



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

Severe AS vascular changes observed in FH patients

The increased ASCVD risk in Familial Hypercholesterolemic (FH) patients is well recognized, but the focus has been on the age of first events. In this retrospective analysis of 120 FH patients hospitalized for CAG, angiographic features were compared to non-FH patients (N=234). Patients were matched for sex, age, and diabetes. Those with FH showed increased AS manifestations (SYNTAX score). They had more often multivessel disease (P=0.004), multiple complex lesions (P=0.022), and significant stenosis location on left circumflex and right coronary arteries, more multiple lesions, with an increased rate of bifurcation lesions or calcifications (P = 0.021 and P = 0.036, respectively). LDL-cholesterol and age were independently associated with anatomical complexity of coronary lesions, OR: 1.948 (1.090–3.480, P = 0.0240 and OR:1.035 (1.014–1.057, P = 0.001) respectively. In FH patients, LDL-c was elevated, with a mean value of 208 mg/dL (174-234 mg/dL), and less than half of these patients were using statin therapy. These findings underline the need for more aggressive lipid-lowering interventions and preventive management strategies.

Yao H, Farnier M, Tribouillard L *et al.* Coronary lesion complexity in patients with

heterozygous familial hypercholesterolemia hospitalized for acute myocardial infarction: data from the RICO survey. *Lipids Health Dis* 2021; 20:45.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=33947397>

Evaluating LDL particles based on size and TG content

Lipid metabolism contains multiple levels of complexity that are not always fully understood by health care professionals managing patients with abnormal plasma lipids. In this post hoc analysis of the Japanese patients enrolled in the diabetes regional cohort study (ViNA cohort), 1085 diabetic participants were evaluated for LDL-TG and sdLDL plasma concentrations. Patients in the highest LDL-TG quartile were more likely to be female or using fibrates. The top quartile of sdLDL was associated with male sex, alcohol consumption, and characteristics of the metabolic syndrome. Correlations between high LDL-TG concentrations and smoking, alcohol consumption, and apo B, the latter being the primary determinant. LDL-TG showed a strong correlation with hsCRP plasma levels, independent of other lipid fractions. Mean plasma concentrations of LDL-TG were not affected by fasting/non-fasting. Statin uses reduced LDL-TG in contrast with fibrates that increased LDL-TG; both drugs reduced sdLDL equally. The authors suggested that LDL-TG concentrations were regulated by the number of LDL particles, not by plasma TG concentrations. LDL-TG and sdLDL had different metabolic properties; low-grade systemic Inflammation showed a stronger association with LDL-TG, whereas higher sdLDL was associated with increased metabolic syndrome features.

Hirano T, Kodera R, Hirashima T *et al.* Metabolic Properties of Low density Lipoprotein (LDL) Triglycerides in Patients with Type 2 Diabetes, Comparison with Small Dense LDL-Cholesterol. *J Atheroscler Thromb* 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33952832>

Legacy effect observed after 8.7 years in HOPE-3 study

The primary prevention Heart Outcomes Prevention Evaluation (HOPE)-3 study evaluated the effects of rosuvastatin 10 mg vs. placebo and 16 mg of candesartan combined with 12.5 mg of hydrochlorothiazide vs. placebo. After 5.6 years, the trial stopped, and rosuvastatin was associated with a 24% reduction of MACE. The observed mean BP reduction of 6 mm Hg showed no difference in MACE outcomes between the treated patients and the ones assigned a placebo in the overall group but only in the patients with elevated BP. This report shows the results after an additional 3.1-year follow-up (in total 8.7 years) to determine the benefits in patients that were randomized to the treatment arms vs. the ones that had placebo. The primary endpoints in this extended follow-up were MACE-1 (the composite of myocardial infarction, stroke, or CV death (major adverse cardiovascular event) and MACE-2 (MACE-1 plus resuscitated cardiac arrest, heart failure, or coronary revascularization). Of the 11 994 original participants, 9326 (78%) consented to participate in

the follow-up. Patients assigned to rosuvastatin 10 mg experienced an additional 20% reduction in MACE-1 and 17% lower risk for AMC-2 complications. Resulting in an overall MACE-1 risk reduction of 21% (0.69-0.89; p=0.005) and 21% lower risk for MACE-2 (0.69-0.89; p=0.002). Blood pressure-lowering benefits were absent in both the initial study as well as during the 3.1-year follow-up period; however, a 24% reduced MACE-1 risk was observed over the 8.7 years of follow-up. The authors concluded that a legacy effect was responsible for the improved outcomes observed both for rosuvastatin and candesartan + hydrochlorothiazide in patients that were followed for an additional three years after cessation of the randomized treatment. Noteworthy is that only 37% of the HOPE-3 participants were prescribed statin therapy after the end of the active phase of the study. Bosch J, Lonn EM, Jung H *et al.* Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants. *Eur Heart J* 2021.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=33963372>

Do end stage renal disease patients benefit from statins?

The use of statins in patients with advanced renal disease remains enigmatic, promoted, and disputed based on conflicting evidence from trials designed to clarify this dilemma. This review presents the data from the 4 large studies that included end-stage renal disease patients, the 4 D (RCT using atorvastatin 20 mg vs. placebo), the AURORA trial (RCT using rosuvastatin 10 mg vs. placebo), the SHARP study (RCT comparing simvastatin 20 mg + ezetimibe 10 mg vs. placebo) and the Jung study, a retrospective cohort of 65 404 dialysis patients, 41 549 (73.2%) using statins or statins + ezetimibe. Both AURORA and the 4D study failed to show improved outcomes in the patients that received statins, in contrast with the SHARP and Jung studies where the use of statins (+ ezetimibe) in end-stage renal disease patients was associated with a reduction in MACE (SHARP) and improved survival (Jung registry). The authors noted that the dosage of rosuvastatin and atorvastatin was lower than commonly prescribed for the prevention of ASCVD events, 20-40 and 40-80 mg, respectively. Further studies are warranted to clarify if more intensive lipid-lowering by using higher dosages or by adding ezetimibe would benefit end-stage renal disease patients.

Abdelnabi M, Eshak N, Almaghraby A *et al.* Usefulness of statins in end-stage renal disease. *Proceedings (Baylor University. Medical Center)* 2021; 34:361-363.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=33953460>

Statins show promising outcomes in liver transplant patients

In this retrospective analysis of 672 primary orthotopic liver transplants (OLT) performed between January 2014 and December 2019, the effect of statin use on VTE risk, hepatic

artery complications, graft failure, and death were evaluated. The 80 patients (11.9 %) that used statins were compared with the 592 patients that did not take statins. Overall, VTE events were observed in 47 (7.0%) of patients, Hepatic artery complications in 40 (6.0%). Graft failure occurred in 42 (6.1) patients, and 61 (9.1%) died. In patients that used statins, VTE complications were not observed; VTE 's were observed in 7.9% of patients not using statins. A similar trend was noted for hepatic artery complications, 1.2% vs. 6.8%; hyperlipidemia was associated with a 2.1-fold increase in the risk for this complication (P=0.05). The combination of thrombotic-free survival (absence of DVT, PE, CAM, MI, HAC, and death) was statistically significantly better in statins users (90%) vs. those that were not using statins 73.9%); HR: 0.37 (P=0.001). The methodological limitation of this study does not allow to draw cause-effect conclusions but warrant prospective studies to examine the consequences of statin use in liver transplant patients.

Frasco PE, Aqel B, Alvord JM *et al.* Statin therapy and the incidence of thromboembolism and vascular events following liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2021.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=33964102>

Relevant publications

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Basic Science publications

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