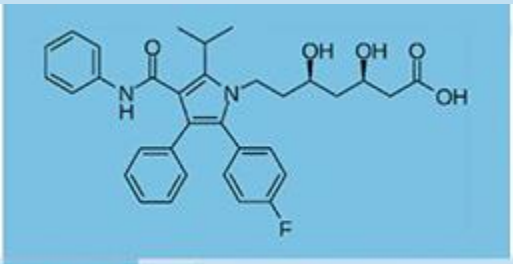
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 25, 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

Parental cholesterol predicts cholesterol levels in their children

For determining ASCVD risk, a positive family history is considered of considerable value and should be part of every personalized risk profile. The authors of this article evaluated a more straightforward approach by determining cholesterol levels in parents and evaluate the impact on their offspring's cholesterol level. Total cholesterol levels were measured in 322 children aged between 6 and 12 years. This was repeated in their biological parents (304 mothers and 206 fathers). A cholesterol level > 240 mg/dl in one or both parents and a plasma cholesterol >200mg in their children showed a significant and robust association, OR: 6.6 (2.85-14.48, P<0.0001). The sensitivity and specificity were 69% and 74%,

respectively, with a positive and negative predictive value of 34% and 93%. These findings were compared to positive family history and children with plasma cholesterol >200 mg/dl. The calculated risk for this relationship resulted in an OR:1.86 (0.84-4.11; P=0.1272). This relationship showed a sensitivity and specificity of 69% and 46%, respectively, with 19% and 89% positive and negative predictive values. For every 10 mg/dl higher total cholesterol of the parents, children showed 2.9 mg/dL and 2.5 mg/dL higher cholesterol, depending on if the increase in plasma cholesterol was observed in their mother or father. Based on these findings measuring parental cholesterol t can help to predict increased plasma cholesterol and ASVCD risk in their offspring.

Robledo JA, Siccardi LJ, Gallindo LM *et al.* Parental hypercholesterolemia and family medical history as predictors of hypercholesterolemia in their children. Arch Argent Pediatr 2019; 117:41-47. http://www.ncbi.nlm.nih.gov/pubmed/?term=30652445

The conundrum of nocebo/drucebo explained

Evaluating the statin side effects in patients is a complex and not seldom a time-consuming challenge. Trials that used an n=1 design showed that most patients classified as statin intolerant die have symptoms when using a placebo or even when not taking any medication. Most importantly, most patients were able to tolerate statins when the results of the studies were shown and explained. For daily clinical practice conducting an n=1 approach is not very practical. The International Lipid Expert Panel (ILEP) has developed two simple tools that very simply can be integrated when evaluating patients with a statin side effect in an outpatient setting. The ILEP introduced a new term DRUCEBO. In contrast, nocebo indicates an inert substance responsible for adverse effects, which refers to adverse events associated with blinded vs. open label drug use. MEDS is an acronym that stands for Minimising disruption to lipid-lowering therapy; Education; Diet and lifestyle changes and symptom intensity. The SLAP acronym provides a series of interventions used in patients presenting with statin-associated muscle symptoms. These are Switching, Lower dosage, Alternate-day dosing, and Polypharmacy using different classes of lipid-lowering as mono-therapy or in combination. The ILEP plans a series of publications and educational activities designed to help clinicians optimally manage patients with statin-related side effects.

Penson PE, Banach M. Nocebo/drucebo effect in statin-intolerant patients: an attempt at recommendations. Eur Heart J 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34151941

Statins in older and adherent diabetic patients free of CVD

Data collected in Danish nationwide registries between 2005 and 2011 were used to evaluate the benefits of statins in newly diagnosed diabetic patients in whom the cardiovascular disease was absent. Patients were aged 40-89 years of age at diagnosis, alive 18 months

following their initial diagnosis, and were prescribed statins < 6 months after diagnosis. Statin compliance was calculated by the proportion of days covered within one year after the initial 6-month period. The endpoints for this analysis were the combination of myocardial infarction, stroke, or all-cause mortality, whichever came first. Included were 77 170 Danish primary prevention diabetic patients; 42 975 (56%) were using statins. A PDC of >80% was observed in 31 061 (72%). The 5-year risk in men aged 70-79 years was 22.9% (21.5-24.3%) and 29.1% (27.4-30.7%), comparing statin users with patients not using statins, respectively. Reflecting a 6.2% (4.0-8.4%; p<0.0001) risk reduction. Age was an important risk modifier, women: 40–49 years, 0.0% (−1.0% to 1.0%); 80–89 years, 10.8% (7.2%–14.4%). Non-compliant patients (PDC<20%) had an increased risk compared to patients that used their statins regularly (PDC >80%), reflected by a 4.2% (2.9-5.6%) increased risk. The findings in the retrospective observational analysis support the use of statins in diabetic patients free of CVD and with significantly improved outcomes in elderly and adherent patients.

Malmborg M, Schmiegelow MDS, Gerds T *et al.* Compliance in Primary Prevention With Statins and Associations With Cardiovascular Risk and Death in a Low-Risk Population With Type 2 Diabetes Mellitus. J Am Heart Assoc 2021; 10:e020395.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34151606

High dose statin pre-PCI effective in East Asian patients

Asian doctors remain reluctant to use high-dose high-intensity statins, even in patients that are classified as (very) high-risk. Partly because a better LDL-c response is expected compared to Caucasian patients, safety concerns are frequently quoted as to why low-dose, low-intensity statins are preferred. This meta-analysis included randomized controlled trials evaluating the benefits of pre-PCI high dose, high-intensity statins in East Asian patients. A total of 15 trials that included 4313 patients were re-analyzed. The primary endpoint, MACE at 30-days, was significantly reduced in patients using high dose statins, OR:0.46 (0.31-0.67. p<0.001). Similar improvements were noted for the secondary endpoint, peri-procedural MI, OR: 0.50 (0.34-0.76,0.001). The authors concluded that this meta-analysis confirmed that high dose preprocedural statins are effective in East Asian patients scheduled for PCI.

Liu J, Zhang B, Chen M, Zheng B. High-dose statin pretreatment decreases periprocedural myocardial infarction and cardiovascular events in East Asian patients undergoing percutaneous coronary intervention: A meta-analysis of fifteen randomized controlled trials. Medicine (Baltimore) 2021; 100:e26278.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34160392

How to interpret and manage CPK elevations

The evaluation of CPK levels in patients using statins that present with mild muscle pain or

weakness is complex. In this case-oriented review, the authors systematically address the different causes that can present with CPK elevation with or without muscle symptoms. The majority of CPK increases are physiological, reflecting recent exercise or muscle trauma. When combined with dehydration, a realistic scenario with exercise, these elevations can be quite impressive. Alcohol excess, seizures, and recent surgery could explain CPK abnormalities. A number of drugs, besides statin, are associated with CPK increases as well. Several Endocrine disorders and hereditary myopathies are on the list as well. The authors provide a stepwise approach to evaluate patients with statin-related muscle complaints with or without CPK elevations. For healthcare providers that manage patients on statins this review provides a complete yet concise review of this relevant topic.
Kim EJ, Wierzbicki AS. Investigating raised creatine kinase. Bmj 2021; 373:n1486.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34162592

Relevant publications

1. **Schwartz GG, Nicholls SJ, Toth PP *et al.* Relation of insulin treatment for type 2 diabetes to the risk of major adverse cardiovascular events after acute coronary syndrome: an analysis of the BETonMACE randomized clinical trial. Cardiovascular diabetology 2021; 20:125.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34158057
2. **Sanz-Cuesta BE, Saver JL. Lipid-Lowering Therapy and Hemorrhagic Stroke Risk: Comparative Meta-Analysis of Statins and PCSK9 Inhibitors. Stroke 2021:Strokeaha121034576.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34154390
3. **Orlowski S, Mourad JJ, Gallo A, Bruckert E. Coronaviruses, cholesterol and statins: Involvement and application for Covid-19. Biochimie 2021; 189:51-64.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34153377
4. **Kupferminc MJ, Kliger C, Rimon E *et al.* Pravastatin is useful for prevention of recurrent severe placenta-mediated complications - a pilot study. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2021:1-7.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34154497
5. **de Beer R, Outhoff K, Phulukdaree A, Soma P. Prevalence of SLCO1B1 single nucleotide variations and their association with hypercholesterolaemia in hypercholesterolemic patients in Gauteng, South Africa. Xenobiotica 2021; 51:949-959.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34154510

6. Awad K, Mohammed M, Zaki MM *et al.* Association of statin use in older people primary prevention group with risk of cardiovascular events and mortality: a systematic review and meta-analysis of observational studies. BMC Med 2021; 19:139. http://www.ncbi.nlm.nih.gov/pubmed/?term=34154589
7. Zhou Z, Ryan J, Ernst ME *et al.* Effect of Statin Therapy on Cognitive Decline and Incident Dementia in Older Adults. J Am Coll Cardiol 2021; 77:3145-3156. http://www.ncbi.nlm.nih.gov/pubmed/?term=34167639
8. Viscasillas M, Lamíquiz-Moneo I, Pérez-Ruiz MR *et al.* Clinical characteristics of premature cardiovascular disease in our health area. Rev Clin Esp (Barc) 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34154974
9. Vasireddi SK, Pivato E, Soltero-Mariscal E *et al.* Postoperative Myocardial Injury in Patients Classified as Low Risk Preoperatively Is Associated With a Particularly Increased Risk of Long-Term Mortality After Noncardiac Surgery. J Am Heart Assoc 2021; 10:e019379. http://www.ncbi.nlm.nih.gov/pubmed/?term=34151588
10. Soška V, Kyselák O. Don't we forget about biological therapy of hypercholesterolemia with PCSK9-inhibitors? Vnitr Lek 2021; 67:138-142. http://www.ncbi.nlm.nih.gov/pubmed/?term=34171952
11. Salib M, Girerd S, Girerd N *et al.* Serum markers of fibrosis, cardiovascular and all-cause mortality in hemodialysis patients: the AURORA trial. Clinical research in cardiology : official journal of the German Cardiac Society 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34170371
12. Sałacka A, Boroń A, Gorący I *et al.* An association of ABCG8: rs11887534 polymorphism and HDL-cholesterol response to statin treatment in the Polish population. Pharmacological reports : PR 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34173968
13. Russo V, Silverio A, Scudiero F *et al.* Preadmission Statin Therapy and Clinical Outcome in Hospitalized Patients With COVID-19: An Italian Multicenter Observational Study. Journal of cardiovascular pharmacology 2021; 78:e94-e100. http://www.ncbi.nlm.nih.gov/pubmed/?term=34173802
14. Ren QW, Yu SY, Teng TK *et al.* Statin associated lower cancer risk and related mortality in patients with heart failure. Eur Heart J 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34157723
15. Ivachevska VV. THE EFFECT OF COMPREHENSIVE TREATMENT OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN COMBINATION WITH PREDIABETES ON THE LIPID PROFILE. Wiadomosci lekarskie (Warsaw, Poland : 1960) 2021; 74:957-760. http://www.ncbi.nlm.nih.gov/pubmed/?term=34156011
16. Feysa SV, Rudakova SO. INFLUENCE OF COMPLEX TREATMENT ON BIOCHEMICAL BLOOD PARAMETERS OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND CONCOMITANT PRE-DIABETES. Wiadomosci lekarskie (Warsaw, Poland : 1960) 2021; 74:986-991. http://www.ncbi.nlm.nih.gov/pubmed/?term=34156017
17. Durmuş M, Bahçecioğlu Ö F, Gök S. Daptomycin in combination with rosuvastatin induced blood creatine phosphokinase elevation. Eur J Hosp Pharm 2021; 28:234-236. http://www.ncbi.nlm.nih.gov/pubmed/?term=34162676

18. Döbert M, Varouxaki AN, Mu AC *et al.* Pravastatin versus Placebo in Pregnancies at High Risk of Term Preeclampsia. Circulation 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34162218
19. Al-Kuraishy HM, Al-Gareeb AI, Samy OM. Statin therapy improves serum Annexin A1 levels in patients with acute coronary syndrome: A case-controlled study. Int J Crit Illn Inj Sci 2021; 11:4-8. http://www.ncbi.nlm.nih.gov/pubmed/?term=34159129
20. Aggarwal P, Sinha SK, Khanra D *et al.* Comparison of original and modified Q risk 2 risk score with Framingham risk score - An Indian perspective. Indian Heart J 2021; 73:353-358. http://www.ncbi.nlm.nih.gov/pubmed/?term=34154755
21. Abdulfattah SY, Al-Awadi SJ. ApoB gene polymorphism (rs676210) and its pharmacogenetics impact on atorvastatin response among Iraqi population with coronary artery disease. Journal, genetic engineering & biotechnology 2021; 19:95. http://www.ncbi.nlm.nih.gov/pubmed/?term=34156559
22. Abdelmasih R, Abdelmaseih R, Reed J. A Rare Case of Statin-Induced Diplopia: An Often-Overlooked but Reported Side Effect. Cureus 2021; 13:e15117. http://www.ncbi.nlm.nih.gov/pubmed/?term=34159019

Basic Science publications

1. Zheng C, Yan S, Lu L *et al.* Lovastatin Inhibits EMT and Metastasis of Triple-Negative Breast Cancer Stem Cells Through Dysregulation of Cytoskeleton-Associated Proteins. Frontiers in oncology 2021; 11:656687. http://www.ncbi.nlm.nih.gov/pubmed/?term=34150623
2. Ping S, Lin W, Liu A *et al.* Ultraviolet photolysis of four typical cardiovascular drugs: mechanisms, influencing factors, degradation pathways, and toxicity trends. Environmental science and pollution research international 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34164790
3. Li WC, Zhao SX, Ren WG *et al.* Co-administration of obeticholic acid and simvastatin protects against high-fat diet-induced non-alcoholic steatohepatitis in mice. Experimental and therapeutic medicine 2021; 22:830. http://www.ncbi.nlm.nih.gov/pubmed/?term=34149876
4. Haseeb M, Thompson PD. The Effect of Statins on RyR and RyR- Associated Disease. Journal of applied physiology (Bethesda, Md. : 1985) 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34166122

5. **Deng F, Tuomi SK, Neuvonen M *et al.* Comparative hepatic and intestinal efflux transport of statins. Drug metabolism and disposition: the biological fate of chemicals 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34162690
6. **Naseroleslami M, Niri NM, Akbarzade I *et al.* Simvastatin-loaded nano-niosomes confer cardioprotection against myocardial ischemia/reperfusion injury. Drug delivery and translational research 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34165730
7. **Ley A, Coumou HC, Frandsen RJN. Heterologous expression of MlcE in Saccharomyces cerevisiae provides resistance to natural and semi-synthetic statins. Metab Eng Commun 2015; 2:117-123.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34150514
8. **Carvalho K, Ferreira AAM, Barbosa NC *et al.* Atorvastatin Attenuates Vascular Remodeling in Mice with Metabolic Syndrome. Arquivos brasileiros de cardiologia 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34161419

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