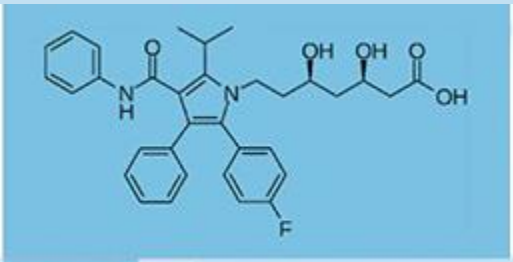
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 02, 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 non-adherence a common barrier when prescribing statins

Patient's unwillingness to use statins remains one of the most critical challenges to prevent future cardiovascular complications. Primary non-adherence, patients that refuse to collect their statins from the pharmacy, is addressed in the study of 61 patients. The majority of the interviewed patients (93%) did not suffer from ASCVD complications; however, they were considered "high CVD risk" patients, and statins were indicated. The study aimed to better understand why patients refused to start with statins by exploring their perceptions on statin use. Common arguments these patients shared to explain their dislike for statins were a preference to use other non-pharmacological strategies (diet, exercise, supplements); fear of side effects; feeling good and healthy so statins were not needed, and some were doubting if statins would benefit them since they were not sick. Less common reasons were mistrust of Pharma/doctors, insufficient explanation by their healthcare providers, earlier negative experiences, and some suggested a high, genetically caused, cholesterol did not

need to be reduced. Noteworthy is that one-third of the patients said they never discussed their decision to not take statins with their physician. Physicians are not always aware of primary non-adherence; lack of communication is partly to blame for this. New strategies are needed to identify and manage this substantial barrier to CVD preventive measures.

Tarn DM, Barrientos M, Pletcher MJ *et al.* **Perceptions of Patients with Primary Nonadherence to Statin Medications.** Journal of the American Board of Family Medicine : JABFM 2021; 34:123-131. http://www.ncbi.nlm.nih.gov/pubmed/?term=33452090

AF a future indication for statins?

The effects of statins in non-valvular atrial fibrillation (AF), a serious problem found in a large number of cardiac patients, remains enigmatic and confusing, due to a lack of randomized clinical trials. In this meta-analysis the authors examined 14 studies (2 post-hoc analysis of randomized clinical trials, 8 prospective and 4 retrospective) with 100,287 AF patients, of whom 23,228 were on statins. all-cause mortality was the primary endpoints secondary endpoints included CV mortality, composite endpoints, strokes, and bleeding complications. Both all cause-mortality and CV mortality were significantly reduced by 41% (HR:0.59 [0.54-0.65]), and 25% (HR: 0.75 [0.58-0.68]) respectively. The absolute reduction of all-cause mortality was 10% in statin users, and benefits were observed after 12 months. Risk for bleeding complications was 40% lower in statin users as well (HR: 0.60 [0.48-0.76]). Results were consistent when corrected for age, sex and manifest cardiovascular or cerebrovascular disease. This first meta-analysis of on the benefits of statins in AF shows promising results in this very high-risk population, with an estimated 1-year mortality of 5.7 %, and most of cardiovascular complications (70 %), despite anticoagulation. Based on these findings properly designed randomized trials are warranted to confirm these results that could significantly decrease the impressive burden of fatal CVD complications in AF patients.

Pastori D, Baratta F, Di Rocco A *et al.* **Statin use and mortality in atrial fibrillation: A systematic review and meta-analysis of 100,287 patients.** Pharmacol Res 2021:105418. http://www.ncbi.nlm.nih.gov/pubmed/?term=33450384

Preventing re-occlusion’s after acute mechanical thrombectomy

Mechanical thrombectomy (MT) is currently a well-accepted treatment for patients presenting with an acute ischemic stroke. Successful recanalization has been observed in almost 80% of patients. However, 3-9% of treated patients experience re-occlusions <24 hrs after MT. This meta-analysis explored predictors and prognosis of post-MT re-occlusions. In total, 5 studies that included 1 883 confirmed acute ischemic stroke patients treated with

emergency MT, of which 126 patients suffered from re-occlusions. Predictors for re-occlusion were AF (OR:0.36 [0.20–0.63]), cardiogenic embolism (OR:0.35 [0.20–0.63]), long term statin use (OR:0.39 [0.21–0.75]), long-term antiplatelet use (OR:0.53 [0.31–0.92]) and target occlusion of the middle cerebral artery-M1 (OR:0.39 [0.19–0.77]) and associated with a reduced risk for re-occlusion. A longer onset-to-reperfusion time, mean difference, 66,51 (36.66-96.35), was associated with increased re-occlusion risk. Patients that experience re-occlusion had early neurological deterioration (OR, 4.87; 95% CI, 2.08–11.40), 90-day modified Rankin Scale score ≤2 (OR, 0.28; 95% CI, 0.18–0.45), and 90-day death rate (OR, 1.85; 95% CI, 1.04–3.29). Actionable options to prevent MT associated re-occlusions long term statin and anti-platelet use and reduce onset to reperfusion time.

Li X, Gu F, Ding J *et al.* **The predictors and prognosis for unexpected reocclusion after mechanical thrombectomy: a meta-analysis.** Annals of translational medicine 2020; 8:1566. http://www.ncbi.nlm.nih.gov/pubmed/?term=33437765

CAC score changes and statin use; a systematic review and meta-analysis

The coronary calcium score (CAC) has gained popularity as a surrogate marker of coronary atherosclerosis and was adopted by several major guidelines to assess CV risk. This meta-analysis explores the effects of CAC changes in patients using statins, compared to patients not using statins and the progression of CAC and ASCVD events. Included were seven studies, four randomized and 3 observational studies that examined 5050 patients, 1244 using statins, and 3806 controls. Only studies that reported Agatston scores at baseline and follow-up from patients with and without statin therapy were included. The patients who used statins had an insignificantly lower CAC score at follow-up than those that did not take statins. In subgroup analysis, statin use was associated with a mildly diminished CAC progression; in those with baseline CAC scores > 400, this regression was statistically significant (P<0.009). Patients with progression of calcification had worse CV outcomes compared to the patients without CAC progression. However, baseline CAC score was associated with more decisive effects on ASCVD complications. Patients using statins showed no increase in CV risk even when CAC score increased. The relationship between CAC progression, cardiovascular outcomes, and statin use needs to be explored further. Larger cohorts, with longer follow-up periods and individual patient data, are some of the critical elements that would enable the expansion of our current understating and ensure improved personalized treatment approaches for patients with a high or very high ASCVD risk.

Lai R, Ju J, Lin Q, Xu H. **Coronary Artery Calcification Under Statin Therapy and Its Effect on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis.** Frontiers in cardiovascular medicine 2020; 7:600497.

http://www.ncbi.nlm.nih.gov/pubmed/?term=33426001

Systematic review of 22 current lipid management guidelines

The different recommendations for lipid management, formulated in national and international guidelines, can be confusing and sometimes conflicting. This systematic review compared 22 guidelines for targeted plasma lipid levels and how frequently patients should be monitored in a secondary prevention setting. Of the 22 guidelines, only 17 provided a cholesterol target, mostly LDL-c, ranging from 1.0-2.6 mmol/L. The most frequently recommended target (in 12 guidelines) was an LDL-c <1.8 mmol/L. Follow-up recommendations varied significantly, ranging from annually (9 guidelines) to ranges between 3-12 months. Most follow-up recommendations were based on clinical opinion and lacked supportive evidence. The authors suggested that further research is needed for more evidence-based guidance on optimal lipid monitoring in secondary prevention. Although this might seem trivial to some, having an evidence-based approach would optimize costs and minimize unnecessary visits to general practitioners. This review provides a concise and up-to-date overview of all major lipid-management guidelines.

Brown RE, Welsh P, Logue J. **Systematic review of clinical guidelines for lipid lowering in the secondary prevention of cardiovascular disease events**. Open heart 2020; 7. http://www.ncbi.nlm.nih.gov/pubmed/?term=33443127

Relevant publications

1. Wong ND, Zhao Y, Sung J, Browne A. Relation of First and Total Recurrent Atherosclerotic Cardiovascular Disease Events to Increased Lipoprotein(a) Levels among Statin Treated Adults with Cardiovascular Disease. Am J Cardiol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33454339
2. Vlad CE, Foia L, Florea L *et al.* Evaluation of cardiovascular risk factors in patients with familial hypercholesterolemia from the North-Eastern area of Romania. Lipids Health Dis 2021; 20:4. http://www.ncbi.nlm.nih.gov/pubmed/?term=33430859
3. Tong ST, Sabo RT, Hochheimer CJ *et al.* Uptake of Statin Guidelines to Prevent and Treat Cardiovascular Disease. Journal of the American Board of Family Medicine : JABFM 2021; 34:113-122. http://www.ncbi.nlm.nih.gov/pubmed/?term=33452089
4. Sun L, Pennells L, Kaptoge S *et al.* Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. PLoS Med 2021; 18:e1003498. http://www.ncbi.nlm.nih.gov/pubmed/?term=33444330

5. Srisawasdi P, Rodcharoen P, Vanavanan S *et al.* Association of CETP Gene Variants with Atherogenic Dyslipidemia Among Thai Patients Treated with Statin. Pharmacogenomics and personalized medicine 2021; 14:1-13. http://www.ncbi.nlm.nih.gov/pubmed/?term=33447072
6. Schwartz GG, Steg PG, Bhatt DL *et al.* Clinical Efficacy and Safety of Alirocumab after Acute Coronary Syndrome According to Achieved Level of Low-Density Lipoprotein Cholesterol: A Propensity Score-Matched Analysis of the ODYSSEY OUTCOMES Trial. Circulation 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33438437
7. Ray KK. Changing the paradigm for post-MI cholesterol lowering from intensive statin monotherapy towards intensive lipid-lowering regimens and individualized care. Eur Heart J 2021; 42:253-256. http://www.ncbi.nlm.nih.gov/pubmed/?term=33454778
8. Omote K, Yokota I, Nagai T *et al.* High-Density Lipoprotein Cholesterol and Cardiovascular Events in Patients with Stable Coronary Artery Disease Treated with Statins: An Observation from the REAL-CAD Study. J Atheroscler Thromb 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33431716
9. Kuo FY, Huang WC, Tang PL *et al.* Impact of statin on long-term outcome among patients with end-stage renal disease with acute myocardial infarction (AMI): a nationwide case-control study. Postgraduate medical journal 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33452152
10. Kanukula R, Salam A, Rodgers A, Kamel B. Pharmacokinetics of Rosuvastatin: A Systematic Review of Randomised Controlled Trials in Healthy Adults. Clinical pharmacokinetics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33428168
11. Jung HH. Statin use and outcome risks according to predicted CVD risk in Korea: A retrospective cohort study. PLoS One 2021; 16:e0245609. http://www.ncbi.nlm.nih.gov/pubmed/?term=33450746
12. Jatem E, Lima J, Montoro B *et al.* Efficacy and Safety of PCSK9 Inhibitors in Hypercholesterolemia Associated With Refractory Nephrotic Syndrome. Kidney international reports 2021; 6:101-109. http://www.ncbi.nlm.nih.gov/pubmed/?term=33426389
13. Jarrah MI, Ababneh MJ, Tawalbeh LI *et al.* Statin eligibility based on the ACC/AHA guidelines among Middle Eastern patients with diabetes mellitus presenting with acute myocardial infarction. Annals of medicine and surgery (2012) 2021; 61:148-154. http://www.ncbi.nlm.nih.gov/pubmed/?term=33425348
14. Guo D, Meng Z, He F *et al.* Infection-Induced Rhabdomyolysis in an Elderly Patient on Stable Rosuvastatin Therapy: A Case Report and Review of the Literature. American journal of therapeutics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33443867

15. Ferro M, Marchioni M, Lucarelli G *et al.* Association of statin use and oncological outcomes in patients with first diagnosis of T1 high grade non-muscle invasive urothelial bladder cancer: results from a multicentre study. Minerva urologica e nefrologica = The Italian journal of urology and nephrology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33439571
16. Dopheide JF, Adam L, Wiedmer S *et al.* Improved lipid target level attainment in patients with peripheral artery disease. Current vascular pharmacology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33430734
17. Zhang Q, Wang L, Wang J. Clinical study of atorvastatin combined with milrinone in the treatment of chronic heart failure. Minerva medica 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33438377
18. Yang SY, Wang CC, Chen KD *et al.* Statin use is associated with a lower risk of recurrence after curative resection in BCLC stage 0-A hepatocellular carcinoma. BMC Cancer 2021; 21:70. http://www.ncbi.nlm.nih.gov/pubmed/?term=33446127
19. Vilar-Gomez E, Gawrieh S, Liang T *et al.* Interrogation of selected genes influencing serum LDL-Cholesterol levels in patients with well characterized NAFLD. J Clin Lipidol 2020. http://www.ncbi.nlm.nih.gov/pubmed/?term=33454241
20. Venkataraman P, Kawakami H, Huynh Q *et al.* Cost-Effectiveness of Coronary Artery Calcium Scoring in People With a Family History of Coronary Disease. JACC. Cardiovascular imaging 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33454262
21. Shi Y, Wahle E, Du Q *et al.* Associations between Statin/Omega3 Usage and MRI-Based Radiomics Signatures in Prostate Cancer. Diagnostics (Basel, Switzerland) 2021; 11. http://www.ncbi.nlm.nih.gov/pubmed/?term=33430275
22. Osborne J, Friedman K, Runeckles K *et al.* Comparison Between Currently Recommended Long-Term Medical Management of Coronary Artery Aneurysms After Kawasaki Disease and Actual Reported Management in the Last Two Decades. Pediatr Cardiol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33439285
23. Oni-Orisan A, Haldar T, Ranatunga DK *et al.* The impact of adjusting for baseline in pharmacogenomic genome-wide association studies of quantitative change. NPJ Genom Med 2020; 5:1. http://www.ncbi.nlm.nih.gov/pubmed/?term=33446660
24. Nelson AJ, Ardissino M, Haynes K *et al.* Gaps in Evidence-Based Therapy Use in Insured Patients in the United States With Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease. J Am Heart Assoc 2021; 10:e016835. http://www.ncbi.nlm.nih.gov/pubmed/?term=33432843
25. Navar AM, Wang TY, Li S *et al.* Patient-Perceived Versus Actual Risk of Cardiovascular Disease and Associated Willingness to Consider and Use Prevention Therapy. Circ Cardiovasc Qual Outcomes 2021; 14:e006548. http://www.ncbi.nlm.nih.gov/pubmed/?term=33435730

26. Mysore Y, Del Amo EM, Loukovaara S *et al.* Statins for the prevention of proliferative vitreoretinopathy: cellular responses in cultured cells and clinical statin concentrations in the vitreous. Scientific reports 2021; 11:980. http://www.ncbi.nlm.nih.gov/pubmed/?term=33441813
27. Lin CH, Chang CH, Tai CH *et al.* A Double-Blind, Randomized, Controlled Trial of Lovastatin in Early-Stage Parkinson's Disease. Movement disorders : official journal of the Movement Disorder Society 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33449392
28. Lim D, Landon-Cardinal O, Ellezam B *et al.* Statin-associated anti-HMGCR immune-mediated necrotizing myopathy with dermatomyositis-like features: A case report. SAGE Open Med Case Rep 2020; 8:2050313x20984120. http://www.ncbi.nlm.nih.gov/pubmed/?term=33447390
29. Kura B, Kalocayova B, Szeiffova Bacova B *et al.* The effect of selected drugs on the mitigation of myocardial injury caused by gamma radiation. Canadian journal of physiology and pharmacology 2021:1-9. http://www.ncbi.nlm.nih.gov/pubmed/?term=33438486
30. Kawada T. Statin use and Parkinson's disease incidence. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33439391
31. Inobhas A, Chansangpetch S, Manassakorn A *et al.* Effect of oral statin use on mitomycin-C augmented trabeculectomy outcomes. PLoS One 2021; 16:e0245429. http://www.ncbi.nlm.nih.gov/pubmed/?term=33449961
32. Drugs for Migraine. The Medical letter on drugs and therapeutics 2020; 62:153-160. http://www.ncbi.nlm.nih.gov/pubmed/?term=33434187

Basic Science publications

1. Ye S, Matthan NR, Lamon-Fava S *et al.* Colon Transcriptome is Modified by a Dietary Pattern/Atorvastatin Interaction in the Ossabaw Pig. The Journal of nutritional biochemistry 2021:108570. http://www.ncbi.nlm.nih.gov/pubmed/?term=33429036

2. Van Ly D, Wang D, Conway RM *et al.* Lipid-Producing Ciliochoroidal Melanoma with Expression of HMG-CoA Reductase. Ocul Oncol Pathol 2020; 6:416-421. http://www.ncbi.nlm.nih.gov/pubmed/?term=33447591
3. Thomas AB, Choudhary DC, Raje A, Nagrik SS. Pharmacokinetics and Pharmacodynamic Herb-Drug Interaction of Piperine with Atorvastatin in Rats. Journal of chromatographic science 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33434916
4. Teisseyre A, Uryga A, Michalak K. Statins as inhibitors of voltage-gated potassium channels Kv1.3 in cancer cells. J Mol Struct 2021; 1230:129905. http://www.ncbi.nlm.nih.gov/pubmed/?term=33437096
5. Taymouri S, Ahmadi Z, Mirian M, Tavakoli N. Simvastatin nanosuspensions prepared using a combination of pH-sensitive and timed-release approaches for potential treatment of colorectal cancer. Pharmaceutical development and technology 2021:1-14. http://www.ncbi.nlm.nih.gov/pubmed/?term=33430677
6. Shabanzadeh AP, Charish J, Tassew NG *et al.* Cholesterol synthesis inhibition promotes axonal regeneration in the injured central nervous system. Neurobiology of disease 2021:105259. http://www.ncbi.nlm.nih.gov/pubmed/?term=33434618
7. Rasmussen P, Yandrapalli S, Aronow W. Statin therapy for primary cardiovascular prevention in older adults over 75 years. Kardiol Pol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33427435
8. Marková I, Malínská H, Hüttl M *et al.* The combination of atorvastatin with silymarin enhances hypolipidemic, antioxidant and anti-inflammatory effects in a rat model of metabolic syndrome. Physiological research / Academia Scientiarum Bohemoslovaca 2021; 70. http://www.ncbi.nlm.nih.gov/pubmed/?term=33453720
9. Kumar GA, Chattopadhyay A. Membrane cholesterol regulates endocytosis and trafficking of the serotonin(1A) receptor: Insights from acute cholesterol depletion. Biochimica et biophysica acta. Molecular and cell biology of lipids 2021; 1866:158882. http://www.ncbi.nlm.nih.gov/pubmed/?term=33429076
10. Koike A, Tsujinaka K, Fujimori K. Statins attenuate antiviral IFN-β and ISG expression via inhibition of IRF3 and JAK/STAT signaling in poly(I:C)-treated hyperlipidemic mice and macrophages. The FEBS journal 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33452755
11. Chen A, Chen Z, Zhou Y *et al.* Rosuvastatin protects against coronary microembolization-induced cardiac injury via inhibiting NLRP3 inflammasome activation. Cell death & disease 2021; 12:78. http://www.ncbi.nlm.nih.gov/pubmed/?term=33436548
12. Zhang J, Wang J, Qiao F *et al.* Polymeric non-spherical coarse microparticles fabricated by double emulsion-solvent evaporation for simvastatin delivery.

Colloids and surfaces. B, Biointerfaces 2021; 199:111560. http://www.ncbi.nlm.nih.gov/pubmed/?term=33429284

13. Faris TM, Harisa GI, Alanazi FK *et al.* Developed simvastatin chitosan nanoparticles co-crosslinked with tripolyphosphate and chondroitin sulfate for ASGPR-mediated targeted HCC delivery with enhanced oral bioavailability. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 2020; 28:1851-1867. http://www.ncbi.nlm.nih.gov/pubmed/?term=33424274
14. Kuo TT, Huang YB, Hsieh CJ. Consumption and market share of cholesterol-lowering drugs in high-risk patients before and after the release of the 2013 ACC/AHA cholesterol guidelines: a retrospective observational study. BMJ Open 2020; 10:e036769. http://www.ncbi.nlm.nih.gov/pubmed/?term=33444173

This activity is supported by an educational grant from Pfizer.