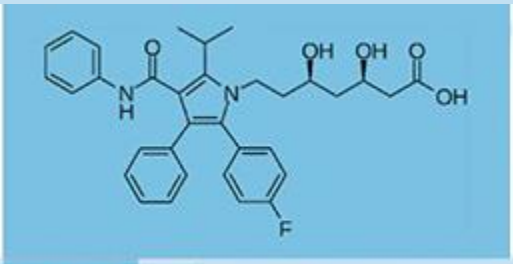
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 43 & 44, 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

Anti-inflammatory effects of statins confirmed by genetic polymorphisms

Inhibition of cholesterol synthesis upstream of the 25-step pathway impacts the downstream steps and several crucial proteins. The impact of statins on LDL-c is self-evident, but inflammation remains a debated issue. Are anti-inflammatory effects of statins clinically relevant? A new perspective is provided by examining the impact of genetic polymorphisms of the HMG-CoA-reductase gene on ankylosing spondylitis (AS). Data collected in five genome-wide association study (GWAS) datasets on ankylosing spondylitis from diverse ethnic backgrounds were queried for genetically fueled effects on LDL-c as a

proxy for HMG-CoA inhibition. Each 1.0 mmol/L lower LDL-c was associated with almost a 50% reduction of AS risk; OR, 0.57 (0.38–0.85; P-value = 5.7x10-3). Similar genetic scores were used to evaluate the PCSK9 gene; OR, 0.89 (0.68–1.16) and the NPC1L1 gene; OR, 1.50 (0.39–5.77). They indicate no protective effects of LDL-c lowering related to polymorphisms in these two genes. These genetic estimates were in line with studies that evaluated the clinical benefits of long-term statin use on AS and could indicate a novel therapeutic approach for this debilitating disease. Zhong Z, Feng X, Su G *et al.* HMG-Coenzyme A Reductase as a Drug Target for the Prevention of Ankylosing Spondylitis. Front Cell Dev Biol 2021; 9:731072. http://www.ncbi.nlm.nih.gov/pubmed/?term=34692687

Lowering LDL-c in a young boy with compound heterozygous FH

The challenges of managing a young boy with a compound heterozygous Familial Hypercholesterolemia (FH) phenotype patient is shared in this case report of a 10-year-old Bulgarian boy. Presenting with the pathogenomic physical features of severe FH, xanthomas on the knee and elbow in combination with severely elevated LDL-c (15 mmol/L) and a family history of both premature atherosclerosis and hypercholesterolemia. Noteworthy is the high plasma concentration of Lp(a) (270 mg/dL) that could not only promote atherosclerosis but increase thrombotic risk as well. Guidelines recommend LDL-apheresis for these severe cases of FH, but this treatment was unavailable in Bulgaria. Using a step-wise approach, LDL-c lowering treatments were intensified, using high dose high-intensity statin, Ezetimibe, and finally evolocumab 140 mg. bimonthly. LDL-c was reduced by 53% and a plasma level of 3 mmol/L. No Lp(a) changes were observed in contrast with observations in two extensive PCSK9ab outcome studies where patients who used PCSK9ab lowered their Lp(a) by 20-30%. This case illustrates that severe compound heterozygous FH patients using a triple therapy of statins, Ezetimibe, and PCSK9ab can successfully reduce plasma LDL-c. Novel therapeutic strategies such as inclisiran and LDL-receptor independent treatment, reducing ANGPTL3 or CETP inhibitors could be even more effective for patients with this uncommon clinical presentation. Vladimirova-Kitova L, Kitov S, Ganev M, Chochkova-Bukova L. Case Report: Difficulties in the Treatment of a 12-Year-Old Patient With Homozygous Familial Hypercholesterolemia, Compound Heterozygous Form - 5 Years Follow-Up. Frontiers in cardiovascular medicine 2021; 8:743341. http://www.ncbi.nlm.nih.gov/pubmed/?term=34692794

Systematic review of the anti-inflammatory effects of statins

This systematic review explored the available evidence that indicates not only a lipid-lowering benefit of statins but also anti-inflammatory properties. Of the 51 787 flagged articles, a total of 12 randomized controlled studies were included in the final analysis. Three large literature databases were queried using Medical Subject Headings (MeSH) for

Inflammatory Biomarkers, Erythrocyte Sedimentation Rate (ESR), High Sensitivity C-Reactive Protein (Hs-CRP), Statin Therapy, HMG-CoA Reductase Inhibitors, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Overall, statins were shown to exhibit anti-inflammatory properties. The most robust evidence was observed for high dose atorvastatin; low and moderate-intensity statins showed significant reductions in inflammatory biomarkers but to a lesser extent. The use of dual lipid-lowering strategies and combining anti-inflammatory agents with statins was also associated with a reduction in systemic inflammation.

Proute MC, Kothur N, Georgiou P *et al.* The Effect of Statin Therapy on Inflammatory Biomarkers: A Systematic Review. Cureus 2021; 13:e18273.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34722051

Single pill formulations effective to reach target BP and LDL-c

Combining anti-hypertensive and cholesterol-lowering drugs in a single pill formulation is gaining traction. In this "real world" study, using clinical data from three Korean tertiary hospitals, the safety, and efficacy of commonly used anti-hypertensive and cholesterol-lowering drugs were evaluated. A total of 15 538 hypertensive patients received single-pill combination (SPC) therapy with amlodipine/losartan (AL); amlodipine/losartan/rosuvastatin (ALR) and amlodipine/losartan/chlorthalidone (ALC). Primary endpoints were achieved targets of blood pressure and LDL-c. Drug adherence was also evaluated and defined as the proportion of days covered (PDC). Blood pressure targets were achieved in all three groups and reached >90%. Patients using AL or ALC were using statins; however, the attainment of the LDL-c targets was superior in patients who used ALR. Safety endpoints were unremarkable; only uric acid and uricemia were significantly lower in the AL and ALR groups compared to ALC patients. Compliance was excellent with a PDC count > 90% in all groups. The ALR combination seemed superior in achieving recommended BP and LDL-c targets and excellent compliance.

Lee J, Choi J, Yum Y *et al.* Clinical effectiveness and safety of amlodipine/losartan-based single-pill combination therapy in patients with hypertension: Findings from real-world, multicenter observational databases. Journal of clinical hypertension (Greenwich, Conn.) 2021; 23:1975-1983. http://www.ncbi.nlm.nih.gov/pubmed/?term=34714968

Are British FH patients receiving adequate LDL-c therapy?

Over the last decade, attention for screening and treating patients with Familial Hypercholesterolemia (FH) has intensified. Major scientific meeting publications and guidelines provided ample evidence on the importance of aggressive LDL-c management. To evaluate if this is reflected in how FH patients are treated in a real-world setting, the UK Clinical Practice Datalink (CPRD) was queried. This registry includes approximately 15% of

the UK population. Three thousand sixty-four adults were diagnosed with FH and had repeated LDL-c measurements. The guideline recommendation to aim for >50% LDL-c reduction in 12 months was attained by 895 individuals (29.2%). The FH patients in this category were older at time of diagnosis (53.4 years vs. 49.7 years) and first statin treatment (53.2 years vs. 49.2 years); predominantly female, and had a higher pre-treatment LDL-c (5.83 (SD 1.36) mmol/L vs. 5.25 (SD 1.40) mmol/L). High and medium potency statins were prescribed more frequently as well; 71.7% vs. 24.3% and 69.3% vs. 20.2%, respectively. The findings of this national registry reveal that guideline-recommended LDL-c management of adult FH patients is far from what we expect; less than 40% are using high-intensity statins and two-thirds fail to reach the >50% recommended LDL-c reduction. Greater awareness and treatment optimization are urgently needed to ensure adequate lipid management in these very-high risk individuals.

Iyen B, Akyea RK, Weng S *et al.* Statin treatment and LDL-cholesterol treatment goal attainment among individuals with familial hypercholesterolaemia in primary care. Open heart 2021; 8. http://www.ncbi.nlm.nih.gov/pubmed/?term=34702779

Relevant publications

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2. **Grundy SM, Vega GL. Statin Intolerance and Noncompliance: An Empiric Approach. Am J Med 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34717898
3. **Soltani F, Janatmakan F, Jorairahmadi S *et al.* Evaluation of the Effect of Atorvastatin Administration on the Outcomes of Patients with Traumatic Brain Injury: A Double-blinded Randomized Clinical Trial. Anesth Pain Med 2021; 11:e117140.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34692441
4. **Khan N, Bernstein D. Statin-induced drug reaction with eosinophilia and systemic symptoms. Ann Allergy Asthma Immunol 2021.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34732377
5. **Oliveira-Junior SA, Carvalho MR, Mendonça MLM, Martinez PF. Anti-Inflammatory Effects of Atorvastatin Therapy in Metabolic Syndrome. Arquivos brasileiros de cardiologia 2021; 117:748-749.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34709301

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cardiovascular medicine (Hagerstown, Md.) 2021; 22:680-685. http://www.ncbi.nlm.nih.gov/pubmed/?term=34714258

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