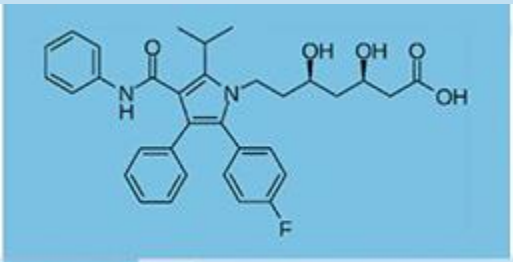
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 32, 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

Using statins before cardiac surgery reduces renal complications

Expanding the use of statins in a larger domain of potential benefits is gaining traction. In cardiac surgery, acute kidney injury (CSA-AKI) is associated with increased morbidity and mortality. The exact pathophysiology remains poorly understood, and strategies to reduce this risk are actively explored. The pre-procedural use of statins as a potential prophylactic approach was evaluated in a large prospective study of 58 399 Chinese patients that had cardiac surgery in a single tertiary care hospital between 2012 and 2019. Less renal damage was observed in statin users vs. patients that did not use statins. All stages of CSA-AKI: 30.7% v 36.3% ($p < 0.001$). Stage 3 CSA-AKI: 0.9% v 2.1%, ($p < 0.001$). After adjustments for confounding factors, statin use showed an association with a reduced risk for postoperative CSA-AKI, OR: 0.885 (0.852-0.920, $p < 0.001$) and stage 3 CSA-AKI, OR: 0.671(0.567-0.795, $p < 0.001$). Using a propensity score-matched analysis, similar outcomes were observed. Preoperative statin was associated with a lower risk of CSA-AKI, 30.7% v 35.3% ($p < 0.001$)

and stage 3 CSA-AKI, 0.9% v 2.2% (p < 0.001) than the control cohort. The authors recommend designing a large prospective randomized controlled study to confirm their findings.

Tian Y, Li X, Wang Y *et al.* Association Betwen Preoperative Statin Exposure and Acute Kidney Injury in Adult Patients Undergoing Cardiac Surgery. Journal of cardiothoracic and vascular anesthesia 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34389211

Statins in PAD patient – Meta-analysis

The benefits of statins in patients with peripheral artery disease (PAD) are stressed in major lipid management guidelines. To date, no placebo-controlled trials to support the use of statins in PAD patients have been published. A meta-analysis was performed to evaluate currently available evidence; a meta-analysis was performed, in which 22 observational cohort studies (N=268 611) were included (1957 – February 2020), including PAD patients and recorded statin use. Outcomes included all-cause mortality (ACM), cardiovascular mortality (CVM), major adverse cardiac events (MACE), and amputation. PAD patients that used statins improved outcomes were observed compared to patients that did not use statins. ACM: OR 0.68 (0.60 – 0.76; NNT=48); HR 0.74 (0.70 - 0.78; (NNT= 10 - 91). MACE, OR 0.84 (0.78 - 0.92; NNT=53); HR 0.78 (0.65 - 0.93) (NNT=167); and amputations: OR 0.59 (0.33 - 1.07; NNT=333); HR 0.74 (0.62 - 0.89; NNT=50). High doses of statins (vs. combined low and moderate doses) were associated with ACM, OR 0.69 (0.43 - 1.09; NNT=17); HR 0.74 (0.62 - 0.89; NNT=16 - 200). for MACE benefits were less robust, OR 0.77 (CI 0.49 - 1.21; NNT=25). This was also observed for amputations in patients on high doses HR 0.78 (0.69 - 0.90; NNT= 53 - 1 000). Although the quality of evidence was variable, high-dose statins were associated with improved ACM and amputation outcomes. Confirmation by larger trials in PAD patients remain needed to confirm these findings.

Sofat S, Chen X, Chowdhury MM, Coughlin PA. Effects of Statin Therapy and Dose on Cardiovascular and Limb Outcomes in Peripheral Arterial Disease: A Systematic Review and Meta-analysis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2021; 62:450-461.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34389230

Public knowledge and awareness on cholesterol and cholesterol management remains poor

One of the major hurdles in CVD prevention is adherence and persistence to medication that address major CV risk factors such as elevated blood pressure and plasma cholesterol. To explore public perceptions of cholesterol and cholesterol management, a nationwide population-based survey was conducted in Singapore. Included were 1000 participants

belonging to three different ethnic groups, Chinese, Malays, and Indians. The consensus was that cholesterol causes symptoms, and lifestyle improvements would be equally effective as medication to reduce cholesterol (65%). Over half of the participants were convinced that statins cause cancer (56%). One-third of the participants thought that herbal medication/supplements were safer and healthier. Cholesterol-lowering drugs should not be used for more extended periods, and when cholesterol is sufficiently lowered, statins could be stopped, was widely held belief as well (45%). When comparing the three different ethnic groups, Malays were less knowledgeable compared to Chinese, OR: 0.68 (0.47-0.98; P=0.039). Intermediate education compared to primary education was associated with better knowledge, OR:1.67 (1.11-2.51; P=0.013). Overall public awareness and knowledge on cholesterol as an essential CV risk factor and cholesterol management was poor in this multi-ethnic Southeast Asian cohort. Efforts directed at improving this knowledge gap could improve current cholesterol management challenges.

Lim CY, Ho JS, Huang Z *et al.* Public perceptions and knowledge of cholesterol management in a multi-ethnic Asian population: A population-based survey. PLoS One 2021; 16:e0256218. http://www.ncbi.nlm.nih.gov/pubmed/?term=34388221

Meta-analysis re-affirms statin benefits in COVID-19 patients

Observational evidence that shows the benefits of statins in patients with COVID-19 is expanding. This recent meta-analysis was based on 25 cohort studies (N=147 824) up to March 2021. In the unadjusted analysis, no benefits were observed, RR:1.16 (0.86-1.57 – 19 studies). After adjustments, statin use did show an association with improved survival, aOR: 0.67 (0.52-0.86 – 11 studies) and aHR: 0.73 (0.58-0.91 – 10 studies). After subgroup analysis, benefits were only noted in patients that used statins for a prolonged period. These outcomes confirm earlier met analyses; however, data from randomized controlled studies must confirm these promising findings.

Diaz-Arocutipa C, Melgar-Talavera B, Alvarado-Yarasca Á *et al.* Statins reduce mortality in patients with COVID-19: an updated meta-analysis of 147 824 patients. Int J Infect Dis 2021; 110:374-381. http://www.ncbi.nlm.nih.gov/pubmed/?term=34375760

Depressed, take a statin?

The effects of statins go beyond simple plasma LDL-cholesterol lowering. Benefits are expanding and could include promising new indications not directly related to lipids and CVD risk. When statins were introduced in the early nineties, there were some reports on depression and sleep disturbances related to statin use. Most were case reports, and randomized trials that evaluated statin-related side-effects were unable to confirm these findings. Intriguingly some studies showed not an increase but a decrease in patients that reported symptoms related to depression. In this review and meta-analyses, the authors

explored the major electronic databases, up until April 2021, for studies that evaluated the effects of statins on depression. In total, 72 studies were retrieved. The 15 studies that explored inflammatory-related symptoms of anhedonia, psychomotor retardation, anxiety, and sleep disturbances in depression, and most studies showed an association with statin and improved outcomes. Only a few studies showed no effect, and a minority of the included trials showed some adverse outcomes. This was a narrative report, and no quantitative outcomes were calculated. Based on their findings, the authors concluded that statins are unlikely to cause depressive symptoms in the general population. Promising results indicated a potential role for statins in the treatment of depression. These findings warrant properly designed randomized placebo-controlled trials to confirm that statin could be used to manage depression.

De Giorgi R, Rizzo Pesci N, Quinton A *et al.* Statins in Depression: An Evidence-Based Overview of Mechanisms and Clinical Studies. Frontiers in psychiatry 2021; 12:702617. http://www.ncbi.nlm.nih.gov/pubmed/?term=34385939

Relevant publications

1. **Zhang Y, Chen H, Chen S *et al.* The effect of concomitant use of statins, NSAIDs, low-dose aspirin, metformin and beta-blockers on outcomes in patients receiving immune checkpoint inhibitors: a systematic review and meta-analysis. Oncoimmunology 2021; 10:1957605.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34377596
2. **Xu XQ, Luo JZ, Li XY *et al.* Effects of perioperative rosuvastatin on postoperative delirium in elderly patients: A randomized, double-blind, and placebo-controlled trial. World journal of clinical cases 2021; 9:5909-5920.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34368309
3. **Wei J, Lvy JH, Sun XJ, Wu XR. (Meta-analysis of the effects of statins on the risk of chronic liver disease and hepatocellular carcinoma). Zhonghua Gan Zang Bing Za Zhi 2021; 29:696-701.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34371542
4. **Wang L, Shu T, Wang W *et al.* Association of statin use and the risk of recurrent pulmonary embolism in real-world Chinese population. Pulmonary circulation 2021; 11:20458940211035006.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34377437
5. **Wang L, Cong H, Zhang J *et al.* Predictive Value of the Triglyceride to High-Density Lipoprotein Cholesterol Ratio for All-Cause Mortality and Cardiovascular Death in Diabetic Patients With Coronary Artery Disease Treated With Statins. Frontiers in**

cardiovascular medicine 2021; 8:718604. http://www.ncbi.nlm.nih.gov/pubmed/?term=34368266

6. Tandaju JR, Ii W, Barati-Boldaji R, Raeisi-Dehkordi H. Meta-analysis of statin and outcomes of coronavirus disease 2019 (COVID-19): Reconsideration is needed. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021; 31:2737-2739. http://www.ncbi.nlm.nih.gov/pubmed/?term=34366177
7. Primus C, Auer J. Bilateral renal artery stenosis in a young man. BMJ case reports 2021; 14. http://www.ncbi.nlm.nih.gov/pubmed/?term=34389585
8. Pitso L, Mofokeng TRP, Nel R. Dyslipidaemia pattern and prevalence among type 2 diabetes mellitus patients on lipid-lowering therapy at a tertiary hospital in central South Africa. BMC endocrine disorders 2021; 21:159. http://www.ncbi.nlm.nih.gov/pubmed/?term=34365977
9. Pincus KJ, Blackman AL, Suen SY *et al.* Statin gap in patients living with HIV: assessing dose appropriateness. HIV medicine 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34369052
10. Nistal D, Ali M, Wei D *et al.* A Systematic Review and Meta-Analysis of Statins in Animal Models of Intracerebral Hemorrhage. World neurosurgery 2021; 155:32-40. http://www.ncbi.nlm.nih.gov/pubmed/?term=34384917
11. Liu Y, Han B. Efficacy evaluation of PCSK9 monoclonal antibody (Evolocumab) in combination with Rosuvastatin and Ezetimibe on cholesterol levels in patients with coronary heart disease (CHD): A retrospective analysis from a single center in China. Transplant immunology 2021:101444. http://www.ncbi.nlm.nih.gov/pubmed/?term=34375677
12. Liao M, Jeziorski KG, Tomaszewska-Kiecana M *et al.* A phase 1, open-label, drug-drug interaction study of rucaparib with rosuvastatin and oral contraceptives in patients with advanced solid tumors. Cancer Chemother Pharmacol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34370076
13. Liao L, Liu Y, Zheng C *et al.* Association of statins with mortality in type 2 diabetes patients with intensive glycemic therapy. Diabetes Res Clin Pract 2021; 179:109005. http://www.ncbi.nlm.nih.gov/pubmed/?term=34391828
14. Kim YH, Her AY, Jeong MH *et al.* Comparative effect of statin intensity between prediabetes and type 2 diabetes mellitus after implanting newer-generation drug-eluting stents in Korean acute myocardial infarction patients: a retrospective observational study. BMC Cardiovasc Disord 2021; 21:386. http://www.ncbi.nlm.nih.gov/pubmed/?term=34372778
15. Karpouzas GA, Ormseth SR, Hernandez E, Budoff MJ. The impact of statins on coronary atherosclerosis progression and long-term cardiovascular disease risk in rheumatoid arthritis. Rheumatology (Oxford) 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34373923

16. Jo YS, Han K, Kim D *et al.* Relationship between total cholesterol level and tuberculosis risk in a nationwide longitudinal cohort. Scientific reports 2021; 11:16254. http://www.ncbi.nlm.nih.gov/pubmed/?term=34376753
17. Hicks CW, Clark TWI, Cooper CJ *et al.* Artherosclerotic Renovascular Disease: A KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference. American journal of kidney diseases : the official journal of the National Kidney Foundation 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34384806
18. Choi J, Sung KC, Ihm SH *et al.* Central blood pressure lowering effect of telmisartan-rosuvastatin single-pill combination in hypertensive patients combined with dyslipidemia: A pilot study. Journal of clinical hypertension (Greenwich, Conn.) 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34384001
19. Alanazi NS, Alenazi TS, Alenzi KA. Hepatotoxicity Induced by Fluvastatin: A Reversible Acute Cholestatic Liver Injury. Am J Case Rep 2021; 22:e931418. http://www.ncbi.nlm.nih.gov/pubmed/?term=34383728
20. Al Rifai M, Blumenthal RS, Stone NJ *et al.* Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) guidelines for management of dyslipidemia and cardiovascular disease risk reduction: Putting evidence in context. Prog Cardiovasc Dis 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34371083
21. Vachal P, Duffy JL, Campeau LC *et al.* Invention of MK-8262, a Cholesteryl Ester Transfer Protein (CETP) Inhibitor Backup to Anacetrapib with Best-in-Class Properties. Journal of medicinal chemistry 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34375108
22. Muñoz AE, Pollarsky FD, Marino M *et al.* Addition of statins to the standard treatment in patients with cirrhosis: Safety and efficacy. World J Gastroenterol 2021; 27:4639-4652. http://www.ncbi.nlm.nih.gov/pubmed/?term=34366626
23. Lee HL, Lee SW, Jang JW *et al.* Anticancer Effect of Statins in Patients Undergoing Liver Transplantation for Hepatocellular Carcinoma. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34374192
24. Goicoechea M, Álvarez V, Segarra A *et al.* Lipid profile of patients treated with evolocumab in Spanish hospital nephrology units (RETOSS NEFRO). Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34389184

Basic Science publications

1. **Zhang S, Yuan L, Li H *et al.* The Novel Interplay between Commensal Gut Bacteria and Metabolites in Diet-Induced Hyperlipidemic Rats Treated with Simvastatin. J Proteome Res 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34365791
2. **Wang Y, Wang C, Xie M *et al.* Atorvastatin causes oxidative stress and alteration of lipid metabolism in estuarine goby Mugilogobius abei. Environ Pollut 2021; 289:117879.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34391042
3. **Heydari P, Zargar Kharazi A, Asgary S, Parham S. Comparing the wound healing effect of a controlled release wound dressing containing curcumin/ciprofloxacin and simvastatin/ciprofloxacin in a rat model: A preclinical study. J Biomed Mater Res A 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34378857
4. **Ding S, Yu B, van Vuuren AJ. Statins significantly repress rotavirus replication through downregulation of cholesterol synthesis. Gut Microbes 2021; 13:1955643.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34369301
5. **Dai L, Wang J, He M *et al.* Lovastatin Alleviates α-Synuclein Aggregation and Phosphorylation in Cellular Models of Synucleinopathy. Frontiers in molecular neuroscience 2021; 14:682320.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34381332

This activity is supported by an educational grant from Viatris.