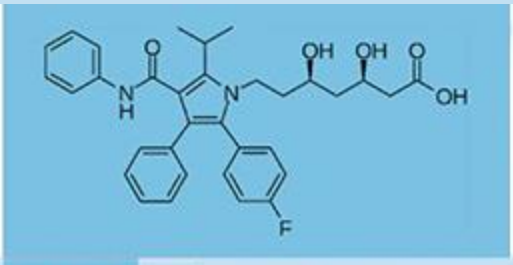
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 36, 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

Elderly patients at risk for CVD – are statins of value

The rationale for using high-dose, high-intensity statins in elderly patients is partly based on sub-analyses of the major randomized controlled CV outcome trials and large observational registries. Recently updated ESC guidelines included elderly patients (>75 years) in both the SCORE-OP (Older Patients) and therapeutic recommendations. IN this

retrospective observational study, based on data of a Californian Health Care organization, Patients > 75 years were more likely to suffer a cardiovascular complication compared to their younger patients (65-75 years). An HR: 1.42 (1.23-1.63) was noted for the very elderly patients. Moderate- or high-intensity statin prescriptions were observed significantly less in this cohort, OR:0.80 (0.74-0.86; P<0.001). Women, OR:0.85 (0.81-0.89) and underweight elderly, OR:0.45 (0.33-0.61), were less likely to be prescribed moderate or high-intensity statins as well. Efforts directed at exploring the reasons for these differences are warranted.
Sarraju A, Spencer-Bonilla G, Chung S *et al.* Statin Use in Older Adults for Primary Cardiovascular Disease Prevention Across a Spectrum of Cardiovascular Risk. Journal of general internal medicine 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34505981

Comparing safety parameters between pitavastatin, atorvastatin and rosuvastatin users

Are Asians more susceptible to statins side effects than Caucasians, and are there clinically relevant differences between statins? These questions were addressed in a sub-analysis of the Taiwan National Health Insurance Research Database. Those that started treatment with atorvastatin, rosuvastatin, or pitavastatin and no diabetes were included. They were divided into three groups, 1. Pitavastatin 2-4 mg, 2. atorvastatin 10 and rosuvastatin 5-10 mg, and 3. Atorvastatin 20-40 mg and rosuvastatin 20 mg. The designated endpoint was a composite of hepatitis, myopathy, and new-onset diabetes (NODM). Patients were propensity score-matched based on age, sex, and year of recruitment. Each group consisted of 50 935 patients. The composite endpoint was observed 9.84% of the patients using pitavastatin and 10.88% plus 10.49% in the cohorts using low dosage and high dosage atorvastatin or rosuvastatin, respectively. The authors concluded that low dose statins, compared to pitavastatin, were associated with an increased risk for the composite endpoint (9.84% vs. 10.88%); HR: 1.12 (1.08-1.17). Noteworthy is that with the use of high-intensity statins, the risk of adverse events was higher (10.48%) compared to pitavastatin but lower compared to low dose statins, HR: 1.06 (1.02-1.10). No data were presented on LDL-c reductions in the three cohorts that would likely be less in the pitavastatin cohort than the high-dose statin users.
Lin JL, Chen PS, Lin HW *et al.* Real-World Analyses of the Safety Outcome among a General Population Treated with Statins: An Asian Population-Based Study. J Atheroscler Thromb 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34497171

Review of the first in class Lp(a) lowering drugs, Pelacarsen

Statins remain the well-established first choice for reducing LDL-c. Despite the impressive success of high-dose, high-intensity statins to significantly reduce ASCVD risk, residual risk remains a formidable challenge in very-high-risk patients. This review provides

clinicians with up-to-date information on a new lipid-lowering drug and even a new class of drugs targeting elevated Lp(a). Pelacarsen is the new kid on the block that uses a unique antisense oligonucleotide approach to block the synthesis of apolipoprotein (a) and the formation of Lp(a). the phase I and II studies showed that a monthly dose of pelacarsen resulted in impressive reductions of Lp(a) of > 50% and, depending on the dosage used, up to 80-90%. The safety profile of this new agent revealed no significant signals in terms of serious adverse events; injection site reactions were the most frequently reported complaints. A large phase III study is ongoing; the HORIZON study aims to evaluate MACE reductions in patients allocated to pelacarsen. In total, 7680 patients with established CVD and elevated Lp(a) (>70 mg/dl) will be included. The study is expected to be completed and published in 2024. Same in-class compounds are in the drug development pipeline. Olpasiran (AMG860) has successfully completed a phase I study showing similar impressive efficacy and safety parameters that persisted over 6 months after a single dose. Olpasiran uses siRNA technology to suppress apo (a) synthesis.

Hardy J, Niman S, Goldfaden RF *et al.* A Review of the Clinical Pharmacology of Pelacarsen: A Lipoprotein(a)-Lowering Agent. Am J Cardiovasc Drugs 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34490591

Switching to a polypill strategy for secondary prevention

Despite recent well-established guidelines on both blood pressure management and lipid control, a large percentage of very high-risk patients are sub-optimally or even not treated. Strategies to simplify pharmacological regimens have successfully shown that a fixed-dose combination pill could be an attractive alternative compared to single pill strategies. In this review and expert opinion-based guideline, the CNIC polypill and algorithms providing guidance on the practical implementation of a polypill-based risk-reducing strategy are presented and explained. The CNIC polypill was developed by the Spanish Centre for Cardiovascular Research (CNIC), headed by prof. Valentin Fuster. The polypill contains three main ingredients, two in different dosages: ASA (100 mg), ramipril (1.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The algorithm was developed by an expert panel from Spain, Germany, Portugal, and Greece. The primary focus is secondary prevention patients grouped by ACS and chronic coronary syndromes, including stroke and peripheral artery disease. Using the polypill strategy would provide better guideline dictated LDL-c and blood pressure goal achievement for patients not on target. Combining the polypill with additional drugs to reach targets is integrated into the algorithm. Patients with well-controlled risk factors would be helped by a simplified treatment strategy to reduce their pill burden. The suggested approach is not a one-size-fits-all solution but does provide substantial improvement for both adherence and achieving guidelines-endorsed targets. Availability of the CNIC polypill in local pharmacies would be an essential hurdle to address before

implantation on a large scale is realistically feasible.
Grigorian-Shamagian L, Edel K, Esteve-Pastor MA *et al.* Practical Decision Algorithms for the Use of the Cardiovascular Polypill in Secondary Prevention in Europe. Frontiers in cardiovascular medicine 2021; 8:663361. http://www.ncbi.nlm.nih.gov/pubmed/?term=34504874

Is atorvastatin the first-choice repurposed drug to improve COVID-19 outcomes

Innovative strategies to improve outcomes in COVID-19 patients that present with serious complications is expanding towards the repurposing of existing FDA approved drugs. Safe, effective, and affordable compounds that could change the course of the disease and reduce hospitalizations, ICU admission and death. A large transcriptomics database was queried for this study, and potential promising signals were combined with in vitro molecular docking analyses using lung organoid models. Over a 1000 FDA approved drugs were analysed and atorvastatin surfaced as one of the most promising candidates. Tests evaluated reduced transcriptional changes, effective binding to SARS-CoV-2 main protease and RNA-dependent polymerase as well as inhibiting viral entry into the organoid lung model. These fundamental studies are in congruence with small clinical trials as well as observational studies that showed protective effects of statins in general and specifically of atorvastatin to in COVID-19 patients admitted to hospital. The author's findings support the currently ongoing larger clinical trials to support their findings. The technology they developed could be similarly applied when confronted with future pandemics.
Duarte RRR, Copertino DC, Jr., Iñiguez LP *et al.* Identifying FDA-approved drugs with multimodal properties against COVID-19 using a data-driven approach and a lung organoid model of SARS-CoV-2 entry. Molecular medicine (Cambridge, Mass.) 2021; 27:105. http://www.ncbi.nlm.nih.gov/pubmed/?term=34503440

Relevant publications

1. Xu W, He Y, Zhang J *et al.* Simvastatin Blocks Reinstatement of Cocaine-induced Conditioned Place Preference in Male Mice with Brain Lipidome Remodeling. Neurosci Bull 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34491535

2. Sri Iswari R, Dafip M, Purwantoyo E. Malondialdehyde (MDA) Production in Atherosclerosis Supplemented with Steamed Tomato. Pak J Biol Sci 2021; 24:319-325. http://www.ncbi.nlm.nih.gov/pubmed/?term=34486316
3. Sanda K, Ayukawa Y, Yasunami N *et al.* Therapeutic effect of fluvastatin on medication-related osteonecrosis of the jaw. Journal of periodontology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34510440
4. Niedzielski M, Broncel M, Gorzelak-Pabiś P, Woźniak E. A comparison of the effects of monotherapy with rosuvastatin, atorvastatin or ezetimibe versus combination treatment with rosuvastatin-ezetimibe and atorvastatin-ezetimibe on the integrity of vascular endothelial cells damaged by oxidized cholesterol. PLoS One 2021; 16:e0256996. http://www.ncbi.nlm.nih.gov/pubmed/?term=34492054
5. Mathur S, Janaudis-Ferreira T, Hemphill J *et al.* User-centered design features for digital health applications to support physical activity behaviors in solid organ transplant recipients: A qualitative study. Clinical transplantation 2021:e14472. http://www.ncbi.nlm.nih.gov/pubmed/?term=34510558
6. Li Z, Luo Y, Zhang J. Atorvastatin pretreatment alleviate the ischemic brain injury linked to peroxisome proliferator-activated receptor coactivator-1α and angiogenic factors in diabetic mice. Neuro endocrinology letters 2021; 42:331-338. http://www.ncbi.nlm.nih.gov/pubmed/?term=34506097
7. Leal K, Saavedra K, Rebolledo C, Salazar LA. MicroRNAs hsa-miR-618 and hsa-miR-297 Might Modulate the Pleiotropic Effects Exerted by Statins in Endothelial Cells Through the Inhibition of ROCK2 Kinase: in-silico Approach. Frontiers in cardiovascular medicine 2021; 8:704175. http://www.ncbi.nlm.nih.gov/pubmed/?term=34485404
8. Laskus-Zakrzewska A, Kazimierczak P, Kolmas J. Porous Composite Granules with Potential Function of Bone Substitute and Simvastatin Releasing System: A Preliminary Study. Materials (Basel, Switzerland) 2021; 14. http://www.ncbi.nlm.nih.gov/pubmed/?term=34501158
9. Kale R, Shete P, Doifode D, Chitlange S. Analytical Method Development and Validation for Simultaneous Determination of Simvastatin and Mupirocin Using Reverse-Phase High-pressure Liquid Chromatographic Method. Turk J Pharm Sci 2021; 18:438-444. http://www.ncbi.nlm.nih.gov/pubmed/?term=34496550
10. Chen J, Yan J, Li S *et al.* Atorvastatin inhibited TNF-α induced matrix degradation in rat nucleus pulposus cells by suppressing NLRP3 inflammasome activity and inducing autophagy through NF-κB signaling. Cell Cycle 2021; 20:2160-2173. http://www.ncbi.nlm.nih.gov/pubmed/?term=34494933

Basic Science publications

1. Zhang X, Chen X, Liang Z *et al.* Pioglitazone combined with atorvastatin promotes plaque stabilization in a rabbit model. Vascular 2021:17085381211040992. http://www.ncbi.nlm.nih.gov/pubmed/?term=34470532
2. Wang C, Tang T, Wang Y *et al.* Simvastatin affects the PPARα signaling pathway and causes oxidative stress and embryonic development interference in Mugilogobius abei. Aquatic toxicology (Amsterdam, Netherlands) 2021; 239:105951. http://www.ncbi.nlm.nih.gov/pubmed/?term=34467877
3. Sanvee GM, Hitzfeld L, Bouitbir J, Krähenbühl S. mTORC2 is an important target for simvastatin-associated toxicity in C2C12 cells and mouse skeletal muscle - Roles of Rap1 geranylgeranylation and mitochondrial dysfunction. Biochem Pharmacol 2021; 192:114750. http://www.ncbi.nlm.nih.gov/pubmed/?term=34461118
4. Ren Y, Li L, Wang MM *et al.* Pravastatin attenuates sepsis-induced acute lung injury through decreasing pulmonary microvascular permeability via inhibition of Cav-1/eNOS pathway. Int Immunopharmacol 2021; 100:108077. http://www.ncbi.nlm.nih.gov/pubmed/?term=34464887
5. Mucha O, Podkalicka P, Kaziród K *et al.* Simvastatin does not alleviate muscle pathology in a mouse model of Duchenne muscular dystrophy. Skelet Muscle 2021; 11:21. http://www.ncbi.nlm.nih.gov/pubmed/?term=34479633
6. Le J, Liao Y, Li S *et al.* High-throughput LC-MS/MS Method for Simultaneous Determination of Pantoprazole and Atorvastatin in Rat Plasma: Application to a Pharmacokinetic Interaction Study. Current drug metabolism 2021; 22:481-490. http://www.ncbi.nlm.nih.gov/pubmed/?term=34455944
7. Gao Y, Li L, Yu J, Zhang Z. Rosuvastatin protects PC12 cells from hypoxia/reoxygenation-induced injury by inhibiting endoplasmic reticulum stress-induced apoptosis. Experimental and therapeutic medicine 2021; 22:1189. http://www.ncbi.nlm.nih.gov/pubmed/?term=34475979
8. El-Say KM, Ahmed TA, Aljefri AH *et al.* Oleic acid-reinforced PEGylated polymethacrylate transdermal film with enhanced antidyslipidemic activity and bioavailability of atorvastatin: A mechanistic ex-vivo/in-vivo analysis. Int J Pharm 2021; 608:121057. http://www.ncbi.nlm.nih.gov/pubmed/?term=34461173
9. Al Rijjal D, Liu Y, Lai M *et al.* Vascepa protects against high-fat diet-induced glucose intolerance, insulin resistance, and impaired β-cell function. iScience 2021; 24:102909. http://www.ncbi.nlm.nih.gov/pubmed/?term=34458694

10. Afrin S, El Sabeh M, Islam MS *et al.* Simvastatin modulates estrogen signaling in uterine leiomyoma via regulating receptor palmitoylation, trafficking and degradation. Pharmacol Res 2021; 172:105856. http://www.ncbi.nlm.nih.gov/pubmed/?term=34461224

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