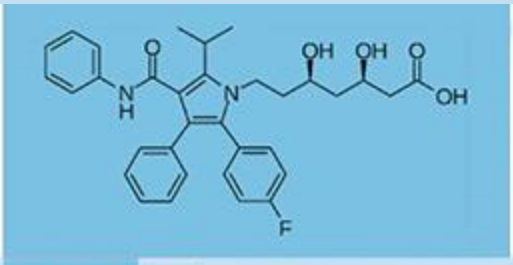
IAS STATIN
NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 33, 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

The impact of clinical features on AS characteristics using advanced imaging techniques

Through advanced imaging techniques using optical coherence tomography (OCT) and intravascular ultrasound (IVUS), patients that were scheduled for a coronary intervention were evaluated for plaque burden (IVUS) and lipid, macrophage and calcium indices and the presence of thrombus, plaque rupture as well as thin-cap fibroatheroma (TCFA) by OCT. 704 Japanese patients (44.5% with acute coronary syndromes) were included in this single-center observational study. The median patient age was 66 years, with 81.8% men, 34.4% diabetes mellitus, and 15.5% pre-admission statins. The median lesion length was 25.7 mm, and 33.0% had a TCFA. After Adjustment, relationships between vascular and clinical characteristics showed the following unique features. Age was related to increased calcium deposits but reduced macrophages. Men were more likely to present with more thrombus formation and plaque ruptures, while women had increased thrombus but lacked plaque ruptures. ACS patients demonstrated multiple features associated with vulnerable plaque: more thrombus with and without rupture, more TCFA, lipids, and macrophages + larger

plaque burden. Diabetics had a greater AS plaque burden consisting of lipids, calcium, and more thrombus without rupture. Increased macrophage content was observed in hypertensive patients and current smokers presented with less calcifications. Statin use before admission did not show any impact on IVUS or OCT plaque morphology. The single observation period and the fact that only 15.5% of the patients were using statins (none used high dose, high-intensity statins) could explain this somewhat contradictory finding. The findings of this study show how the different patient characteristics, especially diabetes, age, and sex, impact the underlying atherosclerotic disease progress, affecting the clinical presentation and prioritizing specific risk factor management strategies.

Zhang W, Mintz GS, Cao Y *et al.* Clinical determinants of coronary artery disease burden and vulnerability using optical coherence tomography co-registered with intravascular ultrasound. Coronary artery disease 2021.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34411011

Statin use associated with increased densification of calcium, but this reflects a decreased AS risk

The impact of statin use on calcium content and plaque features were evaluated in the PARADIGM study, a large multinational observational registry of patients with clinically indicated serial coronary computed tomography angiography (CCTA). This collaboration consists of 13 sites in 7 countries and collected imaging data of 2252 consecutive CAD patients (2013-2017). This analysis included patients who had serial CCTA at two or more year intervals (N=857). The primary endpoint was a progression of CAD. Patients not using statin showed an increase in all 6 plaque composition types. Statin use was associated with volume decrease in the groups with low attenuation plaques (−30 to 75 HU), β, −0.02 (−0.03 to −0.01; P = .001) and fibro-fatty plaques (76-130 HU), β, −0.03 (−0.04 to −0.02; P < .001). Increased progression of high-density calcium plaques (701-1000 HU), β, 0.02 (0.01-0.03; P < .001) and 1K plaques (>1000 HU), β, 0.02 (0.01-0.03; P < .001). Excluding low attenuation plaques and fibro-fatty plaques at baseline statin use was not associated with changes in overall plaque volume, and calcium dense plaques were associated with attenuated plaque progression. This study shows that statin use was associated with increased densification of calcium of the atherosclerotic coronary arteries, but this reflected not an increase but a diminished atherosclerotic risk.

van Rosendael AR, van den Hoogen IJ, Gianni U *et al.* Association of Statin Treatment With Progression of Coronary Atherosclerotic Plaque Composition. JAMA cardiology 2021.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34406326

Concise review on new developments in lipid management

For those seeking a compact and concise update on what is new on the lipid management

horizon, this review might be helpful. The process of atherosclerosis and the role of lipids, lipoproteins endothelial markers, and transcription factors are explained. Clinical presentations of dyslipidemia and the AHA/ACC guidelines from 2018 provide context for health care providers involved with lipid management. The new portfolio of lipid-lowering agents, consisting of bempedoic acid, incliseran, evinacumab, vupanorsen, gemcabene, and ANGPTL3 siRNA are summarized with recent trial data part of this review as well.
Su L, Mittal R, Ramgobin D *et al.* Current Management Guidelines on Hyperlipidemia: The Silent Killer. Journal of lipids 2021; 2021:9883352.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34394993

Review on Colchicine to reduce residual risk in ASCVD patients

Inflammation is a critical risk factor for acute ASCVD complications. Despite the unprecedented success of lipid management with statins as monotherapy or combined with other LDL-c lowering drugs, residual risk remains an important factor. New approaches to reduce inflammation targeting IL -1ß/IL-6 have been tested and showed promising results but at a premium price. The off-patent anti-inflammatory agent colchicine is an attractive alternative for reducing systemic inflammation and subsequently reducing atherosclerosis progression as well as plaque ruptures. In recent studies, safety and efficacy were examined and showed protective effects without alarming side effects. In secondary prevention patients, several large-scale placebo-controlled randomized trials have been published; the LoDoCo and LoDoCo2 (stable CAD patients0, COLCOT, COPS AND CLEAR SYNERGY (recent ACS patients) and the COLCHICINE-PCI trial (post-PCI patients). Based on the evidence by these studies, low-dose colchicine (0.5 mg/day) should be considered in patients with a recent MI (within 30 days and ideally within 3 days) and in stable CAD patients to improve CVD outcomes. Colchicine was well tolerated, and no serious adverse events were observed when combined with high-intensity statins. Patients with severe renal or hepatic function impairment should not take colchicine to prevent toxicity-related adverse events. The benefits of colchicine in diabetics or patients with PAD remain to be established. Marquis-Gravel G, Goodman SG, Anderson TJ *et al.* Colchicine for Prevention of Atherothrombotic Events in Patients with Coronary Artery Disease: Review and Practical Approach for Clinicians. Can J Cardiol 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34418482

Systematic review on cognitive outcomes after traumatic brain injury

This systematic review explored the potential benefits of statins on reducing the risk of developing dementia in patients that suffered a traumatic brain injury (TBI). This risk increased five-fold compared to individuals that did not experience TBI. Statins have shown some surprising benefits in TBI patients. Of the 4948 studies, 18 were selected for the final

analysis; 9 human studies and 9 animal laboratory trials. Simvastatin was the statin most frequently used in an oral formulation. In four RCTs (N=296), statin use was associated with improved cognitive outcomes. The suggested mechanisms to explain the observed benefits were anti-inflammatory properties, lowering TNF-α and CRP.Additionally, a decrease in axonal injury and cortical thickness changes were observed. Four cohort studies (N=867 953) were evaluated separately, showing reduced mortality in statin-treated patients (P=0.05), a drop in the incidence of Alzheimer's disease and related dementia's; RR: 0.77 (0.73-0.81), and in one study, a decreased risk of dementia after concussions (-6.13% (p=0.001). These findings contrasted with one cohort study where statins use was not associated with significantly different outcomes. In the eight animal studies, neuroprotective effects were observed as well. Improved cognitive results and neurological functions showed improvement in statin-treated animals. However, in one animal study, the cognitive abilities showed deterioration. Potential mechanisms suggested were anti-inflammatory effects, stimulated angiogenesis, neurogenesis, neurite outgrowth, proliferation, neural stem cell differentiation, and increased cerebral circulation. The promising results of these studies could promote statins as a therapeutic option for TBI patients. More advanced studies are warranted to confirm the findings, explore optimal dosing, and if statins differ in their capabilities to improve the infaust outcomes in TBI patients.

Sultan W, Sapkota A, Khurshid H *et al.* Statins' Effect on Cognitive Outcome After Traumatic Brain Injury: A Systematic Review. Cureus 2021; 13:e16953.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34405076

Relevant publications

1. **Kurihara O, Takano M, Miyauchi Y *et al.* Vulnerable atherosclerotic plaque features: findings from coronary imaging. Journal of geriatric cardiology : JGC 2021; 18:577-584.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34404993
2. **Katzmann JL, Lehmann M, Tünnemann-Tarr A *et al.* Cutaneous manifestations in familial hypercholesterolaemia. Atherosclerosis 2021; 333:116-123.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34399983
3. **Ezeh KJ, Ezeudemba O. Hyperlipidemia: A Review of the Novel Methods for the Management of Lipids. Cureus 2021; 13:e16412.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34401212
4. **Hussain A, Lee M, Rana J, Virani SS. Epidemiology and risk factors for stroke in young individuals: implications for prevention. Current opinion in cardiology 2021; 36:565-571.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34397463

5. Giugliano RP, Gencer B, Wiviott SD *et al.* Prospective Evaluation of Malignancy in 17,708 Patients Randomized to Ezetimibe Versus Placebo: Analysis From IMPROVE-IT. JACC CardioOncol 2020; 2:385-396. http://www.ncbi.nlm.nih.gov/pubmed/?term=34396246
6. Dagli-Hernandez C, Zhou Y, Lauschke VM *et al.* Pharmacogenomics of statins: lipid response and other outcomes in Brazilian cohorts. Pharmacological reports : PR 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34403130
7. Chu MP, Many G, Isquith DA *et al.* Metabolic and inflammatory risk reduction in response to lipid-lowering and lifestyle modification in the medically underserved individuals. Am J Prev Cardiol 2021; 7:100227. http://www.ncbi.nlm.nih.gov/pubmed/?term=34401861
8. Chang MC, Kwak SG, Park JS, Park D. Relationship between statins and the risk of amyotrophic lateral sclerosis: A PRISMA-compliant meta-analysis. Medicine (Baltimore) 2021; 100:e26751. http://www.ncbi.nlm.nih.gov/pubmed/?term=34397718
9. Blaha MJ, Daubert MA. Assessing the Impact of Coronary Plaque on the Relative and Absolute Risk Reduction With Statin Therapy. JACC. Cardiovascular imaging 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34419396
10. Alameh A, Jabri A, Aleyadeh W *et al.* Pregnancy-Associated Myocardial Infarction: A Review of Current Practices and Guidelines. Current cardiology reports 2021; 23:142. http://www.ncbi.nlm.nih.gov/pubmed/?term=34410528
11. Agha AM, Jones PH, Ballantyne CM *et al.* Greater than expected reduction in low-density lipoprotein-cholesterol (LDL-C) with bempedoic acid in a patient with heterozygous familial hypercholesterolemia (HeFH). J Clin Lipidol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34393074
12. Trivedi A, Sohn W, Kulkarni P *et al.* Evaluation of drug-drug interaction potential between omecamtiv mecarbil and rosuvastatin, a BCRP substrate, with a clinical study in healthy subjects and using a physiologically-based pharmacokinetic model. Clinical and translational science 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34415673
13. Tomsitz D, Biedermann T. Successful treatment of disseminated superficial actinic porokeratosis with topical 2% cholesterol/ 2% lovastatin cream: a case series with 7 patients. Journal of the European Academy of Dermatology and Venereology : JEADV 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34418182
14. Rashed ER, Abdel-Rafei MK, Thabet NM. Roles of Simvastatin and Sildenafil in Modulation of Cranial Irradiation-Induced Bystander Multiple Organs Injury in Rats. Inflammation 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34420155
15. Obasi M, Abovich A, Vo JB *et al.* Statins to mitigate cardiotoxicity in cancer patients treated with anthracyclines and/or trastuzumab: a systematic review and meta-analysis. Cancer Causes Control 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34406595
16. Liu Y, Shao Y, Xie J *et al.* The efficacy and safety of metformin combined with simvastatin in the treatment of polycystic ovary syndrome: A meta-analysis and systematic review. Medicine (Baltimore) 2021; 100:e26622. http://www.ncbi.nlm.nih.gov/pubmed/?term=34397797

17. Lalagkas PN, Poulentzas G, Tsiolis L *et al.* Investigating Potential Drug-Drug Interactions from Greek e-Prescription Data. Current drug safety 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34397333
18. Hearps AC, Angelovich TA, Trevillyan JM *et al.* Effect of Rosuvastatin Therapy on Biomarkers of Inflammation and Immune Activation in People With Human Immunodeficiency Virus at Intermediate Cardiovascular Risk. The Journal of infectious diseases 2021; 224:667-672. http://www.ncbi.nlm.nih.gov/pubmed/?term=34398237
19. Ahmad A, Karam I, Baker DL. A Rapidly Debilitating Myopathy: A Rare Case of Statin-Induced Necrotizing Myositis. Cureus 2021; 13:e16304. http://www.ncbi.nlm.nih.gov/pubmed/?term=34405065

Basic Science publications

1. Sherratt SCR, Juliano RA, Copland C *et al.* EPA and DHA containing phospholipids have contrasting effects on membrane structure. Journal of lipid research 2021; 62:100106. http://www.ncbi.nlm.nih.gov/pubmed/?term=34400132
2. Piermartiri TCB, Figueiredo CP, Rial D *et al.* Corrigendum to "Atorvastatin prevents hippocampal cell death, neuroinflammation and oxidative stress following amyloid-β1-40 administration in mice: Evidence for dissociation between cognitive deficits and neuronal damage": (Experimental Neurology, 226:2 (2010) 274-284). Experimental neurology 2021; 345:113840. http://www.ncbi.nlm.nih.gov/pubmed/?term=34417015
3. Paseban M, Niazmand S. The Comparison of Antioxidant Effect of Aspirin, Metformin, Atorvastatin and Captopril Co-administration in the Heart and Kidney Tissues of Diabetic Rats. Iranian journal of pharmaceutical research : IJPR 2021; 20:27-39. http://www.ncbi.nlm.nih.gov/pubmed/?term=34400938
4. Oktaviono YH, Hutomo SA, Al-Farabi MJ *et al.* Human umbilical cord blood-mesenchymal stem cell-derived secretome in combination with atorvastatin enhances endothelial progenitor cells proliferation and migration. F1000Research 2020; 9:537. http://www.ncbi.nlm.nih.gov/pubmed/?term=3439492

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