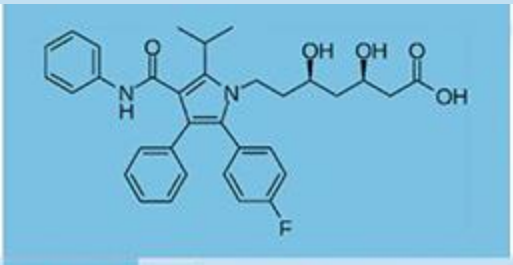
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 23, 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

TAVI and statins – observed benefits, even in octogenarians

This retrospective observational analysis was based on data collected in a Japanese multicentre registry. The Optimized CathEter vAlvular iNtervention (OCEAN-TAVI) registry included 2588 aortic stenosis (AS) patients treated with TAVI. Primary and secondary outcomes were all-cause and CV mortality. The median age was 84.4(±5.2) years, and 69.3% were women. Statin using patients (N=9360) were propensity score-matched with patients that did not take statins using a 1:1 ratio. After a median follow-up period of 660 days statin use at admission was associated with a significant reduction in total mortality, adjusted HR (aHR) 0.76 (0.58 to 0.99, p=0.04) and cardiovascular mortality, aHR: 0.64 9(0.42 to 0.97, p=0.04). For the subgroup of octogenarian's superior outcomes for total mortality was

observed as well, aHR 0.87 (0.75 to 0.99, p=0.04); Those classified as nonagenarians showed a less favorable impact of statin use, aHR: 0.84 (0.62 to 1.13, p=0.25). Patients with a history of ASCVD and not using statins at admission had a significantly increased risk of dying, aHR: 1.33 (1.12 to 1.57,p<0.01), compared to patients without CAD and using statins. These findings showed superior survival in AS patients that used statins, even in the very elderly. To confirm these observational findings, additional randomized studies are warranted.

Yashima F, Hara M, Inohara T *et al.* Statin therapy for patients with aortic stenosis who underwent transcatheter aortic valve implantation: a report from a Japanese multicentre registry. BMJ Open 2021; 11:e044319. http://www.ncbi.nlm.nih.gov/pubmed/?term=34117043

DM2 risk related to lower LDL-c associated with genetic HMG-CoA reductase variants

Mendelian randomizations studies are used to observe long-term benefits or harms of genetic markers associated with phenotype expression of risk or risk markers. The HMG-CoA reductase gene was used to explore the effects of HMG-CoA reductase inhibitor, the primary target of statins, and 22 non-cardiovascular phenotypes. For this analysis, the BioVU biobank and eMERGE (a research consortium that conducts genetic research using electronic medical records) as a control to replicate findings in the BioVu cohort were used. The 53 385 participants were unrelated adults with European ancestry. Only one significant association between HMG-CoA genetic risk score and non-CV phenotype was discovered, diabetes type 2. For each 10-mg/dl decrease of LDL-c the risk of developing DM2 increased 9%, OR: 1.09 (1.04-1.15; $P = 5.58 \times 10^{-4}$). These findings were confirmed in the eMERGE cohort. Non-relevant trends in the BioVU cohort were observed for Parkinson's disease and renal failure; however, these findings were not replicated in the eMERGE cohort. The authors concluded that only DM2 risk was associated with lower LDL-c plasma levels causally related with HMG-CoA variants. Liu G, Shi M, Mosley JD *et al.* A Mendelian Randomization Approach Using 3-HMG-Coenzyme-A Reductase Gene Variation to Evaluate the Association of Statin-Induced Low-Density Lipoprotein Cholesterol Lowering With Noncardiovascular Disease Phenotypes. JAMA network open 2021; 4:e2112820. http://www.ncbi.nlm.nih.gov/pubmed/?term=34097045

Lower -and earlier LDL-c reductions in ACS confirmed in recent meta-analysis

In this meta-analysis, the long-term effect of early initiation of intensive LDL-c lowering in ACS patients was explored. In total, 19 RCTs (N=51199)) were included in the final analysis. The endpoints included the incidence of MACE (myocardial infarction, stroke,

revascularization, heart failure, and death). Overall, a statistically significant 17% reduction of MACE was observed in patients that used a more aggressive LDL-c lowering intervention, OR: 0.83 (0.76–0.90; P= 0.0012). Differences in outcomes were observed and were related to baseline- as well as proportional reduction of LDL-c. Patients with baseline LDL-c >130 mg/dl OR:0.74 (0.57-0.95; p=0.06). Baseline level of LDL-c 100 – 130 mg/dl, OR: 0.77 (0.63-0.94, p=0.02) and patients with baseline LDL-c < 100 mg, 0.90 (0.83-0.99, p=0.07). Reductions of MI, stroke, revascularisations, and heart failure were noted in patients who could reach lower LDL-c levels. These findings suggest that more intensive lipid-lowering strategies are warranted in ACS when admitted to the hospital; patients with higher baseline LDL-c levels and those that showed larger LDL- reductions benefitted most.

Jin S, Nie X, Li Y *et al.* Effect of More Intensive LDL-C-Lowering Therapy on Long-term Cardiovascular Outcomes in Early-Phase Acute Coronary Syndrome: A Systematic Review and Meta-analysis. Clinical therapeutics 2021.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34092409

Can we use statins with thrombolysis in acute-ischemic stroke patients?

The use of statins in ischemic stroke patients is firmly established; what is not clear are the effects of statins in acute stroke patients that have thrombolysis. In this prospective observational study of 180 statin-using patients were compared to 35 patients not prescribed statins. Low-dose statins used were defined as atorvastatin 20 mg, simvastatin 10 mg, and rosuvastatin 10 mg. Baseline characteristics were not the same; patients using statins were more likely to use anti-platelets, had a lower percentage of cardio-embolic strokes during the hospital stay, and were admitted with lower NIHSS ranking score at admission. The evaluated endpoint included NIHSS score at 7 days after admission and modified Rankins Scale (mRS) at 90 days. Safety outcomes included hemorrhage events (intracerebral hemorrhage and gastrointestinal hemorrhage) in the hospital and death within 2 years. Patients using statins had overall better outcomes compared to patients that refrained from using statins. Lower percentages of intracerebral hemorrhage (p < 0.001) and gastrointestinal hemorrhage (p = 0.003) in the hospital were observed. Two- year Mortality (p < 0.001) was reduced in statin users as well (P<0.001). Logistic regression analysis resulted in significant improved NIHSS scores, OR: 4.697, p < 0.001); reduced intracerebral haemorrhage, OR: 0.372 (p = 0.049) and less gastrointestinal haemorrhagic complications, OR: 0.023 (p = 0.016). Mortality was significantly reduced as well, OR = 0.072, p < 0.001). Despite the limitations of the trial design, the observed improved outcomes were impressive and do warrant further exploration by well-designed randomized prospective trials.

Cui C, Li Y, Bao J *et al.* Low dose statins improve prognosis of ischemic stroke patients with intravenous thrombolysis. BMC Neurol 2021; 21:220.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34107911

Are hydrophilic or lipophilic statins superior?

All statins share LDL-c lowering properties; however, they differ in their per mg LDL-c lowering potency. Important differences between statins are pharmacokinetic and pharmacodynamic properties. Lipophilicity (L) and hydrophilicity (H) are two unique properties used to classify statins in one of these two groups. This review aims to highlight the clinical relevance of these properties that are often used in studies proclaiming superior safety or efficacy related to L or H. Are these claims based on factual scientific findings or opinion or even marketing based? Lipophilic statins can more easily enter cells, and hydrophilic statins present with greater hepato-selectivity. Lipophilicity could provide potential better vascular, pleiotropic effects but also harms when muscle problems occur. Conflicting results are not helping to understand these basic properties better either. However, certain patients could benefit more from choosing a water-soluble or lipid-soluble statin. The quick take-home message is that the authors of this review provide no clear-cut answer, but they discuss the context of these properties and why we could expect specific harms or benefit by choosing one over the other. The bottom line is that the most critical property is reducing LDL-c and aiming for guideline dictated LDL-c related targets in the appropriate patients.

Climent E, Benaiges D, Pedro-Botet J. Hydrophilic or Lipophilic Statins? Frontiers in cardiovascular medicine 2021; 8:687585. http://www.ncbi.nlm.nih.gov/pubmed/?term=34095267

Relevant publications

1. **Xia S, Qiu W, Cai A *et al.* The association of lipoprotein(a) and intraplaque neovascularization in patients with carotid stenosis: a retrospective study. BMC Cardiovasc Disord 2021; 21:285.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34107870
2. **Wu KS, Lin PC, Chen YS *et al.* The use of statins was associated with reduced COVID-19 mortality: a systematic review and meta-analysis. Annals of medicine 2021; 53:874-884.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34096808
3. **Vuignier Y, Beaud F, Kosinski C *et al.* Exposure to alirocumab during the first trimester of pregnancy: A case report. Birth Defects Res 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34105316
4. **Talic S, Marquina Hernandez C, Ofori-Asenso R *et al.* Trends in the Utilization of Lipid-Lowering Medications in Australia: An Analysis of National Pharmacy Claims**

Data. Curr Probl Cardiol 2021:100880.
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5. Talic S, Marquina C, Ofori-Asenso R *et al.* Switching, Persistence and Adherence to Statin Therapy: a Retrospective Cohort Study Using the Australian National Pharmacy Data. Cardiovasc Drugs Ther 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34097194
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http://www.ncbi.nlm.nih.gov/pubmed/?term=34106282
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http://www.ncbi.nlm.nih.gov/pubmed/?term=34100008
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11. Kwon GE, Hyun MH, Byun DJ *et al.* Metabolic signatures of cholesterol biosynthesis and absorption in patients with coronary artery disease. J Steroid Biochem Mol Biol 2021; 212:105940. http://www.ncbi.nlm.nih.gov/pubmed/?term=34119628
12. Kim JS. Role of Blood Lipid Levels and Lipid-Lowering Therapy in Stroke Patients with Different Levels of Cerebral Artery Diseases: Reconsidering Recent Stroke Guidelines. J Stroke 2021; 23:149-161.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34102752
13. Ishii T, Ogura M, Nakamori H *et al.* Switching from lipoprotein apheresis to evolocumab in FH siblings on hemodialysis: case reports and discussion. CEN Case Rep 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34100221
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http://www.ncbi.nlm.nih.gov/pubmed/?term=34107181
15. El-Sawaf ES, Saleh S, Abdallah DM *et al.* Vitamin D and rosuvastatin obliterate peripheral neuropathy in a type-2 diabetes model through modulating Notch1, Wnt-10α, TGF-β and NRF-1 crosstalk. Life sciences 2021; 279:119697.
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16. Cho SMJ, Lee H, Lee HH *et al.* Dyslipidemia Fact Sheets in Korea 2020: an Analysis of Nationwide Population-based Data. J Lipid Atheroscler 2021; 10:202-209. http://www.ncbi.nlm.nih.gov/pubmed/?term=34095012
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Basic Science publications

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