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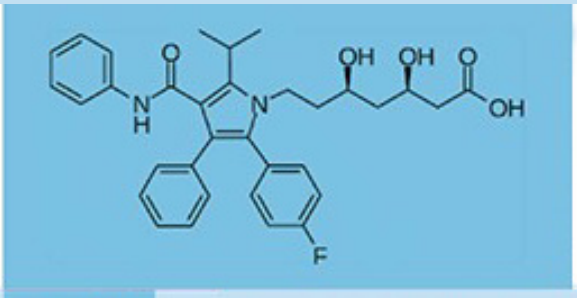
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 51 & 52, 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

High intensity statin + sacubitril/valsartan and rhabdomyolysis risk

Several reports on drug interactions leading to rhabdomyolysis with the use of sacubitril/valsartan and high potency statins were recently published. Reports submitted to the United States Food and Drug Administration's Adverse Event Reporting System (FAERS) from 1991 to Q4/2020 were used to query if exposure of statins alone, sacubitril/valsartan alone, and statin combined with sacubitril/valsartan. Proportional reporting ratios (PRR) were queried in the FAERS, and a lower limit of 95% CI ≥2.0 was interpreted as a safety signal. No safety signal was detected for statins combined with sacubitril/valsartan, except for rosuvastatin and sacubitril/valsartan. The PRRs for rhabdomyolysis were 2.39 (2.01 to 2.84) with rosuvastatin alone and 2.06 (2.01 to 2.12) for sacubitril/valsartan alone. For atorvastatin + sacubitril/valsartan, the PRR was 0.95 (0.64 to 1.40). Combined statin and sacubitril/valsartan seem safe; however, further evidence is warranted to explore mechanisms for additive or synergistic effects on rhabdomyolysis.
Sunaga T, Ryo Y. Potential Safety Signals for Rhabdomyolysis Associated With High-Potency Statin Use With or Without Sacubitril/Valsartan. Am J Cardiol 2021.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34963512

Meta-analysis statins + ezetimibe in diabetics

Statins share a pro-diabetogenic effect that is dose and intensity dependent. This meta-

analysis explored the adverse metabolic properties of ezetimibe alone or when combined with statins in patients with type 2 diabetes. For this meta-analysis, 17 articles were included, and both lipid and glucose parameters were explored in patients who used statin monotherapy or a combination of ezetimibe and statins. All lipid parameters improved significantly with the combination therapy compared to statin monotherapy. The difference in means is 0.691(0.534–0.847). Superior levels of HDL-C, total cholesterol, triglyceride, and apolipoprotein B, but not apolipoprotein A1, were noted with combination therapy compared to statin monotherapy. Fasting blood glucose levels were significantly lower with ezetimibe compared to statin monotherapy. No safety signals were observed when ezetimibe + statins were compared to statins. Monotherapy. The authors concluded that combining statins with ezetimibe improves the overall lipid spectrum and glycaemic biomarkers without increasing the risk for adverse events.

Shin KH, Choi HD. Comparison of Efficacy and Safety of Statin-Ezetimibe Combination Therapy with Statin Monotherapy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Studies. Am J Cardiovasc Drugs 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34927215

Rosuvastatin reduces VTE risk by lowering PPL activity

Prevention of venous thromboembolism (VTE) remains a therapeutic challenge. Currently used oral anticoagulants are effective, but their use is associated with an increased bleeding risk. Subgroup analysis of several statin trials have suggested that statins can reduce the risk of incident and recurrent VTE's; however, little is known regarding the mechanism responsible for this anticoagulant effect. In this RCT (N=255), patients with a history of VTE stopped using oral anticoagulants and were randomized to rosuvastatin 20 mg (N=131) or placebo (N=124). Blood samples were collected at the start of the study and after 28 days. The endpoints of this trial were procoagulant phospholipids (PPL), using a factor Xa dependent clotting assay, and plasma concentration of extracellular vesicles (EV). Rosuvastatin treatment was associated with a 22% (−38.2 to −5.8) reduction in PPL activity. In patients with a history of PE, PPL activity was reduced by 37% (−62.9 to −11.2). These observed PPL activity changes were independent of total cholesterol decrease or change in levels of total-or platelet-derived EVs. The authors concluded that rosuvastatin use was associated with a substantial decrease in PPL activity; this mechanism is a plausible explanation for the reduction in VTE risk observed in patients using statins.

Ramberg C, Hindberg K, Biedermann JS *et al.* Rosuvastatin treatment decreases plasma procoagulant phospholipid activity after a VTE: A randomized controlled trial. Journal of thrombosis and haemostasis : JTH 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34953155

Statin in primary prevention following guidelines or RCT's?

For this analysis, the authors creatively combined data collected in the Copenhagen General Population Study (CGPS) and data from randomized controlled statin trials to estimate the accuracy of commonly used guideline-based recommendations for primary prevention statin use. The following guidelines were evaluated: American College of Cardiology/American Heart Association (ACC/AHA), Canadian Cardiovascular Society(CCS), UK National Institute for Health and Care Excellence (NICE), and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS). In total, 79 171 participants of the CGPS were free of ASCVD and not using statins at baseline. After a follow-up period of 8.2 years, 4031 events accrued in this cohort. Of the individuals eligible for statin therapy with the ACC/AHA, CCS, NICE, and ESC/EAS guidelines, 86%, 88%, 88%, and 84% had direct RCT evidence of statin efficacy, respectively (guideline-positive & RCT-positive). This group represented 26–37% of all CGPS individuals. Guideline-positive & RCT-negative individuals represented 5–7%, guideline-negative & RCT positive individuals 28–39%, and guideline-

negative & RCT-negative individuals represented 30–31%. The ASCVD events per 1000 person-years were 11.4–12.7 (guideline-positive & RCT-positive), 6.3–8.0 (guideline positive & RCT-negative), 4.2–5.2 (guideline-negative & RCT-positive), and 2.3–2.5 (guideline-negative & RCT negative), respectively, while the corresponding NNT to prevent one event in 10 years using high-intensity statin were 19–21, 30–32, 48–60, and 105–125, respectively. The authors concluded that the evaluated data strongly supports the guideline-recommended use of risk calculators as a starting point for a patient-physician discussion on the initiation of statin for primary prevention. More accurate identification of patients is more likely to benefit from evidence-based statin treatment. Of note, patients not qualifying for guideline-based statin treatment but eligible because of RCT evidence may also benefit from initiating statins.
Mortensen MB, Nordestgaard BG. Guidelines versus trial-evidence for statin use in primary prevention: The Copenhagen General Population Study. Atherosclerosis 2022; 341:20-26. http://www.ncbi.nlm.nih.gov/pubmed/?term=34959205

Is a low LDL-c (<70 mg/dL) associated with an increased ICH risk?

The Treat Stroke to Target (TST) study included patients with an ischemic stroke or evidence of atherosclerosis. Patients were randomized to achieve an LDL-c <70 mg/dL (N=1440) or 100±10 mg/dL (N=1433). In this sub-analysis, the risk for an intracranial hemorrhage (ICH) in the two treatment arms was re-evaluated. Over a median follow-up of 3 years, 31 ICH occurred, 18 in patients that achieved and LDL<70 mg/dL and 13 in the higher target group; 3.21/1000 patient-years (2.38–4.04) and 2.32/1000 patient-years (1.61–3.03), respectively. ICH risk factors at baseline failed to predict events, however uncontrolled hypertension; HR 2.51 (1.01–6.31, P=0.041), orals anticoagulants; HR 2.36 (1.00–5.62, P=0.047) during the trial were significant predictors. A low on-treatment LDL-c was not associated with ICH. Amarenco P, Kim JS, Labreuche J *et al.* Intracranial Hemorrhage in the TST Trial. Stroke 2022; 53:457-462. http://www.ncbi.nlm.nih.gov/pubmed/?term=34963300

Relevant publications

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9. Saul H, Gursul D, Cassidy S *et al.* Statins do not commonly cause muscle pain and stiffness. Bmj 2021; 375:n3060. http://www.ncbi.nlm.nih.gov/pubmed/?term=34965931
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Basic Science publications

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