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The IAS statin literature update will keep you up-to-date with all recent statin publications, using a curated approach to select relevant articles.

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## Key publications

### Are statins safe, beneficial in haemorrhagic stroke patients?

In this retrospective observational cohort study, patients presented with an intracerebral hemorrhagic stroke (ICH) to a single Portuguese stroke unit over one year were selected for this evaluation. The aim was to explore the effects of pre-ICH statin use vs. no statin and stopping, or continuing statins in patients admitted for ICH statin on functional outcomes and 30-day mortality. Of the 78 included patients, statin use was noted prior to admission in 33 (42.31%); 13 (39.39%) continued statins during hospitalization. Overall, 11 (14.10%) patients had good functional outcomes, and 16 (20.51%) patients died during the first 30 days. No differences in functional outcomes were observed between the groups. Mortality was significantly improved in patients with statins on-board (N=2, 6.06%) vs. patients that did not use statins (N=14, 31.11%),  $p=0.009$ . After multivariate analysis, no significant difference in mortality between the two groups could be discerned. Comparing patients that continued statins to patients that stopped statins during their hospital stay, no statistically significant difference in functional outcomes was observed. No patients died in the group that continued statins, vs. two patients (10%) that stopped statins ( $p=0.02$ ). The results of this study are in line with earlier reports that statin used before ICH and continuing statins during hospitalization is not associated with worse ICH outcomes, as suggested in the

SPARCL study. The benefits of statins beyond their cholesterol-reducing effects are likely to contribute to these observed benefits. The observational, retrospective design of this study and the small number of patients require more extensive prospective studies to confirm the benefits of statins in ICH patients.

Silva Marques J, Ennis G, Venade G *et al.* Association of Statins With Functional Outcome and 30-Day Mortality in Patients With Intracerebral Hemorrhage. *Cureus* 2021; 13:e14421. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33987069>

## Meta-analysis of statin and non-statin LDL-c lowering drugs on stroke events

This meta-analysis explores the effects of LDL-c reducing interventions and stroke risk. Using a meta-regression analysis model, the linear associations between achieved LDL-c and strokes were charted. In total, 23 trials (N=222 149) were included in the final analysis. For each mmol/L LDL-c decrease a 23.5% lower stroke risk was observed (slope 0.235 (0.007–0.464), P 0.044). No threshold effect was noted, down to 0.78 mmol/l (39.5 mg/dL). In this meta-analysis, studies using PCSK9ab and ezetimibe were included, and similar reductions in stroke risk were observed in trials that evaluated this non-statin lipid-lowering drugs. Observed reductions in stroke risk were irrespective of achieved LDL-c in the treatment arms and significant and consistent (test for subgroup difference, P 0.23, I<sup>2</sup> 31%). No significant increase in hemorrhagic stroke risk, in line with achieved lower LDL-c levels, was observed. The authors concluded that based on the findings in this meta-analysis, lowering LDL-c even to a very low level reduces stroke events. Additional non-statin LDL-cholesterol lowering drugs such as ezetimibe or PCSK9 inhibitors could be used to reduce LDL-c levels further to decrease the risk of stroke events.

Shin J, Chung JW, Jang HS *et al.* Achieved low-density lipoprotein cholesterol level and stroke risk: A meta-analysis of 23 randomised trials. *Eur J Prev Cardiol* 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33978157>

## Fewer CV events in diabetic stroke patients (TST study) reaching LDL-c <70 mg/dL

In this sub-analysis of the Treat Stroke to Target study, diabetic vs. non-diabetic ischemia stroke patients that achieved an LDL-c <100 mg/dL vs. <70 mg/dL were compared. The primary outcome was the composite of ischemic stroke, myocardial infarction, new symptoms requiring urgent coronary or carotid revascularization, and vascular death. Of the 2 860 patients included in the TST study, 643 were diabetics. After a median follow-up time of 3 years, the composite endpoint occurred in 27/860 (8.2%) of the diabetic patients that reached lower LDL-c, vs. 44/135 (14.0%) participants with a higher LDL-c target. Adjusted HR: 0.56 (0.34-0.89; p=0.016). The aHR in non-diabetic patients was 0.87 (0.66-1.14; p=0.31). Intracranial hemorrhages were observed in 3 diabetic patients, 0.9% and 1% in both

treatment groups, respectively. The risk for new-onset diabetes (NODM) was increased in the patients reaching lower LDL-c levels, 90/1070 (9.2%) and in 80/1085 (7.4%), respectively. Adjusted HR: 1.27 (0.94-1.71; P=0.11) HbA1c was the unique multivariable predictor of NODM risk. Reaching a lower LDL-c of 70 mg/dL vs. 100 mg/dL improved outcomes in both diabetic and non-diabetic patients. Overall, the higher ASCVD risk in diabetic patients was associated with a greater absolute risk reduction reflected by an NNT of 17.

Amarencu P, Kim JS, Labreuche J *et al.* Impact of lower vs higher LDL cholesterol targets on cardiovascular events after ischemic stroke in diabetic patients. *Diabetes* 2021.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=33980690>

### **In the HOPE-3 study reducing BP and cholesterol halves stroke risk**

In this predefined sub-analysis of the HOPE-3 (Heart Outcomes Prevention Evaluation–3) trial, the benefits of combined blood pressure and cholesterol-lowering medication on the primary prevention of stroke in individuals at intermediate CV risk were evaluated. The HOPE-3 study included 12 705 individuals from 21 countries with CV risk factors but without signs or symptoms of CV disease. The study randomized patients to candesartan 16 mg + hydrochlorothiazide 12.5 mg or placebo and rosuvastatin 10 mg or placebo, in a 2-by-2 factorial design. For this sub-analysis, stroke subtypes were scored. After a mean follow-up period of 5.6 years, baseline blood pressure (138/82 mm Hg) was reduced by 6.0/3.0 mm Hg. In addition, baseline LDL-c (3.3 mmol/L) was reduced by 0.90 mmol/L. A total of 169 strokes were recorded during the study: 117 ischemic, 29 hemorrhagic, and 23 strokes of undetermined origin. The blood-pressure-lowering effects did not result in a statistically significant reduction in the primary endpoints; stroke HR: 0.80 (0.59–1.08); ischemic stroke HR: 0.80 (0.55–1.15); hemorrhagic stroke HR: 0.71 (0.34–1.48), and strokes of undetermined origin HR: 0.92 (0.41–2.08). In contrast with LDL-c reduction using rosuvastatin; strokes HR: 0.70 (0.52–0.95), with reductions mainly in ischemic stroke HR: 0.53 (0.37–0.78) but no significant effect on hemorrhagic strokes HR: 1.22 (0.59–2.54) or strokes of undetermined origin HR: 1.29 (0.57–2.95). When comparing the combined effects of blood pressure and cholesterol-lowering to double placebo, both strokes HR: 0.56 (0.36–0.87) and ischemic strokes HR: 0.41 (0.23–0.72) were substantially reduced. Based on the data collected in the HOPE-3 study, the authors concluded that patients at intermediate CV risk using a combination of small dose, safe, and well-tolerated blood pressure-lowering medications plus rosuvastatin 10 mg, were able to reduce their risk for a debilitating first ischemic stroke by 59%.

Bosch J, Lonn EM, Dagenais GR *et al.* Antihypertensives and Statin Therapy for Primary Stroke Prevention: A Secondary Analysis of the HOPE-3

Trial. *Stroke* 2021:Strokeaha120030790. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33985364>

### **A paradigm shift in clinical reasoning and CVD prevention**

In this editorial essay, Allan Sniderman presents eloquent arguments for why earlier primary

prevention lipid-lowering interventions make sense. Using risk CVD calculators fails because age is one, if not the most important, risk driver. The 10-year risk of a young patient with treatable increased LDL-c is not very high and rarely reaches threshold levels. Postponing treatment might seem an acceptable alternative if not almost half of all ASCVD events occur before age 60, and very few who experience this (fatal ) complication would have been eligible for statin therapy. The limitations of our prevention strategies based on (short-term) risk prediction seem to fail in primary prevention, prompting the need for alternative approaches to improve individual outcomes and address the alarming trend of CV events increases in developing economies. Sniderman presents four considerations to take into account when deciding to initiate statins; 1. Think longer-term, calculating the 30-year risk can provide a better perspective for an individual patient. 2. Think particles, not just lipids. Measuring apo B is a more accurate risk predictor than LDL-c. 3. Think causes-benefits, not just risk. risk is determined by baseline risk and baseline level of atherogenic lipoproteins 4. Doubt and the status quo. The LDL-c target continues to be the leading primary measure in therapeutic care despite the accepted superiority of apo B. This viewpoint is illustrated with a case example illustrating how this approach can be implemented in clinical practice.

Allan S, Pencina M, Thanassoulis G. Clinical reasoning and prevention of cardiovascular disease. *J Clin Lipidol* 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33992590>

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## Relevant publications

1. Yamashita S, Masuda D, Harada-Shiba M *et al*. Effectiveness and Safety of Lipid-Lowering Drug Treatments in Japanese Patients with Familial Hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) Study. *J Atheroscler Thromb* 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33980760>
2. van Zelst CM, de Boer GM, Türk Y *et al*. Association between elevated serum triglycerides and asthma in patients with obesity: An explorative study. *Allergy Asthma Proc* 2021; 42:e71-e76. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33980342>
3. Tessier CM, Polyzos SA, Athyros VG, Mantzoros CS. Long-term statin treatment for hepatic fibrosis in patients with nonalcoholic fatty liver disease: Is it time to give the emperor a statin robe? *Metabolism* 2021:154796. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33989632>
4. Cheung KS, Mak LY, Lam LK *et al*. Statins associate with better clinical outcomes in chronic hepatitis B patients with HBsAg seroclearance. *Hepatol Int* 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33988834>
5. Talasaz AH, Sadeghipour P, Aghakouchakzadeh M *et al*. Lipid-Modulating Agents for Prevention or Treatment of COVID-19 in Randomized Trials. *medRxiv* 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33972948>

6. Škorňová I, Samoš M, Bolek T *et al.* Does atorvastatin therapy change the anti-Xa activity in xabans-treated patients with atrial fibrillation? Pharmacol Res Perspect 2021; 9:e00730. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33984191>
  7. Olesen KKW, Heide-Jørgensen U, Thim T *et al.* Statin but not Aspirin Treatment is Associated with Reduced Cardiovascular Risk in Patients with Diabetes without Obstructive Coronary Artery Disease. European heart journal. Cardiovascular pharmacotherapy 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33989394>
  8. Lin TH, Lee WL, Lee WJ *et al.* Dyslipidemia, Not Inflammatory Markers or Adipokines, Contributes Significantly to a Higher SYNTAX Score in Stable Coronary Artery Disease (from the Taichung CAD Study). Acta Cardiologica Sinica 2021; 37:232-238. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33976506>
  9. Kim SW, Chen J, Wegener KJ *et al.* Improvement of Statin Utilization in Veterans With Diabetes Through Pharmacy Interventions. Clin Diabetes 2021; 39:215-219. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33981132>
  10. Keech AC, Oyama K, Sever PS *et al.* Efficacy and Safety of Long-Term Evolocumab Use Among Asian Subjects - A Subgroup Analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) Trial. Circulation journal : official journal of the Japanese Circulation Society 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33980763>
  11. Imre E, Gunhan HG, Erel P, Ustay O. SGLT2 inhibitors improve plasma atherogenic biomarkers in patients with type 2 diabetes: a real world retrospective observational study. Minerva Endocrinol (Torino) 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33979071>
  12. Hare AJ, Adusumalli S, Park S, Patel MS. Assessment of Primary Care Appointment Times and Appropriate Prescribing of Statins for At-Risk Patients. JAMA network open 2021; 4:e219050. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33974057>
  13. Evinacumab (Evkeeza) for homozygous familial hypercholesterolemia. The Medical letter on drugs and therapeutics 2021; 63:66-67. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33976097>
  14. Puato M, Zambon A, Nardin C *et al.* Lipid Profile and Vascular Remodelling in Young Dyslipidemic Subjects Treated with Nutraceuticals Derived from Red Yeast Rice. Cardiovasc Ther 2021; 2021:5546800. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33976708>
  15. Alalaqi A, Lawson G, Obaid Y, Tanna S. Adherence to cardiovascular pharmacotherapy by patients in Iraq: A mixed methods assessment using quantitative dried blood spot analysis and the 8-item Morisky Medication Adherence Scale. PLoS One 2021; 16:e0251115. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33989336>
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## Basic Science publications

1. Santarelli R, Pompili C, Gilardini Montani MS *et al.* Lovastatin reduces PEL cell survival by phosphorylating ERK1/2 that blocks the autophagic flux and engages a cross-talk with p53 to activate p21. IUBMB life 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33987937>
2. Rahmani Z, Karimpour Malekshah A, Zargari M, Talebpour Amiri F. Effect of prenatal exposure to Benzo(a)pyrene on ovarian toxicity and reproductive dysfunction: Protective effect of atorvastatin in the embryonic period. Environ Toxicol 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33978294>
3. Patel O, Muller CJF, Joubert E *et al.* Therapeutic effects of an aspalathin-rich green rooibos extract, pioglitazone and atorvastatin combination therapy in diabetic db/db mice. PLoS One 2021; 16:e0251069. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33983968>
4. Ni W, Mo H, Liu Y *et al.* Targeting Cholesterol Biosynthesis Promotes Anti-tumor Immunity by Inhibiting Long Noncoding RNA SNHG29 Mediated YAP Activation. Molecular therapy : the journal of the American Society of Gene Therapy 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33992804>
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6. Ha HS, Kim TY, Han SJ *et al.* Anti-atherosclerotic vaccination against *Porphyromonas gingivalis* as a potential comparator of statin in mice. PeerJ 2021; 9:e11293. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33976982>
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This activity is supported by an educational grant from Viatrix.

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