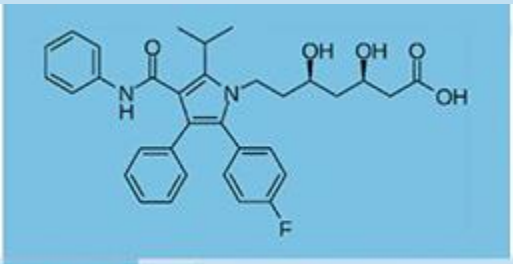
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 20, 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

Mortality risk modifiers in ACS patients that present with cardiogenic shock and/or heart failure

Cardiogenic shock (CS) and heart failure (HF) prompting hospital admission carry a substantial short-term mortality risk. Less clear are the long-term mortality risks in patients that survived 30-days after the acute event. In this Japanese multi-center prospective register (J-MINUET), 3263 patients eligible for this sub-study. Patients were divided into 3 groups: CS-/HF- (N=2467, 75.6%), CS-/HF+ (N=479, 14.7%) and CS+ (N=317, 9.7%). The 30-day mortality in CS+ patients (32.8%) was significantly greater compared to CS- patients. Risk modifiers with significant impact on 30-day mortality were: statin use prior to admission, OR: 0.32 (0.14-0.66, p=0.002); impaired renal function, OR: 8.72 (2.81-38.67, P<0.0001) and thrombolysis in infarction flow grade, OR: 0.42 (0.18-0.99, p=0.046). Mortality beyond 30-days were comparable in the CS+ and CS-/HF+ groups, HR 1.03 (0.63-1.68, P=0.09). Patients in whom CS and HF were absent did much better than CS+ patients, HR:0.55 (0.32-0.59, P<0.0001). Based on these findings, CS+ patients are not only at greater

risk to die within 30-day after their index event, but those that survive also have a greater mortality risk compared to patients that did not present with CS+. Of note, CS-/HF+ patients should be intensively monitored after hospital discharge to prevent life-threatening complications.

Wada H, Ogita M, Suwa S *et al.* Long-Term Clinical Impact of Cardiogenic Shock and Heart Failure on Admission for Acute Myocardial Infarction. Int Heart J 2021; 62:520-527.
http://www.ncbi.nlm.nih.gov/pubmed/?term=33994511

Pharmacists actively involved in patient education on statin therapy

Improving statin initiation and adherence remains one of the most significant challenges for healthcare providers managing patients at risk for ASCVD complications. This study uses online questionnaires before and post face-to-face pharmacists centered education regarding the benefits and harms of statin use. Participants were aged 40-70, had received at least two fills of diabetes medication in the last year, and lacked statin prescriptions. A total of 10 patients completed both the surveys and educational interventions. Prior to the intervention, none of the participants could identify statin benefits other than cholesterol-lowering. After the education activity, 80% were able to identify at least one additional benefit from statin therapy. Starting statins was contemplated by 30% of the participating patients; this increased to 80% after the educational activity. None of the participants felt they needed statin therapy, while 40% stated that they were candidates for statin therapy after the intervention. The outcome of this, albeit relatively small, study shows that patients are willing to receive education from pharmacists about their medication and are willing to do so. Lack of knowledge and understanding on statins, including their benefits beyond lowering cholesterol, are clearly insufficiently addressed; providing educational support by pharmacists is an attractive option that deserves further exploration.

WC, G KG, B ME. Assessment of Patient Education about Statin Therapy on Quality Measures and Knowledge in an Independent Community Pharmacy. Innov Pharm 2019; 10.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34007557

Statins are absent in 25% of patients using non-statin LLT despite having or being at risk for ASCVD

The PALM registry collects data on lipid-lowering therapy (LLT) of ASCVD patients treated in 125 US clinics (starting in 2015). Of the 7720 patients in the registry, 1930 (25.0%) received a non-statin LLT; Fish oil (N=1249), fibrates (N=447), ezetimibe (N=329) and niacin (N=196). Overall, 73.3% of patients used a statin combined with non-statin LLT, 45.4% were using a lower dose as recommended by current guidelines. Compared to patients who used statin monotherapy, those who used combination LLT were more likely to be male, white, and perceived themselves as having a higher ASCVD risk (38.5% s 34.9%, p=0.047). Patients

using only non-statin LLT were less likely to see themselves as having a high ASCVD risk, 27.4%. Almost three-quarters of the patients receiving non-statin LLT reported never having received a statin, despite 30.8% of these patients qualifying for secondary prevention preventive therapies. Of those patients who used statin before, 59.3% were willing to try statin therapy again. The authors concluded that non-statin LLT is used by one in four US patients in the PALM registry with or at risk for ASCVD. This contrasts with guideline recommendations that emphasize the use of high intensity, high dose statins as the first step after lifestyle improvement, emphasizing the need to establish statins as a first-line therapeutic strategy in patients with or at risk for ASCVD.

Lowenstern A, Li S, Navar AM *et al.* Patient perceptions and use of non-statin lipid lowering therapy among patients with or at risk for atherosclerotic cardiovascular disease: Insights from the PALM registry. Clin Cardiol 2021.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34008247

Cholesterol burden in FH patients and impact on MACE

The cholesterol burden comprises a combination of plasma LDL-c levels and lifelong exposure. Familial Hypercholesterolemia (FH) patients are characterized by a very high LDL-c from birth onwards. In this retrospective analysis of 1 050 Japanese FH patients, the impact of cholesterol burden on MACE (including death from any cause and ASCVD related hospitalization were evaluated. The cumulative cholesterol-year-score was calculated as LDL-Cmax (age at diagnosis/statin initiation) + LDL-C at inclusion (age at inclusion − age at diagnosis/statin initiation). The median follow-up period for MACE evaluation was 12.3 (9.1–17.5) years. The cholesterol-year-score showed a robust and significant relationship with MACE, HR:1.37 (1.07-1.53, p=0.0034)/1000 mg/dL-year. This relationship was independent of age, CV risk factors, and LDL-c. The use of the cholesterol-year-score significantly improved the C-statistics compared to other risk factors for ASCVD events, C-index: 0.901 vs. 0.889 (P=0.00473). The impact of cumulative cholesterol exposure on ASCVD events underlines the need for early intervention to prevent premature MACE in (Japanese) FH patients.

Tada H, Okada H, Nohara A *et al.* Effect of Cumulative Exposure to Low-Density Lipoprotein-Cholesterol on Cardiovascular Events in Patients With Familial Hypercholesterolemia. Circulation journal : official journal of the Japanese Circulation Society 2021.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34011825

Lowering statin intensity post stroke is associated with increased mortality risk

The Importance of using high intensity – high dose statins is reflected in this retrospective observational analysis in an extensive US veterans registry of post-stroke/TIA patients.

Included were 9 380 patients hospitalized for a stroke or TIA in 2011 in any 134 VA hospitals. In total, 3194 patients (34.1%) were discharged without a statin. De-intensification of the statin was observed in 1 312 patients (14%), and 1 925 patients (20.5%) did not use statin before hospital admission and were not started on statins at discharge. Compared with patients that used appropriate statin type and dosage at admission and discharge, those that experienced statin de-intensification and patients that did not use statins when admitted and discharged had a higher mortality risk; OR:1.26 (1.02-1.57) and OR:1.59 (1.30-1.93), respectively. The authors suggested that lowering statin dosage immediately after stroke has no benefit and the potential for harm. Therefore, healthcare quality care systems should assess statin prescription at discharge and monitor for statin potency and dose as well.

Dearborn-Tomazos JL, Hu X, Bravata DM *et al.* Deintensification or No Statin Treatment Is Associated With Higher Mortality in Patients With Ischemic Stroke or Transient Ischemic Attack. Stroke 2021:Strokeaha120030089. http://www.ncbi.nlm.nih.gov/pubmed/?term=34015937

Relevant publications

1. **Kuyama N, Kataoka Y, Takegami M *et al.* Circulating Mature PCSK9 Level Predicts Diminished Response to Statin Therapy. J Am Heart Assoc 2021; 10:e019525.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33998287
2. **Xu T, Wang Y, Yuan J, Chen Y. The Effect of Statin Treatment on Outcomes of Cardioembolic Stroke: A Systematic Review and Meta-Analysis of Real-World Studies. CNS drugs 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34019256
3. **Wei H, Xin X, Zhang J *et al.* Effects of coenzyme Q10 supplementation on statin-induced myopathy: a meta-analysis of randomized controlled trials. Irish journal of medical science 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=33999383
4. **Tsu LV, Carroll K, Kindler K, Early N. Pharmacological Management of Hyperlipidemia in Older individuals. The Senior care pharmacist 2021; 36:284-303.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34016226
5. **Tan H, Liu L, Zheng Q *et al.* Effects of Combined Lipid-Lowering Therapy on Low-Density Lipoprotein Cholesterol Variability and Cardiovascular Adverse Events in Patients with Acute Coronary Syndrome. Adv Ther 2021; 38:3389-3398.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34018147
6. **Steffens D, Bramlage P, Müller J *et al.* Intensified lipid-lowering treatment with alirocumab in patients with coronary heart disease. Open heart 2021; 8.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34001653

7. Reeskamp LF, Nurmohamed NS, Bom MJ *et al.* Marked plaque regression in homozygous familial hypercholesterolemia. Atherosclerosis 2021; 327:13-17. http://www.ncbi.nlm.nih.gov/pubmed/?term=34004483
8. Polychronopoulos G, Tzavelas M, Tziomalos K. Heterozygous familial hypercholesterolemia: prevalence and control rates. Expert review of endocrinology & metabolism 2021:1-5. http://www.ncbi.nlm.nih.gov/pubmed/?term=33993819
9. Pek SLT, Yap F, Sreedharan AV *et al.* Persistent hypercholesterolemia in child with homozygous autosomal recessive hypercholesterolemia: A decade of lipid management. J Clin Lipidol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33994332
10. Ortland I, Mirjalili M, Kullak-Ublick GA, Peymani P. Drug-induced liver injury in Switzerland: an analysis of drug-related hepatic disorders in the WHO pharmacovigilance database VigiBase™ from 2010 to 2020. Swiss Med Wkly 2021; 151:w20503. http://www.ncbi.nlm.nih.gov/pubmed/?term=34000058
11. Liu K, Wilkins JT, Colangelo LA, Lloyd-Jones DM. Does Lowering Low-Density Lipoprotein Cholesterol With Statin Restore Low Risk in Middle-Aged Adults? Analysis of the Observational MESA Study. J Am Heart Assoc 2021; 10:e019695. http://www.ncbi.nlm.nih.gov/pubmed/?term=33998284
12. Ikeda S, Shinohara K, Enzan N *et al.* Effectiveness of statin intensive therapy in type 2 diabetes mellitus with high visit-to-visit blood pressure variability. J Hypertens 2021; 39:1435-1443. http://www.ncbi.nlm.nih.gov/pubmed/?term=34001809
13. Grundy SM, Stone NJ. Coronary Artery Calcium: Where Do We Stand after over three Decades? Am J Med 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34019857
14. Golub I, Lakshmanan S, Dahal S, Budoff MJ. Utilizing coronary artery calcium to guide statin use. Atherosclerosis 2021; 326:17-24. http://www.ncbi.nlm.nih.gov/pubmed/?term=34000565
15. Feger S, Elzenbeck L, Rieckmann N *et al.* Effect of Computed Tomography Versus Invasive Coronary Angiography on Statin Adherence: A Randomized Controlled Trial. JACC. Cardiovascular imaging 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34023253
16. Ebert T, Qureshi AR, Lamina C *et al.* Time-dependent lipid profile inversely associates with mortality in hemodialysis patients - independent of inflammation/malnutrition. Journal of internal medicine 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33998741
17. Cao J, Remaley AT, Guan W *et al.* Performance of novel low-density lipoprotein-cholesterol calculation methods in predicting clinical and subclinical atherosclerotic cardiovascular disease risk: The Multi-Ethnic Study of

Atherosclerosis. Atherosclerosis 2021; 327:1-4. http://www.ncbi.nlm.nih.gov/pubmed/?term=34004482

18. Anagnostis P, Papanikolaou D, Ioannidou PG *et al.* The effect of statins on semen parameters in patients with hypercholesterolemia: A systematic review. Andrology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=33998174
19. Agarwala A, Quispe R, Goldberg AC, Michos ED. Bempedoic Acid for Heterozygous Familial Hypercholesterolemia: From Bench to Bedside. Drug design, development and therapy 2021; 15:1955-1963. http://www.ncbi.nlm.nih.gov/pubmed/?term=34007155
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21. Yu Q, Zheng H, Zhang Y. Inducible degrader of LDLR: A potential novel therapeutic target and emerging treatment for hyperlipidemia. Vascul Pharmacol 2021:106878. http://www.ncbi.nlm.nih.gov/pubmed/?term=34015522
22. Selvaraj S, Claggett BL, Packer M *et al.* Effects of Sacubitril/Valsartan on Serum Lipids in Heart Failure with Preserved Ejection Fraction. J Am Heart Assoc 2021:e022069. http://www.ncbi.nlm.nih.gov/pubmed/?term=33998278
23. Purkiss SF, Keegel T, Vally H, Wollersheim D. Estimates of age specific death rates in people with diabetes and associated multimorbidity using Australian administrative pharmaceutical data. Int J Popul Data Sci 2021; 6:1414. http://www.ncbi.nlm.nih.gov/pubmed/?term=34007903
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25. Lindström I, Protto S, Khan N *et al.* STATIN USE, DEVELOPMENT OF SARCOPENIA AND LONG-TERM SURVIVAL AFTER ENDOVASCULAR AORTIC REPAIR. Journal of vascular surgery 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34019985
26. Khirfan G, Li M, Wang X *et al.* Abnormal levels of apolipoprotein A-I in chronic thromboembolic pulmonary hypertension. Pulmonary circulation 2021; 11:20458940211010371. http://www.ncbi.nlm.nih.gov/pubmed/?term=33996028
27. Jeong IG, Lim B, Yun SC *et al.* Adjuvant Low-dose Statin Use after Radical Prostatectomy: The PRO-STAT Randomized Clinical Trial. Clin Cancer Res 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34011557
28. Hou Y, Shao K, Yan Y *et al.* Anti-HMGCR myopathy overlaps with dermatomyositis-like rash: a distinct subtype of idiopathic inflammatory myopathy. Journal of neurology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34021410
29. Hosio M, Urpilainen E, Hautakoski A *et al.* Association of antidiabetic medication and statins with survival from ductal and lobular breast carcinoma in women with

type 2 diabetes. Scientific reports 2021; 11:10445. http://www.ncbi.nlm.nih.gov/pubmed/?term=34001921

30. Collins D, Inglin L, Laatikainen T *et al.* Evaluation and pilot implementation of essential interventions for the management of hypertension and prevention of cardiovascular diseases in primary health care in the Republic of Tajikistan. BMC Health Serv Res 2021; 21:472. http://www.ncbi.nlm.nih.gov/pubmed/?term=34006266
31. Cenarro A, Bea AM, Gracia-Rubio I, Civeira F. Dysbetalipoproteinemia and other lipid abnormalities related to apo E. Clin Investig Arterioscler 2021; 33 Suppl 2:50-55. http://www.ncbi.nlm.nih.gov/pubmed/?term=34006354
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33. Anno T, Yamatsuji T, Tomoda K *et al.* Case Report: Various Abnormalities in Lipid and Glucose Metabolism Induced by Capecitabine. Frontiers in oncology 2021; 11:664475. http://www.ncbi.nlm.nih.gov/pubmed/?term=34017685

Basic Science publications

1. Zhang Y, Ma L, Lu E, Huang W. Atorvastatin Upregulates microRNA-186 and Inhibits the TLR4-Mediated MAPKs/NF-κB Pathway to Relieve Steroid-Induced Avascular Necrosis of the Femoral Head. Frontiers in pharmacology 2021; 12:583975. http://www.ncbi.nlm.nih.gov/pubmed/?term=33995003
2. Zhang KL, Zhu WW, Wang SH *et al.* Organ-specific cholesterol metabolic aberration fuels liver metastasis of colorectal cancer. Theranostics 2021; 11:6560-6572. http://www.ncbi.nlm.nih.gov/pubmed/?term=33995676
3. Yu D, Huang C, Jiang C, Zhu H. Features of a simvastatin-loaded multi-layered co-electrospun barrier membrane for guided bone regeneration. Experimental and therapeutic medicine 2021; 22:713. http://www.ncbi.nlm.nih.gov/pubmed/?term=34007322
4. Bravo M, Raurell I, Barberá A *et al.* Synergic effect of atorvastatin and ambrisentan on sinusoidal and hemodynamic alterations in a rat model of NASH. Disease models & mechanisms 2021; 14. http://www.ncbi.nlm.nih.gov/pubmed/?term=34014280

5. **Barreto GE, Gonzalez J, Reiner Ž *et al.* In silico interactions of statins with cell death-inducing DNA fragmentation factor-like effector A (CIDEA). Chemico-biological interactions 2021:109528.**
http://www.ncbi.nlm.nih.gov/pubmed/?term=34022192

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