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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.

Key publications

Non-HDL-c superior to LDL-c for prediction of new lesions post PCI

Is LDL-cholesterol (LDL-C) the preferred metric to determine ASCVD risk, or are non-HDL-c or even apo B more accurate? In this retrospective observational analysis of 537 consecutive post PCI, stable angina patients, imaging of the coronary arteries was used to evaluate the impact of LDL-c and non-HDL-c on new lesions with myocardial ischemia. All patients used a “strong” statin; this was defined as doses of atorvastatin (10 mg/day) or rosuvastatin (2.5 mg/day), or pitavastatin (2 mg/day) or more. The interval period between PCI and follow-up coronary angiography was 9 months and < 2 years after PCI. Based on a multivariate logistic regression model, diabetes was significantly associated with an increased risk for new lesions < 2-years after PCI, OR: 1.71 (1.06-2.83, p=0.031). Non-HDL-c was associated with an increased risk for new lesions both after 9 months and < 2 years post PCI; OR 1.80 (1.10-3.0, p=0.021) and OR; 1.85 (1.13-3.07, p=0.016), respectively. Both the Friedewald and Martin calculated LDL-c were not significantly related to new lesion formation after multivariate logistic regression analysis, P=0.062, and p=0.091, respectively. Despite limitations of this study, e.g., the relatively small samples size non-HDL was a

robust indicator of increased risk for new lesion formation both at 9 months and <2 years after PCI intervention.

Kanda D, Miyata M, Ikeda Y *et al.* The Priority of Non-HDL-C Assessment to Predict New Lesions among Stable Angina Patients with Strong Statins. J Atheroscler Thromb 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34039817>

Bempedoic acid a systematic review

Bempedoic acid is the most recent addition to the lipid-lowering drug armamentarium. This systematic review provides a concise overview of current evidence on efficacy, safety, and the clinical trials that have been completed and currently ongoing. Approved by FDA and EMA in February and March of 2020, respectively. This LDL-c lowering drug is indicated in patients unable to reach guideline dictated targets despite maximally tolerated statin therapy. Although it inhibits cholesterol synthesis, similarly to statins, it targets ATP citrate lyase, converting citrate into HMG-CoA reductase. It is administered as a pro-drug that can only be converted in its active form by very long-chain acyl-CoA synthetase 1 present in hepatocytes. This would preclude active metabolites forming in myocytes and reduce the chances of developing muscle-related complaints and potentially an attractive alternative for statin-intolerant patients. The current trial portfolio included efficacy and safety of bempedoic acid as monotherapy, combined with low dose statins and combined with ezetimibe (in statin-intolerant patients. the observed LDL-c reduction ranged from $\pm 13\%$ in monotherapy to 24% when combined with ezetimibe. The CLEAR wisdom trial noted decreased HbA1C in diabetic patients (-0.08%) contrasted with an increase in the placebo group (0.13%). A recent meta-analysis of the 4 phase 3 studies reported new-onset or worsening of diabetes in 3.7% of the patients taking bempedoic acid vs. 5.7% in those allocated to placebo. The drug was well tolerated; common adverse events included gout, urinary tract infections, nasopharyngitis, and hyperuricemia. The addition of bempedoic acid to our lipid-lowering arsenal provides a valuable alternative or add-on in patients intolerant for (high dose) statins to show insufficient LDL-c lowering with ezetimibe monotherapy.

Alam U, Al-Bazz DY, Soran H. Bempedoic Acid: The New Kid on the Block for the Treatment of Dyslipidemia and LDL Cholesterol: A Narrative Review. Diabetes Ther 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34037950>

Updated meta-analysis on COVID-19 outcomes in statin users

The global impact of COVID19 is shifting towards improvements in developed economies due to the rollout of massive vaccination programs and a rapid surge of infections, and the need for hospital/ICU care in developing economies. Addressing risk in unvaccinated remains a great challenge because many patients combined with restricted finances to

address the costly care of those presenting with serious complications. The use of repurposed cheap, safe, and globally available drugs such as statins could make a significant difference in the protracted care of those in dire need of specialized support. For this meta-analysis, the data from 24 studies (N=32715) were combined. The three major clinical endpoints were ICU admission, tracheal intubation, and death. Both ICU admissions and death were significantly reduced in statin users than patients who did not use statins. ICU admission, OR: 0.78 (0.58–1.06; n = 10; I2 = 58.5%) and death, OR: 0.70 (0.55–0.88; n = 21; I2 = 82.5%. statin use was not associated with a statistically significant effect on tracheal intubation, OR: 0.79 (0.57–1.11; n = 7; I2 = 89.0%). Statin used during hospital stay improved survival even further, death OR: 0.40 (0.22–0.73, n = 3; I2 = 82.5%), compared to pre-admission statin use, OR: 0.77 (0.60–0.98, n = 18; I2 = 81.8%). Within the caveats of observational data interpretation, the findings of this meta-analysis are provocative and deserve a properly designed randomized study. Currently, ongoing statin trials in COVID-19 patients will help to expand the evidence for statins to reduce COVID-19 associated adverse outcomes.

Vahedian-Azimi A, Mohammadi SM, Heidari Beni F *et al.* Improved COVID-19 ICU admission and mortality outcomes following treatment with statins: a systematic review and meta-analysis. Archives of medical science : AMS 2021; 17:579-595.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=34025827>

Statin use during pregnancy – systematic review and meta-analysis

The use of statins is prohibited during pregnancy and breastfeeding. However, in certain situations, women of childbearing age have used statins, unaware of their gravid status. Evidence is accumulating suggesting that statins could protect the pregnant woman and her fetus from serious pregnancy-related complications such as preeclampsia, HELLP syndrome, and ant-phospholipid syndrome. In this updated meta-analysis, the teratogenic effects of statins were re-assessed, based on data from 23 studies (nine cohort studies, six case reports, six case series, one population-based case-referent study, and one clinical trial) with 1,276,973 participants were included in the systematic review and 6 of them (n =1,267,240 participants) were included in the meta-analysis. The systematic review was inconclusive; no definite conclusions regarding the harm or safety of statins used in pregnant women were deducible from the combined data. The meta-analysis suggested that no clear indications of teratogenicity-related congenital disabilities were noted OR: 1.48 (0.90 - 2.42, p = 0.509). This included cardiac anomalies, OR:2.53 (0.81, 7.93, p = 0.112) and other congenital anomalies OR: 1.19 (0.70, 2.03, p = 0.509). The authors concluded that this systematic review and meta-analysis could not clearly show the harmful effects of statins during pregnancy. Despite this partly re-assuring assumption, women of childbearing age with high CVD risk should be warned to stop statins before terminating their anti-

contraceptive medication or methods. In a small selective group of extremely high-risk women, statins could provide protection from ASCVD and/or pregnancy-related complications. However, they should be managed in either a clinical trial setting or by a team of experienced specialists based on an individual patient evaluation. Starting statins after the first trimester seems to be the preferred approach to minimize potential teratogenic effects. Vahedian-Azimi A, Makvandi S, Banach M *et al.* Fetal toxicity associated with statins: A systematic review and meta-analysis. *Atherosclerosis* 2021; 327:59-67.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=34044205>

The UK THIN registry: significant reduced total mortality in elderly patients using statins

The Health Improvement Network (THIN) primary care database collects electronic health care records of primary care physicians in England and Wales, broadly representing the UK population. This registry was queried to evaluate the effects of statins in patients > 60 years of age. Included participants reached the age of 10 between 1990 and 2000 and were followed until 2017. Patients were free of ASCVD and statin use when included in the evaluation. The adjusted HRs for all-cause mortality associated with statin prescription at ages 65, 70, 75, 80 and 85 years were 0.76 (0.71 to 0.81), 0.71 (0.68 to 0.75), 0.68 (0.65 to 0.72), 0.63 (0.53 to 0.73) and 0.54 (0.33 to 0.92), respectively. Noteworthy is that both relative- and absolute risk reduction increased with advancing age. The findings of this large observational registry with long-term follow-up support the use of statins in patients > 75 years of age. Treatment decisions should be based on clinical indication and after discussion of the potential risks and benefits of statins with the patient.

Gitsels LA, Bakbergenuly I, Steel N, Kulinskaya E. Do statins reduce mortality in older people? Findings from a longitudinal study using primary care records. *Fam Med Community Health* 2021; 9. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34031184>

Relevant publications

1. Santoso A, Yulianto Y, Simarmata H *et al.* Effect of PCSK9 E670G and R46L Polymorphisms on Major Adverse Cardio-Cerebrovascular Events in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Int J Angiol* 2021; 30:22-28.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=34025093>

2. Sabanis N, Paschou E, Drylli A *et al.* Rosuvastatin and Colchicine combined myotoxicity: lessons to be learnt. CEN Case Rep 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34028728>
3. Lepor NE, Sun J, Canton G *et al.* Regression in carotid plaque lipid content and neovasculature with PCSK9 inhibition: A time course study. Atherosclerosis 2021; 327:31-38. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34038761>
4. Huang Q, Wang WT, Wang SS *et al.* Cardiovascular magnetic resonance image analysis and mechanism study for the changes after treatments for primary microvascular angina pectoris. Medicine (Baltimore) 2021; 100:e26038. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34032727>
5. Frasson E, Simonetto M, Bertolasi L *et al.* Statin-associated necrotizing autoimmune myopathy with concurrent myasthenia gravis. Clinical case reports 2021; 9:e03925. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34026125>
6. Fan H, Zhou J, Yuan Z. Meta-Analysis Comparing the Effect of Combined Omega-3 + Statin Therapy Versus Statin Therapy Alone on Coronary Artery Plaques. Am J Cardiol 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34049675>
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8. Camila de Souza Groia Veloso R, Cruzeiro MGM, Dias BM, Reis AMM. Assessment of adherence to statin therapy in patients with coronary artery disease: comparison of three self-reporting measures. Eur J Hosp Pharm 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34031152>
9. Anderson JLC, van der Giet M, Gomes Neto AW *et al.* Statin use and incident cardiovascular events in renal transplant recipients. European journal of clinical investigation 2021:e13594. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34042174>
10. Alves M, Fernandes MA, Bahat G *et al.* Protecting older patients with cardiovascular diseases from COVID-19 complications using current medications. Eur Geriatr Med 2021:1-15. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34031865>
11. Yoshida K, Uwano I, Sasaki M *et al.* Small Unruptured Aneurysm Verification-prevention Effect against Growth of Cerebral Aneurysm Study Using Statin. Neurol Med Chir (Tokyo) 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34024878>
12. Yang HX, Zuo HJ, Jia SJ *et al.* (Gender differences in risk factors and characteristics of young patients hospitalized for first acute coronary syndrome). Zhonghua yi xue za zhi 2021; 101:1403-1409. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34034368>
13. Sobrin L, Yu Y, Han S *et al.* Decreased risk of non-infectious anterior uveitis with statin therapy in a large healthcare claims database. Graefe's archive for clinical

and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2021.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=34050812>

14. Nakayama A, Morita H, Kawahara T *et al.* Association between testosterone and lipid profiles under statin therapy and its clinical impact on the cardiovascular event risk. Heart Vessels 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34036416>
15. Lopez DS, Huang D, Tsilidis KK *et al.* The role of testosterone replacement therapy and statin use, and their combination, in prostate cancer. Cancer Causes Control 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34041642>
16. Krysiak R, Szkróbka W, Okopień B. Correction to: The impact of atorvastatin on cardiometabolic risk factors in brothers of women with polycystic ovary syndrome. Pharmacological reports : PR 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34036550>
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18. Hoskins MJ, Richards S. Statin-induced liver dysfunction triggering fatal myonecrosis. Internal medicine journal 2021; 51:812-813. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34047026>
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20. Goel R, Chandan JS, Thayakaran R *et al.* Reply to comments on 'Cardiovascular and Renal Morbidity in Takayasu Arteritis: A Population-Base Retrospective Cohort Study'. Arthritis & rheumatology (Hoboken, N.J.) 2021. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34042302>
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23. Brandt EJ, Brandt DJ, Desai NR *et al.* Association of vitamins, minerals, and lead with Lipoprotein(a) in a cross-sectional cohort of US adults. Int J Vitam Nutr Res 2021:1-12. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34024154>

24. Aghasizadeh M, Bizhaem SK, Baniasadi M *et al.* Evaluation of LDL goal achievement in statin consumption, south east of Iran. Scientific reports 2021; 11:10786. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34031484>
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Basic Science publications

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2. Watanabe LM, Hashimoto AC, Torres DJ *et al.* Effect of statin treatment in obese selenium-supplemented mice lacking selenocysteine lyase. Molecular and cellular endocrinology 2021; 533:111335. <http://www.ncbi.nlm.nih.gov/pubmed/?term=34052303>
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<http://www.ncbi.nlm.nih.gov/pubmed/?term=34041015>
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<http://www.ncbi.nlm.nih.gov/pubmed/?term=34031791>
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<http://www.ncbi.nlm.nih.gov/pubmed/?term=34046794>