAD. Journal of cardiovascular translational research 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34128181>

The ongoing saga of statin and hepatic safety in NAFLD

Can statins be used safely in patients with non-alcoholic fatty liver disease (NAFLD), and could statins even benefit NAFLD patients? This meta-analysis combined data collected in 22 studies (16 interventional, 5 cross-sectional, and 1 combined interventional – cross-sectional) that included 2345 NAFLD patients. Hepatic parameters included were ALT, AST, and GGT. Patients that participated in the intervention studies had elevated transaminases, those that received statin therapy had a mean difference (MD) reduction of ALT of -27.2 U/L (-35.25/-19.15) and a percentage reduction of -35.41% (-44.78/-26.04). For AST, an MD of -18.82 U/L (-25.63/-12.02); percentage -31.78% (-41.45/-22.11). Similar reductions were observed for GGT as well, MD of -19.93 U/L (-27.10/-12.77); percentage -25.57% (-35.18/-15.97). The cross-sectional studies showed similar AST and GGT values in patients treated with statins and those without. Based on these findings, statin therapy was not associated with worsening hepatic function in NAFLD patients. Potential benefit was noted in the interventional studies that could point towards a new indication for statin therapy beyond ASCVD risk prevention.

Pastori D, Pani A, Di Rocco A *et al.* Statin liver safety in non-alcoholic fatty liver disease: A systematic review and metanalysis. Br J Clin Pharmacol 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34133035>

Risk of SAMS; comparing high intensity with moderate intensity statins

To estimate the relative risk of developing statin-associated muscle symptoms (SAMS) based on statin intensity, a meta-analysis was performed on data collected in high-quality randomized clinical trials with >1000 participants and at least two years of treatment. In total, 2919 trials were evaluated, and 24 studies (N=152 146) were included. Outcomes included muscle symptoms (any myalgia and attrition due to muscle symptoms), rhabdomyolysis, and elevated creatine kinase (CK) (>10 x upper limit of normal). Comparing high intensity with moderate intensity

statins, higher dosing/intensity was associated with increased risk for SAMS. Any muscle problem showed a 4% higher risk, RR 1.04 (1.00 – 1.07; I²=0%). Myalgia, RR=1.04 (1.00 - 1.08; I²=0%), number needed to harm (NNH)=173). Attrition due to muscle problems, RR=1.37 (1.09 - 1.73, I²=0%), NNH=218) and elevated CK, RR=4.69 (2.50 to 8.80; I²=7%), NNH=527. When compared to placebo, the following associations were observed; any muscle problem RR=1.05 (1.01 - 1.09, I²=0%), myalgia (RR=1.13, 95% CI 1.05 to 1.23; I²=0%), NNH=182; attrition due to muscle problems RR=1.55 (1.15 to 2.08, I²=0%), NNH=187 and elevated CK RR=5.37 (2.48 - 11.61; I²=7%), NNH=589. No significant differences were noted when comparing moderate-intensity statins with placebo. The authors estimated that for every 200 patients treated with high-intensity statins, one would experience myalgia or discontinue statin therapy compared with patients using moderate statin therapy.

Davis JW, Weller SC. Intensity of statin therapy and muscle symptoms: a network meta-analysis of 153 000 patients. *BMJ Open* 2021; 11:e043714.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=34130955>

Statins for primary prevention in elderly Korean patients

Elderly use of statins in primary preventions has not been properly evaluated in a randomized clinical trial and observational; registry data can provide insights into the potentially beneficial and harmful effects. This analysis was based on the Korea Korean National Health Insurance Service-Senior Cohort database (n = 558,147). In total, 81 729 elderly patients (>75 years) with absent signs of symptoms of ASCVD were included in this registry. Those that did not use statins in 2003 were followed from 2004 – 2012. Patients that started with statins (N=3670) were propensity score-matched with patients that did not use statins in a ratio of 1:2. The selected endpoints for this evaluation included myocardial infarction, ischemic stroke, and CVD death. Using a Cox proportional hazard analysis, statins users were significantly better protected than patients who were not using statins. CVD death HR: 0.34 (0.29 to 0.40; p < 0.001). Both diabetic and non-diabetic patients had a reduced CVD mortality. In diabetic patient's statin use was associated with a reduced risk for MI, HR: 0.85 (0.55 to 1.33) and ischemic stroke, HR: 0.75 (0.60 to 0.93). This was 0.95 (0.73 to 1.24) and 1.13 (1.01 to 1.26) respectively for patients in whom diabetes was absent. Hypertension was a significant risk factor in the prevention of ischemic stroke by statin treatment as well. The data collected in this large Korean registry confirms early studies showing CVD mortality benefits in elderly patients free of cardiovascular disease that used statins. In diabetic patients, statin use was significantly associated with a reduction of ischemic stroke.

Cho Y, Jeong Y, Seo DH *et al.* Use of statin for the primary prevention of cardiovascular outcomes in elderly patients: A propensity-matched cohort study. *Atherosclerosis* 2021; 328:92-99. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34126505>

Stopping statins in elderly patients, is there a price to pay?

In elderly patients with multiple co-morbidities, polypharmacy is of great concern. The benefits of statins in septuagenarians are not well established, and stopping statins in elderly or very elderly patients to diminish their “pill burden” is not uncommon. However, the effects of stopping statins have not been adequately studied; In this observational retrospective cohort study, 29 047 Italian patients > 65 years of age and who were treated with statins, blood pressure-lowering drugs, anti-diabetic medication, and antiplatelets from October 2013 – until January 2015, were followed through June 2018. Those that discontinued statins but maintained their other medications during the first 6 months after stopping statins were propensity score-matched (1:1) with patients that continued their medication regimen, including statins. Patients that stopped statins (N=5819) had a mean age of 76.5 (\pm 6.5) years, and 62.9% were men. Of those that stopped, 4010 (68.9%) were matched with those that continued using statins. Those that stopped statins and continued with their other medication were at increased risk to be admitted to a hospital for heart failure complications, HR: 1.24 (1.07 - 1.43); have any cardiovascular outcome, HR: 1.14 (1.03 - 1.26); mortality, HR: 1.15 ((1.02 - 1.30) and have an emergency admission for any cause HR: 1.12 (1.05 – 1.19). However, the observational design prohibits drawing causal conclusions. The outcomes illustrate the potential harm from stopping statins in the elderly with co-morbidities and using a combination of different medications. Benefits were noted in younger and older patients, patients with a mild or severe clinical profile, and irrespective if statins were used in a primary or secondary prevention setting.

Rea F, Biffi A, Ronco R *et al.* Cardiovascular Outcomes and Mortality Associated With Discontinuing Statins in Older Patients Receiving Polypharmacy. JAMA network open 2021; 4:e2113186. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34125221>

Relevant publications

1. Zhang H, Ye PC, Wang XM *et al.* (The relationship between genotype of familial hypercholesterolemia and the efficacy of PCSK9 inhibitors). Zhonghua xin xue guan bing za zhi 2021; 49:572-579. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34126724>
2. Zhang H, Jiang M, Hou H, Li Q. Efficacy of simvastatin on carotid atherosclerotic plaque and its effects on serum inflammatory factors and cardiocerebrovascular events in elderly patients. Experimental and therapeutic medicine 2021; 22:819. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34131442>

3. Yu SS, Jin J, Yao RQ *et al.* Association of Preadmission Statin Use and Mortality in Critically Ill Patients: A Meta-Analysis of Cohort Studies. Frontiers in medicine 2021; 8:656694. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34124094>
4. Wong ND, Bang M, Block RC *et al.* Perceptions and Barriers on the Use of Proprotein Subtilisin/Kexin Type 9 Inhibitors in Heterozygous Familial Hypercholesterolemia (From a Survey of Primary Care Physicians and Cardiologists). Am J Cardiol 2021; 152:57-62. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34147211>
5. Wang XN, Wang F, Ye P *et al.* (Cross sectional study of familial hypercholesterolemia in dyslipidemia patients receiving lipid-lowering therapy: DYSIS-China subgroup analysis). Zhonghua xin xue guan bing za zhi 2021; 49:564-571. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34126723>
6. Vuorio A, Kovanen PT. Mucormycosis and glucose-regulated protein 78 in COVID-19: amenable to statin treatment? Journal of internal medicine 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34133038>
7. Smith W, Cheng-Lai A, Nawarskas J. Bempedoic Acid: A New Avenue for the Treatment of Dyslipidemia. Cardiology in review 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34132656>
8. SjulS S, Jensen U, Littmann K *et al.* Effective cholesterol lowering after myocardial infarction in patients with nephrotic syndrome may require a multi-pharmacological approach: a case report. European heart journal. Case reports 2021; 5:ytab151. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34124564>
9. Raittinen PVH, Syväälä H, Tammela TLJ *et al.* Atorvastatin induces adrenal androgen downshift in men with prostate cancer: A post Hoc analysis of a pilot adaptive Randomised clinical trial. EBioMedicine 2021; 68:103432. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34144486>
10. Mortensen MB, Blaha MJ. Is There a Role of Coronary CTA in Primary Prevention? Current State and Future Directions. Curr Atheroscler Rep 2021; 23:44. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34146160>
11. Michelucci E, Giorgi ND, Finamore F *et al.* Lipid biomarkers in statin users with coronary artery disease annotated by coronary computed tomography angiography. Scientific reports 2021; 11:12899. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34145378>
12. McGraw-Senat CM, Dillard N, Guelda T *et al.* Bempedoic Acid: A First-in-Class Agent for Lowering Cholesterol Levels. The Senior care pharmacist 2021; 36:331-336. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34144722>
13. Li YJ, Ma GS. (Clinical benefits and safety of low-level LDL-C in the new era of lipid-lowering). Zhonghua xin xue guan bing za zhi 2021; 49:548-553. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34126721>
14. Kassner U, Grunwald S, Spira D *et al.* (Diagnostics and treatment of statin-associated muscle symptoms). Internist (Berl) 2021; 62:827-840. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34143250>
15. Hess CN, Cannon CP, Beckman JA *et al.* Effectiveness of Blood Lipid Management in Patients With Peripheral Artery Disease. J Am Coll Cardiol 2021; 77:3016-3027. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34140105>

16. George RT, Abuhatzira L, Stoughton SM *et al.* MEDI6012: Recombinant Human Lecithin Cholesterol Acyltransferase, High-Density Lipoprotein, and Low-Density Lipoprotein Receptor-Mediated Reverse Cholesterol Transport. J Am Heart Assoc 2021; 10:e014572. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34121413>
17. Gebremichael LG, Suppiah V, Wiese MD *et al.* Efficacy and safety of statins in ethnic differences: a lesson for application in Indigenous Australian patient care. Pharmacogenomics 2021; 22:553-571. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34120458>
18. Eikelboom R, Amir T, Gupta S, Whitlock RP. Optimal medical therapy after coronary artery bypass grafting: a primer for surgeons. Current opinion in cardiology 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34138766>
19. De Spiegeleer A, Van Migerode J, Bronselaer A *et al.* Statin Intake and All-Cause Mortality among Older Nursing Home Residents. Gerontology 2021:1-5. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34134106>
20. Chen LL, Zheng JH. Effects of atorvastatin on the insulin resistance in women of polycystic ovary syndrome: A systematic review and meta-analysis. Medicine (Baltimore) 2021; 100:e26289. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34128863>
21. Cannon CP, de Lemos JA, Rosenson RS *et al.* Use of Lipid-Lowering Therapies Over 2 Years in GOULD, a Registry of Patients With Atherosclerotic Cardiovascular Disease in the US. JAMA cardiology 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34132735>
22. Bonano JC, Aratani AK, Sambare TD *et al.* Perioperative Statin Use May Reduce Postoperative Arrhythmia Rates After Total Joint Arthroplasty. The Journal of arthroplasty 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34127349>
23. Yagi R, Inoue K. Trends in Brand-name Statin Prescriptions Among Physicians Prescribing PCSK9 inhibitors in 2016-2018. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34126248>
24. Wang S, Cao YF, Sun XY *et al.* Plasma Amino Acids and Residual Hypertriglyceridemia in Diabetic Patients Under Statins: Two Independent Cross-Sectional Hospital-Based Cohorts. Frontiers in cardiovascular medicine 2021; 8:605716. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34136538>
25. Ronsein GE, Vaisar T, Davidson WS *et al.* Niacin Increases Atherogenic Proteins in High-Density Lipoprotein of Statin-Treated Subjects. Arterioscler Thromb Vasc Biol 2021; 41:2330-2341. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34134520>
26. Lee VWY, Li JTS, Fong FYH, Yan BPY. Effects of pill splitting training on drug physiochemical properties, compliance, and clinical outcomes in the elderly population: a randomised trial. Hong Kong medical journal = Xiangqiang yi xue za zhi 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34127559>
27. Kalaycıoğlu E, Çetin M, Kırış T, Özyıldız AG. Paradoxical association between lipoprotein cholesterol levels and left atrial function in hypertensive diabetic patients: A speckle tracking study. J Clin Ultrasound 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34137047>
28. Idrees T, Prieto WH, Casula S *et al.* Use of Statins Among Patients Taking Levothyroxine: an Observational Drug Utilization Study Across Sites. Journal of the Endocrine Society 2021; 5:bvab038. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34141994>

29. Feng JL, Dixon-Suen SC, Jordan SJ, Webb PM. Statin use and survival among women with ovarian cancer: an Australian national data-linkage study. Br J Cancer 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34135470>
30. Fanous MM, Gianos E, Sperling LS *et al.* Early use of PCSK9 inhibitor therapy after heart transplantation from a hepatitis C virus positive donor. J Clin Lipidol 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34120877>
31. de Carvalho RDP, Côrrea Viana Casarin R, Lima PO, Cogo-Müller K. STATINSWITH POTENTIAL TO CONTROL PERIODONTITIS: FROM BIOLOGICAL MECHANISMS TO CLINICAL STUDIES. J Oral Biosci 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34146687>
32. D LEM, Yadang FSA, Tchamgoue AD *et al.* Cafeteria Diet-Induced Metabolic and Cardiovascular Changes in Rats: The Role of Piper nigrum Leaf Extract. Evidence-based complementary and alternative medicine : eCAM 2021; 2021:5585650. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34122598>
33. Li K, Liu MM, Yang X *et al.* Evaluation of efficacy and safety of combined rosuvastatin and atorvastatin in treating with coronary heart disease: A protocol for systematic review and meta-analysis. Medicine (Baltimore) 2021; 100:e26340. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34128881>

Basic Science publications

1. Zhang L, Wang J, Xu Q *et al.* Influences of tirofiban combined with atorvastatin on coronary blood flow restoration and changes in inflammatory factors, Cys-C, Hcy and MMP-9 in AMI patients after PCI. Minerva medica 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34142775>
2. Xu Y, Zhang B, Chen Y *et al.* Simvastatin increases circulating endothelial progenitor cells and inhibits the formation of intracranial aneurysms in rats with diet-induced hyperhomocysteinemia. Neurosci Lett 2021; 760:136072. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34147541>
3. Warita K, Ishikawa T, Sugiura A *et al.* Concomitant attenuation of HMGCR expression and activity enhances the growth inhibitory effect of atorvastatin on TGF- β -treated epithelial cancer cells. Scientific reports 2021; 11:12763. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34140545>

4. Pan T, Lin SC, Lee YC *et al.* Statins reduce castration-induced bone marrow adiposity and prostate cancer progression in bone. *Oncogene* 2021; 40:4592-4603.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=34127814>
5. Okubo K, Miyai K, Kato K *et al.* Simvastatin-romidepsin combination kills bladder cancer cells synergistically. *Translational oncology* 2021; 14:101154.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=34144348>
6. Esmail M, Anwar S, Kandeil M *et al.* Effect of Nigella sativa, atorvastatin, or L-Carnitine on high fat diet-induced obesity in adult male Albino rats. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* 2021; 141:111818.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=34126354>
7. Cisneros K, Chowdhury N, Coleman E *et al.* Long-Term Controlled Release of Simvastatin from Photoprinted Triple-Networked Hydrogels Composed of Modified Chitosan and PLA-PEG Micelles. *Macromol Biosci* 2021:e2100123.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=34128589>
8. Asad M, Asdaq SMB, Mohzari Y *et al.* Pharmacokinetic and pharmacodynamic interaction of Rosuvastatin calcium with guggulipid extract in rats. *Saudi journal of biological sciences* 2021; 28:3490-3496.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=34121889>
9. Alhakamy NA, Badr-Eldin SM, Aldawsari HM *et al.* Fluvastatin-Loaded Emulsomes Exhibit Improved Cytotoxic and Apoptosis in Prostate Cancer Cells. *AAPS PharmSciTech* 2021; 22:177. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34128106>
10. Abdel Hakiem AF, Mohamed NA, Ali HRH. FTIR spectroscopic study of two isostructural statins: Simvastatin and Lovastatin as authentic and in pharmaceuticals. *Spectrochimica acta. Part A, Molecular and biomolecular spectroscopy* 2021; 261:120045. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34126397>

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