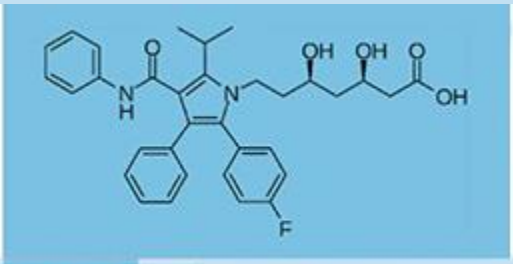
IAS STATIN
NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 37, 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

The SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) trial

The infamous muscle side effects of statins are re-targeted in this specially designed randomized trial. Patients received 12 bottles, each for one month, that contained atorvastatin 20 mg (4), placebo (4), and 4 bottles were empty. Patients were recruited from 17 referral centers across the UK; all stopped taking statins with no intention of restarting them. Symptoms were recorded daily in a specially developed app. Of the 60 participants, 49 completed the 12-month study. The symptom score was 8.0 (4.7 – 11.3) during the empty bottle period, 16.3 (13.0-19.6; p<0.001) when taking atorvastatin. However, this last score was not different from the reported side effects when taking a placebo, 15.4 (12.1-18.7; p<0.001). The between-group P-value was 0.388. The nocebo ratio, symptoms caused by statins that were also reported when taking nocebo were practical the same, 0.90, OR: 1.02. Comparing individual patient data, neither symptom intensity on starting, OR:1.02 (0.98-1.06; p=0.28) nor extent of symptom relief on stopping, OR: 1.01 (0.98-1.05; p=0.48)

distinguished statin from placebo use. Patients using atorvastatin were not more likely to stop using their medication when compared to taking the placebo's (P=0.173). Symptom relief was no different when stopping with a placebo or statin. Half of the patients (N=30) that were evaluated six months after the trial reported using statins. The authors show that traditional cues and experiments used to determine side effects, such as stopping, evaluating, and restarting the medication, can paradoxically confirm non-existing causation. This 3-armed cross-over trial showed that 50% of the patients labeled as statin intolerant were able to successfully restart a statin.

Howard JP, Wood FA, Finegold JA *et al.* Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment. J Am Coll Cardiol 2021; 78:1210-1222.

Toth PP. That Myalgia of Yours Is Not From Statin Intolerance. J Am Coll Cardiol 2021; 78:1223-1226. http://www.ncbi.nlm.nih.gov/pubmed/?term=34531022

Combining statins with fenofibrate effectively lowers high TG's

Statins, either as monotherapy or combined with non-statin LDL-c lowering drugs such as ezetimibe or PCSK9ab, enabled an unprecedented lowering of plasma LDL-c. Despite these well-controlled LDL-c levels, patients continue to experience ASCVD complications, and this residual risk is a renewed focus of basic research and clinical studies. Elevated triglycerides in patients treated with statins are considered an important residual risk marker that can respond favorably to high-dose high-intensity statins but frequently remains elevated. In this multi-centered prospective randomized, double-blind study, 127 statin-treated patients with LDL-c on target but elevated TG were assigned to monotherapy of statin + placebo (n=63) or a combination or fenofibrate and statin (n=64). Patients used atorvastatin 10 -20 mg or rosuvastatin 10 mg in both groups. Fenofibrate was prescribed in a dosage of 178.8 mg. The treatment period was 8 weeks, and after study completion, both TG and HDL-c improved significantly in patients using combination therapy. TG's were lowered from 269.8 mg/dl to 145.5 mg/dl (p<0.0001). TG's remained unchanged in the monotherapy group, from 271.1 mg/dl to 280.5 mg/dl. HDL-c increased from 45.0 mg/dl to 50.4 mg/dl (p=0.0004). No serious adverse events (nephrotoxicity, hepatotoxicity, and myopathy) were reported by the patients using statin + fenofibrate. Only 3 patients (4.6%) in the combination group and 4 (6.3%) in the control group reported mild side effects. This relatively small and short study in Korean patients with optimal LDL-c levels and elevated TG's showed that the addition of fenofibrate effectively and safely reduces triglycerides >40%.

Park MS, Youn JC, Kim EJ *et al.* Efficacy and Safety of Fenofibrate-Statin Combination Therapy in Patients With Inadequately Controlled Triglyceride Levels Despite Previous Statin Monotherapy: A Multicenter, Randomized, Double-blind, Phase IV Study. Clinical therapeutics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34518033

Exploring loss of statin therapy in pregnant, lactating FH women

In patients diagnosed with familial hypercholesterolemia, statins are life-saving drugs that should be initiated at a young age. Consequently, young women use statins during their reproductive ages and are advised to stop statins when they aspire to become pregnant, during pregnancy, and lactation. This study explored the duration of being exposed to elevated LDL-c levels because statins were stopped. This was a cross-sectional analysis of anonymous, questionnaire-based data that were collected online. In total, 103 women diagnosed with FH and managed in Norwegian (N=70) and Dutch (N=32) lipid clinics. Total pregnancy-related off-statin time could be estimated in 80 participants. This ranged from 0 - 14.2 years with a median period of 2.3 years. For 67 women, the percentage of time they were untreated could be estimated as well; this ranged from 0-100% with a median of 18%, based on a median age of 31 (SD: 4.3) years at their last pregnancy. Breastfeeding was more frequent as well as for a more extended period observed in Norwegian women, 83% for 1-43 months with a median time of 8.5 months. Dutch women breastfed their infants in 63% for a median period of 3.6 months and a range of 0-14 months. An important finding was that 86% of the women expressed the need for more information on pregnancy and breastfeeding related to FH. FH women that need to stop statins because of pregnancy need to be monitored closely, and strategies should be implemented to reduce the off-station periods. The impact of these prolonged therapeutic pauses on ASCVD risk increase is not clear and need to be explored by long term follow-up of pregnant FH women in appropriate registries. Klevmoen M, Bogsrud MP, Retterstøl K *et al.* Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia. Atherosclerosis 2021; 335:8-15. http://www.ncbi.nlm.nih.gov/pubmed/?term=34520888

Comparing high dose vs low dose statin + ezetimibe in post primary PCI patients

Managing LDL-c in very high-risk patients is evolving, and recently updated lipid management guidelines advocate combining a statin with ezetimibe or PCSK9ab. This study, using data from the Korean nationwide medical insurance registry, compared the risk of ASCVD events in post-primary PCI patients using high dose, high-intensity statins (atorvastatin 20-40 mg or rosuvastatin 20 mg) vs. moderate dose statin (atorvastatin 5-10 and rosuvastatin 5-10 mg) plus ezetimibe 10 mg. This retrospective observational population-based cohort study included patients between January 1st, 2015, and December 31st, 2016. Of the 20 070 patients, 19 148 used high-intensity statins, and 922 were prescribed combination therapy. Major coronary events (MACE) were recorded at 12 months and shoed 138. 0 vs. 154.0/1000 patients' years in the combination therapy and intensive statin therapy, respectively. This resulted in an adjusted HR of 1.11 (0.86-1.42; p=0.043). The

multi-variable-adjusted HR was 1.05 (0.74-1.47; p=0.80). Noteworthy is the observation that at 12 months, a significantly greater number of patients were adherent in the group that used combination therapy (66.6%) vs. the patients that used monotherapy of high dose high-intensity statins (52.9%); P<0.001. The findings in this registry reassure that using a combination of low-intensity statins plus ezetimibe vs. a monotherapy of high-intensity statin results in similar outcomes. The long-term effects beyond 1-year will need to be confirmed in studies with longer follow-up time.

Kim J, Kang D, Park H *et al.* Moderate-Intensity Statins Plus Ezetimibe vs. High-Intensity Statins After Coronary Revascularization: A Cohort Study. Cardiovasc Drugs Ther 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34533691
http://www.ncbi.nlm.nih.gov/pubmed/?term=34531021

A simple roadmap how to reach guideline dictated LDL-c goals

This concise review by a portfolio of well-recognized US cardiologists, including Scott M. Grundy, provides clinicians a practical and straightforward road map of how to steer patients towards optimal LDL-c targets. Reflecting on both US and European guidelines, they emphasize using high-intensity statins (HIS) or patients with statin intolerability to combine a statin with ezetimibe. Secondary prevention patients are prime candidates for HIS aiming for an LDL-c reduction of at least 50%. The subgroup of ASCVD patients classified as very high risk will need add-on therapies such as ezetimibe, PCSK9ab, or bempedoic acid to reach their more stringent targets of <55 mg/dl. For primary prevention, those with a 10-year ASCVD risk >20%, patients with familial hypercholesterolemia, diabetics with associated risk factors are categorized as high risk, and treatment targets are the same as in ASCVD patients. In those with a 10-year risk between 7.5% - 20%, a coronary calcium score could help reclassify patients to low-risk (Ca score =0) or high risk (Ca score >300 Agatston units). Combining statins with a non-statin is recommended for patients unable to tolerate high dose, high-intensity statins. Simple strategies and tips to overcome the most common barriers to intensive LDL-c management are part of the review, and links to resources for clinicians and patients are provided as well.

Grundy SM, Stone NJ, Blumenthal RS *et al.* High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better. Mayo Clinic proceedings 2021; 96:2660-2670.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34531060

Relevant publications

1. Trias F, Pintó X, Corbella E *et al.* Differences in the diabetogenic effect of statins in patients with prediabetes. The PRELIPID study. Med Clin (Barc) 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34517987
2. Sonaglioni A, Cara MD, Nicolosi GL *et al.* Rapid Risk Stratification of Acute Ischemic Stroke Patients in the Emergency Department: The Incremental Prognostic Role of Left Atrial Reservoir Strain. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2021; 30:106100. http://www.ncbi.nlm.nih.gov/pubmed/?term=34525440
3. Shinohara K, Ikeda S, Enzan N *et al.* Efficacy of intensive lipid-lowering therapy with statins stratified by blood pressure levels in patients with type 2 diabetes mellitus and retinopathy: Insight from the EMPATHY study. Hypertension research : official journal of the Japanese Society of Hypertension 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34526672
4. Santoleri F, Romagnoli A, Costantini A. Adherence and persistence in the use of statins and ezetimibe over 8 years in a real-life study. Current medical research and opinion 2021:1-6. http://www.ncbi.nlm.nih.gov/pubmed/?term=34515600
5. Rey JR, Merino Llorens JL, Iniesta Manjavacas Á M *et al.* Influence of statin treatment in a cohort of patients admitted for COVID-19. Med Clin (Barc) 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34511251
6. Oyama K, Giugliano RP, Tang M *et al.* Effect of evolocumab on acute arterial events across all vascular territories : results from the FOURIER trial. Eur Heart J 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34537830
7. Moon IT, Kang SH, Lee W *et al.* Impact of statin intensity on adverse cardiac and cerebrovascular events in older adult patients with myocardial infarction. Journal of geriatric cardiology : JGC 2021; 18:609-622. http://www.ncbi.nlm.nih.gov/pubmed/?term=34527027
8. Kadoglou NPE, Velidakis N, Khattab E *et al.* The interplay between statins and adipokines. Is this another explanation of statins' 'pleiotropic' effects? Cytokine 2021; 148:155698. http://www.ncbi.nlm.nih.gov/pubmed/?term=34537488
9. Jamialahmadi T, Baratzadeh F, Reiner Ž *et al.* The Effects of Statin Dose, Lipophilicity, and Combination of Statins plus Ezetimibe on Circulating Oxidized Low-Density Lipoprotein Levels: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Mediators Inflamm 2021; 2021:9661752. http://www.ncbi.nlm.nih.gov/pubmed/?term=34526854
10. Hernandez P, Passi N, Modarressi T *et al.* Clinical Management of Hypertriglyceridemia in the Prevention of Cardiovascular Disease and Pancreatitis. Curr Atheroscler Rep 2021; 23:72. http://www.ncbi.nlm.nih.gov/pubmed/?term=34515873

11. Handhle A, Viljoen A, Wierzbicki AS. Elevated Lipoprotein(a): Background, Current Insights and Future Potential Therapies. Vasc Health Risk Manag 2021; 17:527-542. http://www.ncbi.nlm.nih.gov/pubmed/?term=34526771
12. Gong Z, Zhan D, Nie M *et al.* Dexamethasone enhances the efficacy of atorvastatin in inhibiting excessively inflammation-induced abnormal angiogenesis by regulating macrophages. Journal of neuroinflammation 2021; 18:203. http://www.ncbi.nlm.nih.gov/pubmed/?term=34526068
13. Gao F, Wang ZJ, Ma XT *et al.* Effect of alirocumab on coronary plaque in patients with coronary artery disease assessed by optical coherence tomography. Lipids Health Dis 2021; 20:106. http://www.ncbi.nlm.nih.gov/pubmed/?term=34511134
14. Choi D, Chen Q, Goonewardena SN *et al.* Efficacy of Statin Therapy in Patients with Hospital Admission for COVID-19. Cardiovasc Drugs Ther 2021:1-9. http://www.ncbi.nlm.nih.gov/pubmed/?term=34524566
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16. Bao W, Yang M, Xu Z *et al.* Coronary Inflammation Assessed by Perivascular Fat Attenuation Index in Patients with Psoriasis: A Propensity Score-Matched Study. Dermatology 2021:1-9. http://www.ncbi.nlm.nih.gov/pubmed/?term=34535598
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18. Sohrevardi SM, Nasab FS, Mirjalili MR *et al.* Effect of atorvastatin on delirium status of patients in the intensive care unit: a randomized controlled trial. Archives of medical science : AMS 2021; 17:1423-1428. http://www.ncbi.nlm.nih.gov/pubmed/?term=34522273
19. Sahashi Y, Sahashi M, Hikasa Y. Effect of Pravastatin as an Adjunctive Therapeutic for Mitral Insufficiency with Hyperlipidemia in a Dog. Case Rep Vet Med 2021; 2021:6054125. http://www.ncbi.nlm.nih.gov/pubmed/?term=34532150
20. Peterson MN, Dykhoff HJ, Crowson CS *et al.* Risk of rheumatoid arthritis diagnosis in statin users in a large nationwide US study. Arthritis Res Ther 2021; 23:244. http://www.ncbi.nlm.nih.gov/pubmed/?term=34537063
21. Parikh P, Onuorah N, Vashisht P. A rare overlap of statin-induced anti-3-hydroxy-3-methyl-glutaryl-coenzyme A necrotizing autoimmune myositis and dermatomyositis. Rheumatol Adv Pract 2021; 5:rkab064. http://www.ncbi.nlm.nih.gov/pubmed/?term=34527856
22. Barre DE, Mizier-Barre KA. Selected 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors. A look into their use and potential in pre-diabetes and type 2

diabetes. Endocr Regul 2021; 55:182-192.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34523296

23. Asakura M, Hibi K, Shimizu W *et al.* Design and rationale of the EVOCATION trial: A prospective, randomized, exploratory study comparing the effect of evolocumab on coronary microvascular function after percutaneous coronary intervention in patients with stable coronary artery disease. J Cardiol 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34518072 *et al.*

Basic Science publications

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http://www.ncbi.nlm.nih.gov/pubmed/?term=34523310
2. Kamuf J, Garcia Bardon A, Ziebart A *et al.* Influence of rosuvastatin treatment on cerebral inflammation and nitro-oxidative stress in experimental lung injury in pigs. BMC anesthesiology 2021; 21:224.
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3. Faraji E, Mohammadi M, Mahboobian MM. Development of the Binary and Ternary Atorvastatin Solid Dispersions: In Vitro and In Vivo Investigations. BioMed research international 2021; 2021:6644630.
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4. Emami S, Shayanfar A. Comments on "Dissolution Enhancement of Atorvastatin Calcium by Cocrystallization". Advanced pharmaceutical bulletin 2021; 11:578-579.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34513634
5. Dey KK, Lodhi L, Ghosh M. Study of the Variation of the Electronic Distribution and Motional Dynamics of Two Independent Molecules of an Asymmetric Unit of Atorvastatin Calcium by Solid-State NMR Measurements. ACS omega 2021; 6:22752-22764. http://www.ncbi.nlm.nih.gov/pubmed/?term=34514246

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