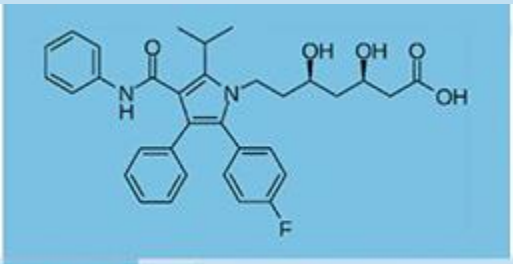
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 34, 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

Statin for VTE prophylaxis in patients with endometrial cancer

The repurposing of existing drugs for indications beyond their primary target is an attractive and plausible strategy. Endometrial cancer (EC) is associated with an increased VTE risk. Although this type of cancer prognosis is favorable, addressing the frequently reported comorbidities, including VTE, can improve long-term outcomes. In this review, both aspirin and statins are evaluated for their efficacy to prevent VTE's. Studies that assessed the effects of both drugs on VTE in women with EC are presented, seven statins studies plus four aspirin trials and one meta-analysis. Metabolic pathways of thrombosis and the specific inhibitory properties of aspirin and statins are explained. The authors suggest that aspirin

use was associated with a modest benefit on VTE prophylaxis and improved survival in obese older women (<60 years) that presented with type I cancer. Statin use was associated with enhanced survival and reduced VTE risk in women with type II endometrial cancer. The combination of statin + aspirin would be the preferred choice for obese women with type II cancer.

Matsuzaki S, Miller H, Takiuchi T *et al.* Effects of aspirin and statin use on venous thromboembolism prophylaxis and survival in patients with endometrial cancer. Expert opinion on drug safety 2021:1-13. http://www.ncbi.nlm.nih.gov/pubmed/?term=34437828

Combining a statin with ezetimibe, what to expect?

The combination of statin + ezetimibe is an effective combination therapy for lowering LDL-c. Similar strategies that have been widely accepted for blood pressure control are now embraced by recent European and US lipid management guidelines—comparing the safety and LDL-c lowering efficacy of rosuvastatin (R) 2.5 mg, 5 mg monotherapy, and ezetimibe (E) 10 mg vs. rosuvastatin 2.5 mg + ezetimibe 10 mg, in Korean hypercholesterolemic patients. This was a multi-center randomized controlled 8-week study in 297 patients. The combination of R (2.5 mg) + E (10 mg) showed superior LDL-c reductions of −45.7% (±18.6%) vs −16.7% (±14.7%, p < 0.0001) in the E 10 group, −32.6% (±15.1%, p < 0.0001) in the R 2.5 group , and −38.9% (±13.9%, p = 0.0003) in the R 5 group. All patients in the R 2.5 + E 10 group reached guideline dictated LDL-c targets, vs. 13% in the E 10 group, 46.5% in the R 2.5 group, and 65.2% in the R 5 group. Adverse events were reported by 7 (2.5%) of the participants. Discontinuation occurred in one patient in the R+E group and one patient in the R 2.5 group. A combination of low-dose rosuvastatin with ezetimibe was associated with superior LDL-c reductions compared to monotherapy with R 2.5, 5, or E 10. Lee SA, Kim W, Hong TJ *et al.* Effects of Fixed-Dose Combination of Low-Intensity Rosuvastatin and Ezetimibe Versus Moderate-Intensity Rosuvastatin Monotherapy on Lipid Profiles in Patients With Hypercholesterolemia: A Randomized, Double-Blind, Multicenter, Phase III Study. Clinical therapeutics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34429197

Can statins improve survival in newly initiated dialysis patients?

This sub-analysis of the South Korean nationwide claims database evaluated the benefits of starting statins therapy in newly initiated dialysis patients. This was a retrospective observational propensity score-matched cohort study of 1 596 patients who started dialysis between 2010 and 2017 and initiated statins within the first year of dialysis. Propensity score matching was based on the following criteria: age, sex, time of dialysis initiation, and underlying diabetes mellitus and hypertension. Primary endpoints were all-cause mortality and major cardiovascular events (MACE). The total number of follow-up years was 9438; during this follow-up, 468 patients died, and 264 MACE occurred. Statin use was associated

with improved survival, all-cause mortality; aHR: 0.72 (0.60-0,87, P=0.001) No significant difference was noted for MACE, aHR: 1.06 (0.83-1.36, p=0.62). A subgroup of patients that used the recommended KDIGO guideline statin dosage had the lowest risk. For all-cause mortality, aHR: 0.55 (0.40-0.75, P<0.001). These findings are intriguing and contrast with the 4D and AURORA studies where end-stage renal disease patients failed to show improved outcomes when using atorvastatin or rosuvastatin. The observational design of this study cannot provide solid evidence to support initiating statins in patients that start dialysis, but does warrant prospective studies to validate these findings.

Kim JE, Park S, Kim MS *et al.* Statin initiation and all-cause mortality in incident statin-naïve dialysis patients. Atherosclerosis 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34429195

Should cardiotoxic chemotherapy be combined with statins to preserve LVEF

A new specialization, cardio-oncology, provides expert care for the molecular and clinical alterations in the cardiovascular system during the different methods of treatment of cancer, especially chemotherapy and targeted therapy. In this review, the authors explored the potential benefits of statins on left ventricular ejection fraction and cardiomyopathy in patients treated with cardiotoxic chemotherapy. For this meta-analysis, seven studies with 3042 patients were included; 1382 used concomitant statins with their chemotherapy regimen; 1660 control patients used chemotherapy only. Statin use was associated with improved cardiac outcomes. Patients in the control group had a more significant decline in LVEF (-6.08% (-8.55—3.61. P<001). The incidence of cardiomyopathy was significantly lower in the statins users, OR:0.41 (0.28-0.60. P<0.001). The findings of this meta-analysis provide support for the cardioprotective effects of statins in cancer patients treated with cardiotoxic chemotherapeutic agents. Additional large-scale RCTs are warranted to corroborate these findings.

Kim J, Nishimura Y, Kewcharoen J, Yess J. Statin Use Can Attenuate the Decline in Left Ventricular Ejection Fraction and the Incidence of Cardiomyopathy in Cardiotoxic Chemotherapy Recipients: A Systematic Review and Meta-Analysis. Journal of clinical medicine 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34442027

REDUCE-IT and STRENGTH a conundrum explained

Recently, two large placebo-controlled randomized trials using omega-3 fatty acids plus statins in high-risk, hypertriglyceridemic individuals showed contrasting and confusing results. The REDUCE-IT study compared eicosapentaenoic acid (EPA) with a mineral oil-based placebo, and in the STRENGTH study, a combination of EPA and EPA + docosahexaenoic acid (DHA) vs. a corn oil-based placebo. The REDUCE-IT study showed an

impressive 25% reduction in major cardiovascular events; the STRENGTH trial was terminated prematurely due to futility. The debates on these contrasting outcomes focus on the different types of fish oils to explain the superior benefits of EPA vs. no effect of EPA + DHA. An alternative explanation suggests that mineral oil is not an inert placebo and negatively affects LDL-c and ASCVD risk. The benefits of the EPA result from an increase of ASCVD risk in the "placebo" group that used mineral oil. The authors of this study used patient data collected in the Copenhagen General Population Study (CGPS). Patients were selected based on the inclusion criteria of both studies. Follow-up periods (4.9 years in REDUCE-IT and 3.5 years in STRENGHT) were extrapolated as well. Biomarkers at baseline and study completion (LDL-c, triglycerides, and hs CRP) were also mirrored. When comparing the outcomes for both studies in the CGPS, a risk reduction, HR of 0.88 (0.84-0.93) in the CGPS mimicking the REDUCE-IT study and an HR of 0.96 (0.93-0.99) was observed for CGPS participants simulating the STRENGHT study. This contrasts with the reported results of HR: 0.75 (0.68-0.83) in the REDUCE-IT and HR: 0.99 (0.90-1.09) in the STRENGHT studies. The authors concluded that the contrasting outcomes in the two studies could be partly explained by a difference in the oils used in the placebo group, but not the active fish oils triggered changes on hsCRP, LDL-c, and triglycerides. The observed 13% risk reduction is likely the result of other effects of EPA or mineral oil. Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs. Eur Heart J 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34455435

Relevant publications

1. **Borovac JA, Leth-Olsen M, Kumric M *et al.* Efficacy of high-dose atorvastatin or rosuvastatin loading in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials with GRADE qualification of available evidence. Eur J Clin Pharmacol 2021.**
http://www.ncbi.nlm.nih.gov/pubmed/?term=34423376
2. **Xie L, Zhu G, Shang J *et al.* An overview on the biological activity and anti-cancer mechanism of lovastatin. Cell Signal 2021; 87:110122.**
http://www.ncbi.nlm.nih.gov/pubmed/?term=34438015

3. Wichaiyo S, Supharattanasitthi W. Bempedoic Acid: A New Non-statin Drug for the Treatment of Dyslipidemia. Clinical drug investigation 2021; 41:843-851. http://www.ncbi.nlm.nih.gov/pubmed/?term=34435333
4. Warren T, McAllister R, Morgan A *et al.* The Interdependency and Co-Regulation of the Vitamin D and Cholesterol Metabolism. Cells 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34440777
5. Picard F, Bhatt DL, Ducrocq G *et al.* Generalizability of the REDUCE-IT trial and cardiovascular outcomes associated with hypertriglyceridemia among patients potentially eligible for icosapent ethyl therapy: An analysis of the REduction of Atherothrombosis for Continued Health (REACH) registry. Int J Cardiol 2021; 340:96-104. http://www.ncbi.nlm.nih.gov/pubmed/?term=34450192
6. Oberoi M, Fanciullo J. Statin Associated Muscle Adverse Effects: From Presentation to Management. South Dakota medicine : the journal of the South Dakota State Medical Association 2021; 74:272-276. http://www.ncbi.nlm.nih.gov/pubmed/?term=34449167
7. Matías-Pérez D, Pérez-Santiago AD, Sánchez Medina MA *et al.* PCSK9 Gene Participates in the Development of Primary Dyslipidemias. Balkan J Med Genet 2021; 24:5-14. http://www.ncbi.nlm.nih.gov/pubmed/?term=34447653
8. Marco-Benedí V, Laclaustra M, Sánchez-Hernández RM *et al.* Cataract Surgery in Elderly Subjects with Heterozygous Familial Hypercholesterolemia in Prolonged Treatment with Statins. Journal of clinical medicine 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34441790
9. Lillo JL. The Challenge: Finding the Most Appropriate Statin and Dose for Each Patient. The Journal of family practice 2021; 70:S53-s58. http://www.ncbi.nlm.nih.gov/pubmed/?term=34432625
10. Kim YH, Her AY, Jeong MH *et al.* Efficacy of Statin Treatment According to Baseline Renal Function in Korean Patients with Acute Myocardial Infarction Not Requiring Dialysis Undergoing Newer-Generation Drug-Eluting Stent Implantation. Journal of clinical medicine 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34441800
11. Jankowski P, Kozieł P, Setny M *et al.* Dyslipidemia Management in Patients with Coronary Artery Disease. Data from the POLASPIRE Survey. Journal of clinical medicine 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34442006
12. Jadhav SB, Crass RL, Chapel S *et al.* Pharmacodynamic effect of bempedoic acid and statin combinations: predictions from a dose-response model. European heart journal. Cardiovascular pharmacotherapy 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34448822
13. Barry AR, Dixon DL. Omega-3 fatty acids for the prevention of atherosclerotic cardiovascular disease. Pharmacotherapy 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34431129

14. Agarwala A, Bekele N, Deych E *et al.* Racial Disparities in Modifiable Risk Factors and Statin Usage in Black Patients With Familial Hypercholesterolemia. J Am Heart Assoc 2021; 10:e020890. http://www.ncbi.nlm.nih.gov/pubmed/?term=34431361
15. Acton EK, Khazaal O, Willis AW *et al.* Statins for the Prevention of Post-Stroke Seizure and Epilepsy Development: A Systematic Review and Meta-Analysis. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2021; 30:106024. http://www.ncbi.nlm.nih.gov/pubmed/?term=34438280
16. Abbasi F, Lamendola C, Harris CS *et al.* Statins Are Associated With Increased Insulin Resistance and Secretion. Arterioscler Thromb Vasc Biol 2021:Atvbaha121316159. http://www.ncbi.nlm.nih.gov/pubmed/?term=34433298
17. Perrone MA, Feola A, Pieri M *et al.* The Effects of Reduced Physical Activity on the Lipid Profile in Patients with High Cardiovascular Risk during COVID-19 Lockdown. International journal of environmental research and public health 2021; 18. http://www.ncbi.nlm.nih.gov/pubmed/?term=34444607
18. Mohd Jaafar F, Monsion B, Belhouchet M *et al.* Inhibition of Orbivirus Replication by Fluvastatin and Identification of the Key Elements of the Mevalonate Pathway Involved. Viruses 2021; 13. http://www.ncbi.nlm.nih.gov/pubmed/?term=34452303
19. Lin TY, Lan WH, Chiu YF *et al.* Statins' Regulation of the Virulence Factors of Helicobacter pylori and the Production of ROS May Inhibit the Development of Gastric Cancer. Antioxidants (Basel) 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34439541
20. Kim SY, Yoo DM, Min C, Choi HG. Association between Statin Use and Meniere's Disease: Results from a National Health Screening Cohort. International journal of environmental research and public health 2021; 18. http://www.ncbi.nlm.nih.gov/pubmed/?term=34444440
21. Ianevski A, Yao R, Zusinaite E *et al.* Active Components of Commonly Prescribed Medicines Affect Influenza A Virus-Host Cell Interaction: A Pilot Study. Viruses 2021; 13. http://www.ncbi.nlm.nih.gov/pubmed/?term=34452402
22. Fortini F, Vieceli Dalla Sega F, Marracino L *et al.* Well-Known and Novel Players in Endothelial Dysfunction: Updates on a Notch(ed) Landscape. Biomedicines 2021; 9. http://www.ncbi.nlm.nih.gov/pubmed/?term=34440201
23. Feng Y, Lu SL, Jin XG *et al.* Effect of "Natural Polypill", Xuezhikang on Serum Cholesterol Metabolism Markers in Early Menopausal Women with Hypercholesterolemia. Chin J Integr Med 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34432203
24. Coskinas X, Schou IM, Simes J, Martin A. Reacting to prognostic covariate imbalance in randomised controlled trials. Contemporary clinical trials 2021; 110:106544. http://www.ncbi.nlm.nih.gov/pubmed/?term=34454099

25. Colvin CL, Poudel B, Bress AP *et al.* Race/ethnic and sex differences in the initiation of non-statin lipid-lowering medication following myocardial infarction. J Clin Lipidol 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34452823
26. Caldas M, Pérez-Aisa Á, Tepes B *et al.* The Role of Statins on Helicobacter pylori Eradication: Results from the European Registry on the Management of H. pylori (Hp-EuReg). Antibiotics (Basel, Switzerland) 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34439015
27. Ahangari N, Sahebkar A, Azimi-Nezhad M *et al.* A Novel Splice Site Variant in the LDLRAP1 Gene Causes Familial Hypercholesterolemia. Iranian biomedical journal 2021; 25:374-379. http://www.ncbi.nlm.nih.gov/pubmed/?term=34425670

Basic Science publications

1. Yadav A, Kossenkov AV, Showe LC *et al.* Lack of Atorvastatin Effect on Monocyte Gene Expression and Inflammatory Markers in HIV-1-infected ART-suppressed Individuals at Risk of non-AIDS Comorbidities. Pathogens & immunity 2021; 6:1-26. http://www.ncbi.nlm.nih.gov/pubmed/?term=34447895
2. Sun J, Wang Z, Chen L, Sun G. Hypolipidemic Effects and Preliminary Mechanism of Chrysanthemum Flavonoids, Its Main Components Luteolin and Luteoloside in Hyperlipidemia Rats. Antioxidants (Basel) 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34439559
3. Shwe TH, Pothacharoen P, Phitak T *et al.* Atorvastatin Attenuates Programmed Death Ligand-1 (PD-L1) Induction in Human Hepatocellular Carcinoma Cells. Int J Mol Sci 2021; 22. http://www.ncbi.nlm.nih.gov/pubmed/?term=34445462
4. Qian J, Shen Q, Yan CX *et al.* Atorvastatin improves bone marrow endothelial progenitor cell function from patients with immune-related hemocytopenia. Annals of translational medicine 2021; 9:1142. http://www.ncbi.nlm.nih.gov/pubmed/?term=34430583
5. Özer T, Aktaş A, Avağ C *et al.* Evaluation of the Effects of Locally Applied Rosuvastatin on Bone Formation in a Three-Dimensional Reconstruction Rabbit

Xenograft Model. Turk J Med Sci 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34428883

6. Ning D, Yang X, Wang T *et al.* Atorvastatin treatment ameliorates cardiac function and remodeling induced by isoproterenol attack through mitigation of ferroptosis. Biochem Biophys Res Commun 2021; 574:39-47.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34438345
7. Knapik-Kowalczuk J, Kramarczyk D, Jurkiewicz K *et al.* Ternary Eutectic Ezetimibe-Simvastatin-Fenofibrate System and the Physical Stability of Its Amorphous Form. Molecular pharmaceutics 2021; 18:3588-3600.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34420300
8. Kapelouzou A, Katsimpoulas M, Kontogiannis C *et al.* A High-Cholesterol Diet Increases Toll-like Receptors and Other Harmful Factors in the Rabbit Myocardium: The Beneficial Effect of Statins. Curr Issues Mol Biol 2021; 43:818-830.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34449561
9. Kamaruddin NN, Hajri NA, Andriani Y *et al.* Acanthaster planci Inhibits PCSK9 and Lowers Cholesterol Levels in Rats. Molecules (Basel, Switzerland) 2021; 26.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34443682
10. Ibrahim SSA, Kandil LS, Ragab GM, El-Sayyad SM. Micro RNAs 26b, 20a inversely correlate with GSK-3 β/NF-κB/NLRP-3 pathway to highlight the additive promising effects of atorvastatin and quercetin in experimental induced arthritis. Int Immunopharmacol 2021; 99:108042.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34426107
11. Buist M, Fuss D, Rastegar M. Transcriptional Regulation of MECP2E1-E2 Isoforms and BDNF by Metformin and Simvastatin through Analyzing Nascent RNA Synthesis in a Human Brain Cell Line. Biomolecules 2021; 11.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34439919
12. Basso PJ, Sales-Campos H, Nardini V *et al.* Peroxisome Proliferator-Activated Receptor Alpha Mediates the Beneficial Effects of Atorvastatin in Experimental Colitis. Frontiers in immunology 2021; 12:618365.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34434187
13. Arruda de Faria C, Silva Júnior WA, Caetano Andrade Coelho KB *et al.* Mesenchymal stromal cells-based therapy in a murine model of elastase-induced emphysema: Simvastatin as a potential adjuvant in cellular homing. Pulmonary pharmacology & therapeutics 2021; 70:102075.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34428598
14. Erratum to chemoprotective effect of atorvastatin against benzo(a)pyrene-induced lung cancer via the inhibition of oxidative stress and inflammatory parameters.

Annals of translational medicine 2021; 9:1214.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34430655

This activity is supported by an educational grant from Viatris.