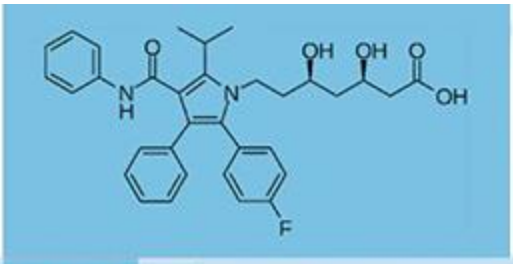
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 14, 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

Managing pediatric FH patients

The autosomal dominant genetic background of Familial Hypercholesterolemia (FH) warrants that 50% of the children from an FH parent are affected. Specialized pediatric care is needed for optimal management and to increase our understanding of effective cholesterol treatment, safety, and long-term outcomes. This review shares data collected in a dedicated Australian paediatric multidisciplinary lipid clinic between 1999 and 2017. Overall, 108 patients were managed, 53 boys and 55 girls. The LDL-c levels in the majority of the children were>75th percentile before treatment was initiated. The children who initiated statin therapy achieved a mean LDL-c of 2.4 (1.4-2.7) mmol/L and 1.9 (0.8-2.8) mmol/L for boys and girls. Only four children had premature ASCVD manifestations; this correlated with more severe expression of FH. Five patients reported side effects that needed medication adjustment. Statins were well tolerated by most of the patients. The major reasons that eligible patients did not start statins were parental refusal and loss to follow-up (75%). The findings in the relatively small study confirmed the efficacy and safety of statins in FH children; however, current treatment recommendations are not easily achieved. To improve family engagement, greater awareness and coordinated services are warranted.

Yeung J, Chisholm K, Spinks C, Srinivasan S. Familial hypercholesterolaemia: Experience of a tertiary paediatric lipid clinic. Journal of paediatrics and child health 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33830584

Suboptimal lipid management in Canadian hospitalized ACS patients

The recently updated lipid management guidelines aim for lower LDL-c targets in very high-risk patients. Data collected in a single. Alberta, Canada hospital was queried to determine lipid management in 27 979 hospital admitted ACS patients. Lipid testing was not executed during their hospital stay or 90 days post-discharge in 375 (13.4%) of the patients. Untested patients were more likely to be older, female, from rural areas, have more comorbidities, already using cardioprotective therapies, unstable angina, unstable angina, and less likely to have invasive interventions. Guideline recommended lipid levels were not reached by 18 767/ 24 299 (77.5%) patients. Additional lipid testing <1 year after discharge was not done in 7284 (38.8%) of the patients. Those that did get an in-hospital lipid panel test were more likely to start or escalate dosing of lipid-lowering drugs; OR: 2.13 (1.97-2.30). PCSK9ab was indicated in 9592 (39.6%) of the evaluated patients. The authors concluded that almost 80% of hospital admitted Canadian ACS patients did not meet guideline-recommended lipid thresholds. More than one-third would be eligible for PCSK9 ab.

Sarak B, Savu A, Kaul P *et al.* Lipid Testing, Lipid-Modifying Therapy, and PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Eligibility in 27 979 Patients With Incident Acute Coronary Syndrome. Circ Cardiovasc Qual Outcomes 2021; 14:e006646. http://www.ncbi.nlm.nih.gov/pubmed/?term=33813856

Early and persistent statin use associated with lower CVD risk in Korean hypercholesterolemic patients

Adherence to statin therapy remains a challenge and requires motivation and trust of patients eligible for LDL-c reducing therapy. The impact of non-adherence was evaluated in the Korean National Health Insurance Service – Health Screening Cohort (NHIS-HEALS). This was a retrospective cohort study in 11 320 primary prevention participants, aged 40-79 years with an elevated LDL-cholesterol (>240 mg/dl) and who started with statin therapy < 24 months after the national health screening (2004-2012). Primary outcomes were CVD (hospital admission or death due to ischaemic heart disease, acute myocardial infarction, revascularization, or stroke). The HRs of CVD according to statin adherence was calculated according to the SCORE (Systematic Coronary Risk Evaluation). Patients who started statins late had significantly increased CVD risk compared to patients who started statins late; HR: 1.24 (1.02-2.51). Patients who started statin but discontinued taking them had a significantly higher risk than those who persisted in taking their medication; HR was 1.71 (1.0-2.67). Those that restarted statins were observed to have a

slightly mitigated risk; HR 1.34 (0.79 – 2.30). Based on these findings, the authors concluded that early statin initiation in Korean primary prevention patients with elevated LDL- was associated with a significantly lower CVD risk. Patients that stopped taking statins compared with those that continued statins were associated with an increased CVD risk. Ryou IS, Chang J, Son JS *et al.* Association between CVDs and initiation and adherence to statin treatment in patients with newly diagnosed hypercholesterolaemia: a retrospective cohort study. BMJ Open 2021; 11:e045375. http://www.ncbi.nlm.nih.gov/pubmed/?term=33827840

HIJ-PROPER Study: benefit of ezetimibe add-on was observed when baseline LDL-c >131 mg/dl

The HIJPROPER study was a multicentre, prospective, randomized, open-label, blinded endpoint trial comparing intensive lipid-lowering treatment, aiming to reach an LDL-c < 70 mg/dL (pitavastatin + ezetimibe) against standard lipid-lowering strategy, with an LDL-c target of 90-100 mg/DLL (pitavastatin monotherapy), in 1739 Japanese ACS patients. In this sub-analysis, 1420 statin naïve patients were queried for baseline LDL-c levels. Those with LDL-c >130 mg/dl were compared to patients with LDL-c < 130 mg/dl. Over a median follow-up time of 3.2 years, LDL-c was reduced by -34% and -49.8% in those taking pitavastatin monotherapy vs. pitavastatin + ezetimibe patients with an LDL-c < 130 mg/dl. For the participants with an LDL-c >130 mg/dl, the reductions of LDL-c were -42.9% and -56.4%, respectively (P<0.0001). The Kaplan-Meier analysis for the primary endpoint, a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and ischemia-driven coronary revascularization, showed no significant differences between the two treatment arms for those that started with an LDL-c < 130 mg/dL. In patients with a high baseline LDL-c of >130 mg/dl, the use of pitavastatin + ezetimibe was superior to pitavastatin monotherapy, HR:0.72 (0.56-0.91; P=0.007, P-value for interaction = 0.012). The authors concluded that only Japanese ACS patients with an LDL-c >130 mg/dL benefitted from adding ezetimibe to pitavastatin and reaching an LDL-c target < 70 mg/dL. Im J, Kawada-Watanabe E, Yamaguchi J *et al.* Baseline low-density lipoprotein cholesterol predicts the benefit of adding ezetimibe on statin in statin-naïve acute coronary syndrome.Scientific reports 2021; 11:7480.
http://www.ncbi.nlm.nih.gov/pubmed/?term=33820931

Tailored lipid lowering treatment for post MI patients is needed to improve outcomes

Guideline recommended LDL-c targets are frequently not reached. In this retrospective analysis of the German health claims database (2010 -2015), the impact of treatment intensity and adherence were evaluated. Post MI patients who started lipid-lowering therapy (LLT) between 2011 and 2013 were included (N=14 944). The follow-up period started approximately one year

after the second LLT prescription. Treatment intensity was based on expected LDL-c reduction; adherence was calculated using a proportion of days covered. Uniting adherence with intensity, a combined score was created. Based on Cox proportional hazards model, corrections for age, sex, Charlson Comorbidity Index, and CV risk factors at baseline were added. For each 10% increase in treatment intensity, adherence or adherence adjusted intensity the MACE risk was reduced by -17% (HR: 0.83 [0.79-0.87]), -5% (HR: 0.95 [0.94-0.97]), and -14% (HR:0.86 [0.83-0.90]), respectively. Based on these findings, the authors suggested that future strategies to reduced CVD risk should be tailored to post MI patient profiles to improve outcomes.
Ahrens I, Khachatryan A, Monga B *et al.* Association of Treatment Intensity and Adherence to Lipid-Lowering Therapy with Major Adverse Cardiovascular Events Among Post-MI Patients in Germany. Adv Ther 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33830461

Relevant publications

1. Tomlinson B, Patil NG, Fok M, Lam CWK. Managing dyslipidemia in patients with type 2 diabetes. Expert Opin Pharmacother 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33823719
2. Sánchez-Hernández RM, González-Lleó AM, Tugores A *et al.* Familial hypercholesterolemia in Gran Canaria: Founder mutation effect and high frequency of diabetes. Clin Investig Arterioscler 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33814196
3. Razavi AC, Kelly TN, Budoff MJ *et al.* Atherosclerotic cardiovascular disease events among statin eligible individuals with and without long-term healthy arterial aging.Atherosclerosis 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33824003
4. Nemati M, Srai M, Rudrangi R. Statin-Induced Autoimmune Myopathy. Cureus 2021; 13:e13576. http://www.ncbi.nlm.nih.gov/pubmed/?term=33815984
5. Mehta A, Rigdon J, Tattersall MC *et al.* Association of Carotid Artery Plaque With Cardiovascular Events and Incident Coronary Artery Calcium in Individuals With Absent Coronary Calcification: The MESA. Circulation. Cardiovascular imaging 2021; 14:e011701. http://www.ncbi.nlm.nih.gov/pubmed/?term=33827231
6. Mashayekhi-Sardoo H, Atkin SL, Montecucco F, Sahebkar A. Potential Alteration of Statin-Related Pharmacological Features in Diabetes Mellitus. BioMed research international 2021; 2021:6698743. http://www.ncbi.nlm.nih.gov/pubmed/?term=33834073

7. Lim LS. In older adults without CVD, treating 100 persons with statins for 2.5 y prevents 1 MACE. Annals of internal medicine 2021; 174:Jc39. http://www.ncbi.nlm.nih.gov/pubmed/?term=33819067
8. Li X, Gu D, Wang X *et al.* Trends of Coronary Artery Bypass Grafting Performance in a Cohort of Hospitals in China Between 2013 and 2018. Circ Cardiovasc Qual Outcomes 2021; 14:e007025. http://www.ncbi.nlm.nih.gov/pubmed/?term=33813854
9. Hariyanto TI, Kurniawan A. Statin and outcomes of coronavirus disease 2019 (COVID-19): A systematic review, meta-analysis, and meta-regression. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33838992
10. Ghayda RA, Lee JY, Yang JW *et al.* The effect of statins on all-cause and cardiovascular mortality in patients with non-dialysis chronic kidney disease, patients on dialysis, and kidney transplanted recipients: an umbrella review of meta-analyses.Eur Rev Med Pharmacol Sci 2021; 25:2696-2710. http://www.ncbi.nlm.nih.gov/pubmed/?term=33829456
11. Ghayda RA, Han CH, Lee KH *et al.* The effect of statins on mortality among patients with infection: umbrella review of meta-analyses. Eur Rev Med Pharmacol Sci 2021; 25:2685-2695. http://www.ncbi.nlm.nih.gov/pubmed/?term=33829455
12. Chen LQ, Weber J, Christian T *et al.* Long-term all-cause mortality among asymptomatic individuals with 80th percentile of coronary calcium score based on age and gender in the St. Francis Heart Study. Coronary artery disease 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33826539
13. Beshir SA, Hussain N, Elnor AA, Said ASA. Umbrella Review on Non-Statin Lipid-Lowering Therapy. Journal of cardiovascular pharmacology and therapeutics 2021:10742484211002943. http://www.ncbi.nlm.nih.gov/pubmed/?term=33836639
14. Baral N, Gautam S, Yadav SA *et al.* Pharmacotherapies in Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cureus 2021; 13:e13604. http://www.ncbi.nlm.nih.gov/pubmed/?term=33816003
15. Ballantyne CM, Bays H, Catapano AL *et al.* Role of Bempedoic Acid in Clinical Practice. Cardiovasc Drugs Ther 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33818688
16. Xu I, Taub PR. Baseline testosterone level may modulate statin efficacy. Coronary artery disease 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33826543
17. Wendt FR, Koller D, Pathak GA *et al.* Biobank Scale Pharmacogenomics Informs the Genetic Underpinnings of Simvastatin Use. Clinical pharmacology and therapeutics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33837531

18. Tanner M. In at-risk patients without CVD, polypill plus aspirin reduced a composite of major CV events at 4.6 y. Annals of internal medicine 2021; 174:Jc41. http://www.ncbi.nlm.nih.gov/pubmed/?term=33819061
19. Sugimoto H, Takeuchi M, Taniguchi Y, Sato J. Sudden Cardiac Arrest in a Patient With Sarcoidosis and Familial Hypercholesterolemia. Cureus 2021; 13:e13649. http://www.ncbi.nlm.nih.gov/pubmed/?term=33824802
20. Samieirad S, Labafchi A, Famili K, Hashemzadeh H. Medication-Related Osteonecrosis of the Jaw (MRONJ) due to Simvastatin: An Unusual Case Report.World J Plast Surg 2021; 10:132-135. http://www.ncbi.nlm.nih.gov/pubmed/?term=33833966
21. Salvador P, Oliveira P, Costa T *et al.* Clinical Features and Prognostic Factors of 245 Portuguese Patients Hospitalized With COVID-19. Cureus 2021; 13:e13687. http://www.ncbi.nlm.nih.gov/pubmed/?term=33833912
22. Krysiak R, Kowalcze K, Okopień B. The impact of hypotestosteronemia on cardiometabolic effects of atorvastatin in men with hypercholesterolemia: a pilot study. Coronary artery disease 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33826536
23. Khandelwal Gilman KA, Han S, Won YW, Putnam CW. Complex interactions of lovastatin with 10 chemotherapeutic drugs: a rigorous evaluation of synergism and antagonism. BMC Cancer 2021; 21:356. http://www.ncbi.nlm.nih.gov/pubmed/?term=33823841
24. Gupta A, Lin M, McAlister FA, Ye C. Prior adherence to statins is a predictor of subsequent adherence and persistence to oral, but not parenteral, osteoporosis medications. J Bone Miner Metab 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33821305
25. Derington CG, Colantonio LD, Herrick JS *et al.* Factors Associated With PCSK9 Inhibitor Initiation Among US Veterans. J Am Heart Assoc 2021; 10:e019254. http://www.ncbi.nlm.nih.gov/pubmed/?term=33821686
26. Chen Z, Chen L, Sun B *et al.* LDLR inhibition promotes hepatocellular carcinoma proliferation and metastasis by elevating intracellular cholesterol synthesis through the MEK/ERK signaling pathway. Molecular metabolism 2021; 51:101230. http://www.ncbi.nlm.nih.gov/pubmed/?term=33823318
27. Budenholzer B. In statin-treated patients at high CV risk, adding omega-3 fatty acidsvs. corn oil to usual care did not reduce MACE. Annals of internal medicine 2021; 174:Jc40. http://www.ncbi.nlm.nih.gov/pubmed/?term=33819062
28. Beuret H, Hausler N, Nanchen D*et al.*Comparison of Swiss and European risk algorithms for cardiovascular prevention in Switzerland.Eur J Prev Cardiol2021; 28:204-210.http://www.ncbi.nlm.nih.gov/pubmed/?term=33838036

Basic Science publications

1. **Wang JR, Wang MZ, Zheng SH, Li ZY. Neural Remodeling of the Left Atrium in Rats by Rosuvastatin Following Acute Myocardial Infarction. Open Life Sci 2019; 14:603-610.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33817198
2. **Shakeel F, Alshehri S, Ibrahim MA *et al.* Solubilization and thermodynamic properties of simvastatin in various micellar solutions of different non-ionic surfactants: Computational modeling and solubilization capacity. PLoS One 2021; 16:e0249485.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33831070
3. **Murali VP, Guerra FD, Ghadri N *et al.* Simvastatin loaded chitosan guided bone regeneration membranes stimulate bone healing. Journal of periodontal research 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33830521
4. **Malviya R, Raj S, Fuloria S *et al.* Evaluation of Antitumor Efficacy of Chitosan-Tamarind Gum Polysaccharide Polyelectrolyte Complex Stabilized Nanoparticles of Simvastatin. International journal of nanomedicine 2021; 16:2533-2553.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33824590
5. **Huang X, Zheng C, Wang W *et al.* The Effect and Possible Mechanism of Intradiscal Injection of Simvastatin in the Treatment of Discogenic Pain in Rats. Frontiers in neuroscience 2021; 15:642436.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33815046
6. **Bagheri F, Darakhshan S, Mazloomi S*et al.*Dual loading of Nigella sativa oil-atorvastatin in chitosan-carboxymethyl cellulose nanogel as a transdermal delivery system.Drug development and industrial pharmacy2021:1-10.**http://www.ncbi.nlm.nih.gov/pubmed/?term=33819116

This activity is supported by an educational grant from Viatris.