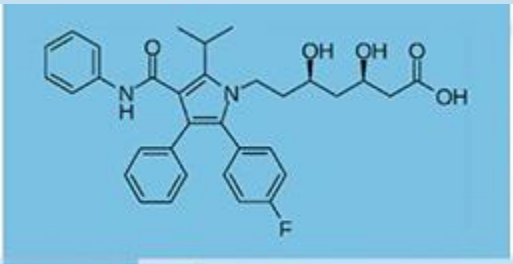
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 35, 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

How well are CEE health care providers managing LDL-cholesterol?

The DA-VINCI study aimed to evaluate the lipid management strategies of Central and Eastern European (CEE) health care providers. Over the last 20 years, economic advancements have improved healthcare in CEE, reflected by reductions in CVD mortality and morbidity. The countries included in this evaluation, the Czech Republic, Hungary, Poland, Romania, Slovakia, and Ukraine, have adopted the 2016 and 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines. How well are these guidelines implemented, and are patients in a primary and a secondary prevention setting reaching the recommended LDL-c goals? This cross-sectional observational study was

done between June 2017 and November 2019 (N=2154). Majority of the included patients used moderate (53%) or high intensity (32%) statins. The ESC/EAS recommended LDL-c targets were reached by 21% (Ukraine) - 50% (Hungary and Romania) of the patients. The more stringent 2019 ESC/EAS LDL-c targets were achieved by 24% of the overall population (11% in Ukraine – 32% in Poland). These findings underline the significant gap between guideline-recommended targets vs. the reality of clinical practice. Three-quarters of the participants failed to attain evidence-based LDL- recommendations and remained exposed to an avoidable increased risk of first or recurrent ASCVD events. Strategies to improve cholesterol management are urgently warranted to ensure a downward curve of ASCVD morbidity and mortality in CEE countries.

Vrablik M, Seifert B, Parkhomenko A *et al.* Lipid-lowering therapy use in primary and secondary care in Central and Eastern Europe: DA VINCI observational study. Atherosclerosis 2021; 334:66-75. http://www.ncbi.nlm.nih.gov/pubmed/?term=34482090

The impact of combining statins + ezetimibe in a single pill vs. a two-pill regimen

Managing LDL-c according to recent guidelines has become more challenging, whereby mono-therapy, similar as in hypertension management, is unlikely to enable patients to reach the updated LD-c targets. Adherence to medication that enables patients to lower their plasma LDL-c levels is notoriously poorly accepted. This retrospective observational study evaluated 256 012 patients from the Lombardy region in Italy to compare adherence to a single pill (N=5351) vs. a two-pill (N=2881) combination of statin + ezetimibe. The adherence was measured after 1-year as the proportion of days covered (PDC). This is the ratio between the number of days the drug was available and the days of follow-up. A PDC of > 75% was labeled as highly adherent and a PDC < 35 as poorly adherent to drug therapy. Patients that were prescribed a single pill had an 87% (75–99%) greater odds of being highly adherent and a 79% (72–84%) lower odds of being poorly adherent. Impressive was the noted 55% reduction in ASCVD events in highly adherent patients. These findings underline the impact of a simple strategy to combine a very effective and safe combination of statin + ezetimibe in a single formulation pill that would improve not only adherence but consequentially significantly reduce ASCVD events as well.

Rea F, Savaré L, Corrao G, Mancia G. Adherence to Lipid-Lowering Treatment by Single-Pill Combination of Statin and Ezetimibe. Adv Ther 2021; 38:5270-5285. http://www.ncbi.nlm.nih.gov/pubmed/?term=34480293

Initiation of statins after carotid artery stenting

In patients that needed a coronary stent procedure, statin therapy is a “conditio sine qua non.” The use of statins after the placement of carotid stenting lacks randomized placebo-

controlled trial evidence. This retrospective observational study in a single Chinese hospital re-evaluated the outcomes of patients that started with statins after their carotid stent placement vs. patients that did not initiate statin therapy. TheThe authors selected 100 patients from their registry, 50 individuals the started a statin post-intervention, and 50 patients that did not. All patients had an indication for carotid artery stent (CAS) placement, aged 20 – 75 years old. The outcome endpoints were degree of neurological defect (as measured by the National Institute of Health Stroke Scale), lipid profiles (mg/dL), and CAS complications <30days post-intervention. No differences were observed between the two groups for NIH Stroke Scale and mortality. Significant improvements were observed for total cholesterol (P=.03), LDL-c (P=.01), the risk for TIA (P=.03), ischemic stroke (P=.04), and cardiac complications (P=.03). These improvements were noted <30 days after the CAS procedure. These observational findings point toward the potential benefit of post CAS statin initiation for important cardiac and stroke outcomes. These findings do need to be confirmed in larger prospective studies to corroborate the suggested benefits.

Liu W, Zhao XF, Liang YL *et al.* A retrospective study on the preventive effect of statin after carotid artery stenting. Medicine (Baltimore) 2021; 100:e26201.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34477113

Patients with diabetic nephropathy showed significant improvement in renal function with atorvastatin

The benefit of atorvastatin in patients with diabetic nephropathy was studied in a small group of Chinese diabetic patients diagnosed with diabetic nephropathy. Patients were randomly assigned to atorvastatin 20 mg or control and followed for three months. The authors evaluated rheological parameters (whole blood viscosity, erythrocyte aggregation index, and fibrinogen), renal function biomarkers (macrophage migration inhibitory factor (MIF), vascular cell adhesion molecule (VCAM)-1, Secreted frizzled-related protein-5 (SFRP5), and mAlb/Cr) and inflammatory markers (C-reactive protein (CRP), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α)). Compared to the control group, blood viscosity, erythrocyte aggregation index, FIB, MIF, VACM-1, mAlb/Cr, CRP, IL-1, and TNF-α levels in the observation group significantly decreased. The levels of SERP-5 significantly increased (overall P<0.05). These findings show that atorvastatin could benefit patients with diabetic nephropathy by improving rheological parameters as well as renal function and inflammatory biomarkers.

Li R, Shi T, Xing E, Qu H. Atorvastatin calcium tablets on inflammatory factors, hemorheology and renal function damage indexes in patients with diabetic nephropathy. Pak J Med Sci 2021; 37:1392-1396. http://www.ncbi.nlm.nih.gov/pubmed/?term=34475918

Should aspirin be included in the fixed dose poly-pill?

The burden of CVD disease is increasing exponentially in developing economies; the impact on human suffering and the economic burden is unprecedented and will continue to grow exponentially if measures to improve risk factors causally associated with ASCVD are properly managed. The models used in developed economies are not applicable for the poorer regions of the world due to lack of infrastructure, trained staff, and costs for such sophisticated health care infrastructure. Alternative simple and low-cost approaches are needed to turn the tide of exploding ASCVD in not seldom relatively young patients. The polypill concept was developed to provide individuals at risk, based on age and sex, a cheap, safe, and effective solution to adequately lower blood pressure and LDL cholesterol. This meta-analysis combined the findings of three large poly pill studies (TIPS-3, HOPE-3, and PolyIran) that included 18 162 participants. The key question of this meta-analysis was if the addition of aspirin to a fixed-dose single pill formulation would improve outcomes or if this would increase bleeding complications. The primary outcome was the time to the first occurrence of a composite of cardiovascular death, myocardial infarction, stroke, or arterial revascularization. Secondary outcomes included individual cardiovascular outcomes and death from any cause. The estimated 10-year ASCVD risk was 17·7% (8·7). The median follow-up was 5 years. The primary was observed in 276 (3·0%) participants that used the polypill, compared with 445 (4·9%) in the control group; HR: 0·62 (0·53–0·73, p<0·0001). myocardial infarction HR: 0·52 (0·38–0·70); revascularization HR: 0·549 (0·36–0·80), stroke HR: 0·59, (0·45–0·78), and cardiovascular death HR: 0·65 (0·52–0·81). Patients that used an aspirin-containing poly-pill showed greater reduction when compared to patients in whom aspirin was not part of their polypill. No differences were observed for different lipid, blood pressure levels and in the presence or absence of diabetes, obesity, or smoking. Bleeding complications in aspirin users were uncommon; GI bleeds in 19 (0.4%) in patients using aspirin vs. 11 (0.2%) in those that did not (p=0.15). Hemorrhagic stroke, fatal bleeding and peptic ulcer were rarely experienced; 10 (0·2%) vs 15 (0·3%), 2 (<0·1%) vs 4 (0·1%) and 32 (0·7%) vs 34 (0·8%), respectively. Using a fixed-dose combination polypill is an effective strategy to reduce fatal and non-fatal ASCVD events in primary prevention. Low costs and wide applicability make this an attractive and realistic approach to reducing the imminent ASCVD complications surge in developing economies.

Joseph P, Roshandel G, Gao P *et al.* Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis. Lancet 2021; 398:1133-1146.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34469765

Relevant publications

1. Zhang X, Chen Y, Tong N *et al.* Maternally inherited diabetes and deafness coexists with lipoprotein lipase gene mutation-associated severe hyperlipidemia that was resistant to fenofibrate and atorvastatin, but sensitive to bezafibrate: A case report. Journal of diabetes investigation 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34460997
2. Xenogiannis I, Zenati M, Bhatt DL *et al.* Saphenous Vein Graft Failure: From Pathophysiology to Prevention and Treatment Strategies. Circulation 2021; 144:728-745. http://www.ncbi.nlm.nih.gov/pubmed/?term=34460327
3. Wei J, Liao JK, Bairey Merz CN. Challenging Statin Pleiotropy: Preeclampsia. Circulation 2021; 144:680-683. http://www.ncbi.nlm.nih.gov/pubmed/?term=34460319
4. Wang QN, Bao XY, Zou ZX *et al.* The role of atorvastatin in collateral circulation formation induced by encephaloduroarteriosynangiosis: a prospective trial. Neurosurg Focus 2021; 51:E9. http://www.ncbi.nlm.nih.gov/pubmed/?term=34469867
5. Venkataraman P, Huynh Q, Nicholls SJ *et al.* Impact of a coronary artery calcium-guided statin treatment protocol on cardiovascular risk at 12 months: Results from a pragmatic, randomised controlled trial. Atherosclerosis 2021; 334:57-65. http://www.ncbi.nlm.nih.gov/pubmed/?term=34482089
6. Tomoi Y, Soga Y, Imada K *et al.* Use of Proprotein Converse Subtilisin/Kexin Type 9 Inhibitor to Treat Cholesterol Crystal Embolisms after Catheterization: A Report of Three Cases. Intern Med 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34471031
7. Tokgozoglu L, Kayikcioglu M. Familial Hypercholesterolemia: Global Burden and Approaches. Current cardiology reports 2021; 23:151. http://www.ncbi.nlm.nih.gov/pubmed/?term=34480646
8. Sharma KK, Natani V, Gupta N *et al.* Statins in Patients with Uncomplicated Hypertension: A Prescription Audit. The Journal of the Association of Physicians of India 2021; 69:11-12. http://www.ncbi.nlm.nih.gov/pubmed/?term=34470187
9. Shah T, McCarthy M, Nasir I *et al.* Design and rationale of the colchicine/statin for the prevention of COVID-19 complications (COLSTAT) trial. Contemporary clinical trials 2021:106547. http://www.ncbi.nlm.nih.gov/pubmed/?term=34461322
10. Sardari S, Fallahi F, Emadi F *et al.* Daily Consumption of Caper Fruit Along With Atorvastatin Has Synergistic Effects in Hyperlipidemic Patients: Randomized Clinical Trial. Galen Med J 2019; 8:e1345. http://www.ncbi.nlm.nih.gov/pubmed/?term=34466497
11. Saeed A, Zhu J, Thoma F *et al.* Cardiovascular Disease Risk-Based Statin Utilization and Associated Outcomes in a Primary Prevention Cohort: Insights From a Large Health Care Network. Circ Cardiovasc Qual Outcomes 2021; 14:e007485. http://www.ncbi.nlm.nih.gov/pubmed/?term=34455825

12. **Plutzky J, Benson MD, Chaney K *et al.* Population health management of low-density lipoprotein cholesterol via a remote, algorithmic, navigator-executed program. Am Heart J 2021; 243:15-27.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34481756
13. **Moledina SM, Shoaib A, Sun LY *et al.* Impact of the admitting ward on care quality and outcomes in non-ST-segment elevation myocardial infarction (NSTEMI): insights from a national registry. European heart journal. Quality of care & clinical outcomes 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34482404
14. **Kobayashi N, Shibata Y, Kurihara O *et al.* Impact of Low Body Mass Index on Features of Coronary Culprit Plaques and Outcomes in Patients With Acute Coronary Syndrome. Am J Cardiol 2021; 158:6-14.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34465460
15. **Karvaly GB, Karádi I, Vincze I *et al.* A pharmacokinetics-based approach to the monitoring of patient adherence to atorvastatin therapy. Pharmacol Res Perspect 2021; 9:e00856.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34478238
16. **Haque W, Grandhi GR, Kanaya AM *et al.* Implications of the 2019 American College of Cardiology/American Heart Association Primary Prevention Guidelines and potential value of the coronary artery calcium score among South Asians in the US: The Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. Atherosclerosis 2021; 334:48-56.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34481175
17. **Han D, Kuronuma K, Rozanski A *et al.* Implication of thoracic aortic calcification over coronary calcium score regarding the 2018 ACC/AHA Multisociety cholesterol guideline: results from the CAC Consortium. Am J Prev Cardiol 2021; 8:100232.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34467259
18. **Eid WE, Sapp EH, Flerlage E, Nolan JR. Lower-Intensity Statins Contributing to Gaps in Care for Patients With Primary Severe Hypercholesterolemia. J Am Heart Assoc 2021; 10:e020800.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34465130
19. **Cilla A, López-García G, Collado-Díaz V *et al.* Hypercholesterolemic patients have higher eryptosis and erythrocyte adhesion to human endothelium independently of statin therapy. Int J Clin Pract 2021:e14771.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34473881
20. **Chiang CW. Meta-analysis Comparing the Effect of Combined Omega-3 + Statin Therapy Versus Statin Therapy Alone on Coronary Artery Plaques. Am J Cardiol 2021; 158:149-150.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34465459
21. **Campbell PJ, Axon DR, Taylor AM *et al.* Hypertension, cholesterol and diabetes medication adherence, health care utilization and expenditure in a Medicare Supplemental sample. Medicine (Baltimore) 2021; 100:e27143.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34477169

22. Marti JLG, Beckwitt CH, Clark AM, Wells A. Atorvastatin facilitates chemotherapy effects in metastatic triple-negative breast cancer. Br J Cancer 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34462586
23. Kessing LV. Incomplete systematic review and meta-analysis on statin use and depression risk - A commentary. Journal of affective disorders 2021; 295:215. http://www.ncbi.nlm.nih.gov/pubmed/?term=34481149
24. Blaum C, Brunner FJ, Goßling A *et al.* Target Populations and Treatment Cost for Bempedoic Acid and PCSK9 Inhibitors: A Simulation Study in a Contemporary CAD Cohort. Clinical therapeutics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34462126
25. Anderson K, Nelson CH, Gong Q *et al.* Assessment of the Effect of Filgotinib on the Pharmacokinetics of Atorvastatin, Pravastatin, and Rosuvastatin in Healthy Adult Participants. Clinical pharmacology in drug development 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34468080

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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