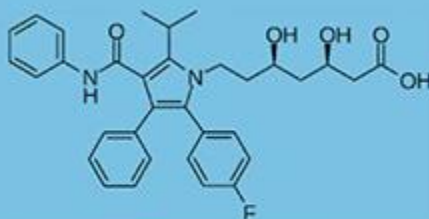


IAS STATIN
NEWSLETTER



INTERNATIONAL
ATHEROSCLEROSIS
SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 10, 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

Secondary dyslipidaemia's; a primer for those that manage lipids

The first step when evaluating abnormal lipids is to distinguish primary dyslipidemia (e.g., FH) from secondary dyslipidemia. Most physicians are familiar with the most frequently encountered secondary causes such as lifestyle, diabetes, and the use of certain drugs. This review provides a concise overview of the complete spectrum of secondary dyslipidemia. The authors estimate that 30-40% of dyslipidemia have a secondary source, and addressing this root cause can result in a normalization of dyslipidemia. The authors categorize secondary dyslipidaemias as those that manifest with isolated cholesterol, such

as hypothyroidism and biliary-related pathology, Isolated hypertriglyceridemia frequently surfaces in patients with chronic kidney disease, severe obesity, including bulimia, and excess alcohol, and smoking. A mixed phenotype is typical in nephrotic syndrome diabetes, Cushing disease, and pheochromocytoma. Certain drugs can increase cholesterol and/or triglycerides, but this is specific for certain drug classes; a simple table provides an overview of the different medications and the resulting impact on LDL-c, TG, and HDL-c. Recognizing secondary causes of dyslipidemia is essential not only to address the underlying causes but also to prevent harm. Treating hypothyroidism patients with statins can result in rhabdomyolysis and life-threatening complications.

Yanai H, Yoshida H. Secondary dyslipidemia: its treatments and association with atherosclerosis. *Glob Health Med* 2021; 3:15-23.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=33688591>

Outcomes Statin use prior to AF related IS associated with improved

AF-triggered ischemic strokes are associated with an increased mortality and morbidity risk. To determine the impact of pre-stroke statin use on these severe outcomes, 453 patients from 4 hospitals were divided into those that used statins before admission (N=220) and those that were not on statins (N=233). Patients were followed for 3-months, and comprehensive medical examinations were conducted at discharge and after study completion. Plasma suppressor of cytokine signaling-3 (SOCS-3) and matrix metalloproteinase-9 (MMP-9) levels were measured on admission and day 3 and 7 after enrolment. The primary endpoints were death, significant disability (modified Rankin Scale score ≥ 3), and a composite outcome (death/major disability) after three months. Patients that used statins prior to the acute event had significantly increased plasma levels of SOCS-3 and reduced MMP-9 ($P < 0.0001$). The 3-month mortality risk was increased in patients with reduced plasma concentrations of SOCS-3, aOR: 1.012 (1.006-1.018; $P < 0.001$) and increased MMP-9 levels, aOR: 1.037 (1.022-1.053; $P < 0.001$). Similar results were observed for major disability scores aOR: 1.013 (1.007-1.02; $P < 0.001$) and aOR: 1.038 (1.022-1.055; $p < 0.001$). The authors concluded that statin use prior to an AF-related ischemic stroke was associated with improved 3-month mortality as well as disability scores. Both SOCS-3 and MMP-9 plasma concentrations were associated with both statin use and outcomes.

Lu T, Yang X, Cai Y *et al*. Prestroke Statins Improve Prognosis of Atrial Fibrillation-Associated Stroke through Increasing Suppressor of Cytokine Signaling-3 Levels. *European neurology* 2021:1-7. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33684912>

Can statins reduce VTE risk?

In this re-analysis of both the JUPITER and HOPE-3 studies (N=30 507), rosuvastatin's potential benefits to reduce VTE risk were evaluated. Using individual participant data, a

meta-analysis was performed. The median follow-up time was 3.62 years, 1.92 years in JUPITER, and 5.6 years in HOPE-3. All participants were free of ASCVD when recruited for the studies. All were randomized to rosuvastatin or placebo. The primary outcome of this meta-analysis was VTE during the study period. In both trials, incident VTE were predefined ancillary endpoints, defined as the development of deep vein thrombosis or pulmonary embolism during follow-up. There were 139 VTE events (0.128/100person years). The pooled analysis showed a significantly reduced risk in patients that were randomized to rosuvastatin; HR: 0.53 (0.37-0.75). Results were consistent when aggregate trial-level data were pooled using a random-effect model. There were no differences in a broad range of demographic factors, cardiovascular risk factors, and cancer history ($P < 0.05$ for all subgroups). This re-analysis confirms the VTE preventive benefits of statins in patients, with and without VTE risk factors, and warrant further research.

Joseph P, Glynn R, Lonn E *et al.* Rosuvastatin for the prevention of venous thromboembolism: a pooled analysis of the HOPE-3 and JUPITER randomized controlled trials. Cardiovascular research 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33705531>

Statin Web-based Investigation of Side Effects (StatinWISE) study

Using high dose, high-intensity statins and adherence are hampered by fears of muscle-related side-effects. Conflicting data from real-world registries and randomized controlled clinical trials confuses doctors and patients. In this investigator-initiated study, and funded by the National Institute for Health Research (NIHR) Health Technology Assessment program, the aims were to establish (1) the effect of statins on all muscle symptoms and (2) the effect of statins on muscle symptoms that are perceived to be statin-related. Using the model of N-of-1 trials and set up in UK primary care practices, 200 patients participated in double-blind placebo-controlled trials. Patients included were contemplating stopping statins or who had discontinued statins three years before the study started. All included were randomly assigned to a sequence of six 2-month treatment periods during which they received 20 mg of atorvastatin daily or a matched placebo. Primary outcomes were self-reported muscle complaints. Of the 200 patients, 114 completed the entire six-month treatment period. An end-of-trial discussion with their GP or research nurse was completed by 113 (56.65) of the participants. At 15 months, 58 patients (51.3% of 113 patients) had a statin prescription, and 74 (65.5%) planned to resume statins or had already done so. The study was considered helpful by 99 (65.5%) of the participants. Based on these findings, re-challenging patients that reported statin attributed muscle pain is a successful strategy. Among individual patients, a majority of those completing the trial decided to restart statins. The authors concluded that the N-of-1 trial design could be a valuable method to determine if statin-reported muscle complaints are genuinely related to the statin used and could guide individual therapy.

Herrett E, Williamson E, Brack K *et al.* The effect of statins on muscle symptoms in primary care: the StatinWISE series of 200 N-of-1 RCTs. Health technology assessment (Winchester, England) 2021; 25:1-62. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33709907>

Increased 30-day most AMI mortality in SMuRFs free patients

The National SWEDEHEART registry collects data of all national admitted to cardiac care units in Sweden; in this retrospective analysis, the impact of common modifiable cardiovascular risk factors, SMuRFs (hypertension, diabetes, hypercholesterolemia, and smoking) vs. patients in whom SMuRFs were absent. The primary outcome was mortality, 30-days post-STEMI. Secondary outcomes included cardiovascular mortality, heart failure, and myocardial infarction at 30 days. Both primary and secondary endpoints were examined during hospital admission and after 12 months. Data of 62 048 patients were collected between January 1, 2005, and May 25, 2018. In total, 9228 (14.9%) STEMI patients were SMuRFs free. Baseline characteristics such as age and PCI rates were comparable in the two cohorts. Post-discharge, significantly fewer SMuRFs free patients were using statins, ACEi/ARB's or beta-blockers. At 30-days, mortality was significantly higher in patients without SMuRFs; HR:1.47 (1.37-1.57, P<0.0001). Women without SMuRFs had the highest 30-day mortality; 381 (17.6%) of 2164, followed by women with SMuRFs; 2032 (11.1%) of 18 220. The death rate in men lacking SMuRFs; 660 (9.3%) of 7064 vs. Men with SMuRFs 2117 (6.1%) of 34 600. After adjusting for age, sex, left ventricular ejection fraction, creatinine, and blood pressure, 30-day mortality remained significantly higher in SMuRFs free men. However, it was attenuated when corrected for ACEi or ARB, beta-blocker, or statins at discharge. SMuRFs-less patients had a significantly higher rate of in-hospital all-cause mortality compared to patients with one or more SMuRFs; 883 (9.6%) vs. 3411 (6.5%), p<0.0001. This contrasted with rates of myocardial infarction and heart failure at 30 days that were lower in SMuRFs-less patients. The increased mortality risk was observed up to 8 years in men and 12-years in women. Considering the large number of SMuRFs-less and the observed high 30-day mortality rate underlines the need to find new biomarkers, to improve early identification and primary prevention of atherosclerosis, where traditional risk algorithms are currently failing.

Figtree GA, Vernon ST, Hadziosmanovic N *et al.* Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. Lancet 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=33711294>

Relevant publications

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2. Shaw PB. Hyperlipidemia: effective disease management with a focus on PCSK9 inhibitors. The American journal of managed care 2021; 27:S63-s69.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=33710845>
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<http://www.ncbi.nlm.nih.gov/pubmed/?term=33706084>
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12. Lindsley J. Guideline recommendations, clinical trial data, and new and emerging therapies. The American journal of managed care 2021; 27:S70-s75.
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