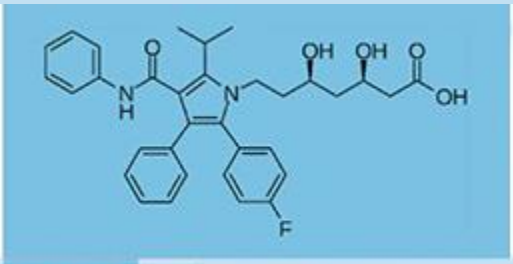
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 09, 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

VICE and DICE scores improve management of COVID-19 patients

COVID-19 remains an enigmatic viral infection with effects that can range from mild to devastating. Risk scores have been developed to recognize and improve the management of those at increased risk for severe and not seldom fatal complications. The VICE (ventilation in COVID-19 estimator) and DICE (death in COVID-19 estimator) risk scores are based on a retrospective analysis of clinical data collected in a cohort of COVID-19 patients admitted to the Mass General Brigham hospitals in Boston, US. In total 1042 Patients, admitted before May 19, 2020, were included (median age 64 yr., 56.8% males, all with a laboratory-confirmed diagnosis). The patients were divided into a derivation (N=578) and validation cohort (N=464). For mechanical ventilation requirements, four factors were critical (DM, SpO2:FiO2 ratio, CRP, and LDH). The DICE

score is based on 10 variables (age, male sex, coronary artery disease, DM, chronic statin use, SpO2:FiO2 ratio, body mass index, neutrophil to lymphocyte ratio, platelet count, and procalcitonin). Chronic statin use was associated with reduced mortality risk, OR: 0.467 (0.237-0.920, p=0.028). Both scores had a good performance, with C-statistics of 0.84 and 0.91, respectively. These risk scores support clinicians to stratify risk in COVID-19 patients; this could improve early recognition and management of those that would benefit from more intensive treatment as well as increase the efficiency of resource utilization. Both VICE and DICE are freely available for HCP's and researchers (https://covid-calculator.com/) Nicholson CJ, Wooster L, Sigurslid HH *et al.* **Estimating risk of mechanical ventilation and in-hospital mortality among adult COVID-19 patients admitted to Mass General Brigham: The VICE and DICE scores.** EClinicalMedicine 2021; 33:100765. http://www.ncbi.nlm.nih.gov/pubmed/?term=33655204

Metabolic syndrome in NHANES participants is a risk enhancing factor

Metabolic syndrome (MS) constitutes a greater burden of lifetime risk tenacity than the sum of the individual risk components. In this NHANES analysis (1999 - 2016), MS's impact as a risk enhancing factor was evaluated in 26 796 US adults (14-75 yrs.). Based on the pooled cohort risk equation (PCE), patients were grouped into three 10-year risk categories, low risk (<7.5%), intermediated risk (7.5% - 20.0%), and high risk (>20%). In 90.4% of the NHANES participants were no ASCVD was present. IN those categorized as low risk, 15% and 17% of the females and males were MS+; this increased to 30.6% and 29.6% in those considered intermediate risk and 21.5% and 32.2% in the high-risk category. For DM+ this was 6.1% - 5.3% (F - M) of low-risk individuals, 20.1 - 14.8% (F - M) of intermediate-risk subjects, and 44.3% - 39.4% (F - M) of high-risk persons. Both MS+ and DM+ incidence increased with age in women and men. Based on their findings, the authors suggested using MS as a lifetime risk enhancing factor for determining statin eligibility based on the intermediate-risk group, according to the PCE estimation. For females in the intermediate-risk category, a calcium score = 0 could identify those in whom statin therapy could be delayed. In males, a calcium score measurement would not be advised; only a small percentage of the male NHANES participants were found to have CAC score=0. Noteworthy is that almost 2/3 of the patients were diagnosed with DM or MS in the high-risk category.

Vega GL, Wang J, Grundy SM. **Utility of metabolic syndrome as a risk enhancing factor in decision of statin use.** J Clin Lipidol 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=33663990

Can statins prevent AF recurrence after cardioversion?

A single-center registry was used to evaluate the effects of statins on AF recurrence after cardio conversion (CV). Between 2012 and 2015, 454 consecutive patients treated with electrical or pharmacological cardioversion were included. Using a Cox regression statistical model, statin users were compared with patients that did not take statins. Statins were used by 183 (40.3%) of the included patients. After a median follow-up of 373 (207_805) days, AF recurrence was observed in 150 (33%) of the patients. Those that used statins had a significantly reduced risk (log-rank p<0.001) for AF recurrence. This translated into an HR of 0.333 (0.225-0.493) based on univariate analysis and an HR: 0.238 (0.151-0.375; p<0.001) after adjustments. Based on propensity score matching, statin use was associated with a 27.5% lower risk for AF recurrence in 21 (18.1%) statins users vs. 53 (45.7%) controls; P<0.001). The authors concluded that prolonged statin use was associate with a reduced long-term risk for AF recurrence.

Fiedler L, Hallsson L, Tscharre M *et al.* Upstream Statin Therapy and Long-Term Recurrence of Atrial Fibrillation after Cardioversion: A Propensity-Matched Analysis. Journal of clinical medicine **2021; 10.**

http://www.ncbi.nlm.nih.gov/pubmed/?term=33671264

Statins and antiplatelets associated with reduce VTE and mortality risk in COVID-19 patients

Patients suffering from COVID-19 complications have an increased risk for thromboembolic complications. Patients admitted to New York Metropolitan hospitals between March 1 and April 27 were evaluated for VTE rates and mortality within 8-hrs of admission. Of the 10 871-hospital admitted COVID-19 patients, 118 (1.09 %) had symptomatic VTE (101 pulmonary embolism and 17 DVT events). In total, 28 (0.26%) patients died during the initial assessment. Key medications included corticosteroids (22.6%). Statins (21.2%), antiplatelets (20.6%) and anticoagulants (20.6%). Elevated D-dimer levels (> 6 x the ULN) were found in 51.4% of the patients. both statin and anti-platelet use were significantly associated with a decrease in both VTE and mortality risk (P<0.01). to better understand the potential benefits of statins and anti-platelets, prehospital admission, in patients presenting with COVID-19 complications, additional studies are warranted.

Giannis D, Barish MA, Goldin M *et al.* Incidence of Venous Thromboembolism and Mortality in Patients with Initial Presentation of COVID-19. Journal of thrombosis and

thrombolysis 2021:1-5. http://www.ncbi.nlm.nih.gov/pubmed/?term=33665766

Statin associated myopathy an update on novel insights

This review provides insights into the current understanding of statin-associated myopathy. It shares new insights into the role of specific ion channels (CLC-1 chlorine channel) that could be a potential susceptible target for statin side effects. Changes in these channels due to aging or pre-existing myopathies increase the risk of statin-triggered muscle complications. Oxidative as well as glycolytic metabolic changes and sarcopenia, prime muscle fibers to become sensitized for stress conditions and trigger myopathy. Elderly patients and those with specific risk factors such as diabetes, hypothyroidism, renal disease are at risk for metabolic changes that promote muscle complaints and statins exacerbate. Careful monitoring of these high-risk patients or even avoiding statin prescriptions could prevent muscle complications. Potential treatments to increase CL channel activity are suggested. Pharmacological agents that target AMPK and Coenzyme Q10 supplements could both help to reduce this risk are discussed in this review.

Camerino GM, Tarantino N, Canfora I *et al.* **Statin-Induced Myopathy: Translational Studies from Preclinical to Clinical Evidence.** Int J Mol Sci 2021; 22. http://www.ncbi.nlm.nih.gov/pubmed/?term=33669797

Relevant publications

1. Nomani H, Mohammadpour AH, Reiner Ž *et al.* Statin Therapy in Post-Operative Atrial Fibrillation: Focus on the Anti-Inflammatory Effects. J Cardiovasc Dev Dis 2021; 8. http://www.ncbi.nlm.nih.gov/pubmed/?term=33652637
2. Youens D, Doust J, Robinson S, Moorin R. Regularity and Continuity of GP Contacts and Use of Statins Amongst People at Risk of Cardiovascular Events. Journal of general internal medicine 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33655384
3. Ying Q, Chan DC, Watts GF. New Insights Into the Regulation of Lipoprotein Metabolism by PCSK9: Lessons From Stable Isotope Tracer Studies in Human

Subjects. Front Physiol 2021; 12:603910. http://www.ncbi.nlm.nih.gov/pubmed/?term=33643062

4. Yen CL, Fan PC, Lin MS *et al.* Fenofibrate Delays the Need for Dialysis and Reduces Cardiovascular Risk among Patients with Advanced CKD. J Clin Endocrinol Metab 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33677489
5. Turgeon RD, Sedlak T. Use of Preventive Medications in Patients With Nonobstructive Coronary Artery Disease: Analysis of the PROMISE Trial. CJC Open 2021; 3:159-166. http://www.ncbi.nlm.nih.gov/pubmed/?term=33644729
6. Tiemann J, Lindenkamp C, Plümers R *et al.* Statins as a Therapeutic Approach for the Treatment of Pseudoxanthoma Elasticum Patients: Evaluation of the Spectrum Efficacy of Atorvastatin In Vitro. Cells 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=33669724
7. Pulipati VP, Davidson MH. The clinical black, white, and gray lessons. Curr Opin Lipidol 2021; 32:151-156. http://www.ncbi.nlm.nih.gov/pubmed/?term=33651748
8. Nagayama D, Saiki A, Watanabe Y *et al.* Prevention of Cardiovascular Events with Pitavastatin is Associated with Increased Serum Lipoprotein Lipase Mass Level: Subgroup Analysis of the TOHO-LIP. J Atheroscler Thromb 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33642441
9. Marrache MK, Rockey DC. Statins for treatment of chronic liver disease. Current opinion in gastroenterology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33654016
10. Malik A, Ramadan A, Vemuri B *et al.* ω-3 Ethyl ester results in better cognitive function at 12 and 30 months than control in cognitively healthy subjects with coronary artery disease: a secondary analysis of a randomized clinical trial. The American journal of clinical nutrition 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33675344
11. Li L, Cui N, Hao T *et al.* Statins use and the prognosis of colorectal cancer: a meta-analysis. Clin Res Hepatol Gastroenterol 2021; 45:101588. http://www.ncbi.nlm.nih.gov/pubmed/?term=33662632
12. Kanagalingam T, Lazarte J, Wong DKH, Hegele RA. Liver Injury Associated With Ezetimibe Monotherapy. CJC Open 2021; 3:195-197. http://www.ncbi.nlm.nih.gov/pubmed/?term=33644733
13. Huh KY, Lee SW, Lee SB *et al.* Pharmacokinetic Interaction Among Ezetimibe, Rosuvastatin, and Telmisartan. Clinical pharmacology in drug development 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33647189

14. Furtado RHM, Genestreti PR, Dalçóquio TF *et al.* Association between Statin Therapy and Lower Incidence of Hyperglycemia in Patients Hospitalized with Acute Coronary Syndromes. Arquivos brasileiros de cardiologia 2021; 116:285-294. http://www.ncbi.nlm.nih.gov/pubmed/?term=33656078
15. Chhibber A, Hansen S, Biskupiak J. Statin use and mortality in rheumatoid arthritis: an incident user cohort study. Journal of managed care & specialty pharmacy 2021; 27:296-305. http://www.ncbi.nlm.nih.gov/pubmed/?term=33645241
16. Chacko SR, DeJoy R, 3rd, Lo KB *et al.* Association of pre-admission statin use with reduced in-hospital mortality in COVID-19. Am J Med Sci 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33667433
17. Boppana SH, Syed HA, Antwi-Amoabeng D *et al.* Atorvastatin-Induced Necrotizing Myopathy and its Response to Combination Therapy. Cureus 2021; 13:e12957. http://www.ncbi.nlm.nih.gov/pubmed/?term=33659112
18. Bai F, Chen J, Pandey D *et al.* Stroke Risk Factor Status and Use of Stroke Prevention Medications Among Hispanic/Latino Adults in HCHS/SOL. Stroke 2021:Strokeaha120031216. http://www.ncbi.nlm.nih.gov/pubmed/?term=33657859
19. Bahiru E, Hsiao R, Phillipson D, Watson KE. Mechanisms and Treatment of Dyslipidemia in Diabetes. Current cardiology reports 2021; 23:26. http://www.ncbi.nlm.nih.gov/pubmed/?term=33655372
20. Alsuhibani A, Albogami Y, Diaby V *et al.* Evaluation of statin discontinuation stratified by primary versus secondary prevention following bariatric surgery: a retrospective cohort study. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33648887
21. Ali AH, Younis N, Abdallah R *et al.* Lipid-Lowering Therapies for Atherosclerosis: Statins, Fibrates, Ezetimibe and PCSK9 monoclonal antibodies. Curr Med Chem 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33655822
22. Afshar M, Yazdan-Ashoori S, Engert JC, Thanassoulis G. Drugs for prevention and treatment of aortic stenosis: how close are we? Can J Cardiol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33677100
23. Yelshibayeva E, Dautov T, Rakhimzhanova R *et al.* COMPUTED TOMOGRAPHY IN DETECTING FEATURES OF CORONARY ATHEROSCLEROSIS IN DIFFERENT ETHNIC GROUPS OF KAZAKHSTAN POPULATION. Georgian medical news 2021:68-77. http://www.ncbi.nlm.nih.gov/pubmed/?term=33658412

24. **Wright RS, Ray KK, Raal FJ *et al.* Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis. J Am Coll Cardiol 2021; 77:1182-1193. http://www.ncbi.nlm.nih.gov/pubmed/?term=33663735**
25. **Sun M, Lemaçon A, Legault MA *et al.* Genetic meta-analysis of cancer diagnosis following statin use identifies new associations and implicates human leukocyte antigen (HLA) in women. Pharmacogenomics J 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33649522**
26. **Su VY, Pan SW, Yen YF *et al.* Statin use and impact on tuberculosis risk. Expert Rev Anti Infect Ther 2021:1-6. http://www.ncbi.nlm.nih.gov/pubmed/?term=33641582**
27. **Michael L, Caspar M, Alexander K *et al.* Major Depressive Disorder (MDD) and Antidepressant Medication Are Overrepresented in High-Dose Statin Treatment. Frontiers in medicine 2021; 8:608083. http://www.ncbi.nlm.nih.gov/pubmed/?term=33644093**
28. **Liebow M, Larson MC, Thompson CA *et al.* Aspirin and other nonsteroidal anti-inflammatory drugs, statins and risk of non-Hodgkin lymphoma. International journal of cancer. Journal international du cancer 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33644854**
29. **Kauerova S, Bartuskova H, Muffova B *et al.* Statins Directly Influence the Polarization of Adipose Tissue Macrophages: A Role in Chronic Inflammation. Biomedicines 2021; 9. http://www.ncbi.nlm.nih.gov/pubmed/?term=33669779**
30. **Hernández-Muñoz JJ, Wong ES, Kamdar CR. Prevalence of statin utilization and adherence among privately insured subjects in the Commonwealth of Puerto Rico. Journal of managed care & specialty pharmacy 2021; 27:392-398. http://www.ncbi.nlm.nih.gov/pubmed/?term=33645248**
31. **Gopaul VS, Pieterman EJ, Princen HMG *et al.* Effects of mineral oil administration on the pharmacokinetics, metabolism and pharmacodynamics of atorvastatin and pravastatin in mice and dogs. Eur J Pharm Sci 2021:105776. http://www.ncbi.nlm.nih.gov/pubmed/?term=33667667**
32. **Cárdenas-Jaén K, Vaillo-Rocamora A, Gracia Á *et al.* Simvastatin in the Prevention of Recurrent Pancreatitis: Design and Rationale of a Multicenter Triple-Blind Randomized Controlled Trial, the SIMBA Trial. Frontiers in medicine 2020; 7:494. http://www.ncbi.nlm.nih.gov/pubmed/?term=33644082**

Basic Science publications

1. Zhu L, Liu F, Hao Q *et al.* Dietary Geranylgeranyl Pyrophosphate Counteracts the Benefits of Statin Therapy in Experimental Pulmonary Hypertension. Circulation 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33660517
2. Yuvaraj S, Ramprasath T, Saravanan B *et al.* Chrysin attenuates high-fat-diet-induced myocardial oxidative stress via upregulating eNOS and Nrf2 target genes in rats. Molecular and cellular biochemistry 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33677805
3. Sharma T, Abohashrh M, Baig MH *et al.* Screening of drug databank against WT and mutant main protease of SARS-CoV-2: Towards finding potential compound for repurposing against COVID-19. Saudi journal of biological sciences 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33649700
4. Ren G, Zhou Q, Lu M, Wang H. Rosuvastatin corrects oxidative stress and inflammation induced by LPS to attenuate cardiac injury by inhibiting the NLRP3/TLR4 pathway. Canadian journal of physiology and pharmacology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33641435
5. Nenna A, Nappi F, Larobina D *et al.* Polymers and Nanoparticles for Statin Delivery: Current Use and Future Perspectives in Cardiovascular Disease. Polymers (Basel) 2021; 13. http://www.ncbi.nlm.nih.gov/pubmed/?term=33652927
6. Liu P, Gao Q, Guan L *et al.* Atorvastatin attenuates surgery-induced BBB disruption and cognitive impairment partly by suppressing NF-κB pathway and NLRP3 inflammasome activation in aged mice. Acta biochimica et biophysica Sinica 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33674828
7. Kwak SY, Park S, Kim H *et al.* Atorvastatin Inhibits Endothelial PAI-1-Mediated Monocyte Migration and Alleviates Radiation-Induced Enteropathy. Int J Mol Sci 2021; 22. http://www.ncbi.nlm.nih.gov/pubmed/?term=33673196
8. Kuba JO, Yu Y, Klauda JB. Estimating Localization of Various Statins within a POPC Bilayer. Chemistry and physics of lipids 2021:105074. http://www.ncbi.nlm.nih.gov/pubmed/?term=33676920
9. Grune C, Zens C, Czapka A *et al.* Sustainable preparation of anti-inflammatory atorvastatin PLGA nanoparticles. Int J Pharm 2021:120404. http://www.ncbi.nlm.nih.gov/pubmed/?term=33647413

10. **Fan Q, Gong T, Zheng C *et al.* Statins repress hedgehog signaling in medulloblastoma with no bone toxicities. Oncogene 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33649536**
11. **Dai B, Li X, Xu J *et al.* Synergistic effects of magnesium ions and simvastatin on attenuation of high-fat diet-induced bone loss. Bioact Mater 2021; 6:2511-2522. http://www.ncbi.nlm.nih.gov/pubmed/?term=33665494**
12. **Barreto A, Santos J, Amorim MJB, Maria VL. Polystyrene Nanoplastics Can Alter the Toxicological Effects of Simvastatin on Danio rerio. Toxics 2021; 9. http://www.ncbi.nlm.nih.gov/pubmed/?term=33652851**

This activity is supported by an educational grant from Viatris.