Literature update week 07 (2019)

[1] *Sartore G, Chilelli NC, Seraglia R et al.* **Long-term effect of pioglitazone vs glimepiride on lipoprotein oxidation in patients with type 2 diabetes: a prospective randomized study**. Acta diabetologica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30740640
ABSTRACT
AIMS: Type 2 diabetes (DM2) is associated to oxidative modifications of high-density lipoproteins (HDL), which can interfere with their function. Pioglitazone has proved effective in raising HDL cholesterol (HDL-C) and lowering small dense low-density lipoprotein (LDL), but no clinical studies have examined its effect on lipoprotein oxidation in patients with DM2. METHODS: We assessed the effect of pioglitazone vs glimepiride after 1 year on HDL oxidation, expressed as relative abundance of peptides containing Met(112)O in ApoA-I (oxApoA-I) estimated by mass spectrometry (MALDI/TOF/TOF), in 95 patients with DM2. The oxLDL and AGE were quantified by ELISA. RESULTS: Patients receiving pioglitazone showed a significant increase in the concentration of ApoA-I (Delta = 7.2 +/- 14.8 mg/dL, $p < 0.02$) and a reduction in oxApoA-I (Delta = - 1.0 +/- 2.6%, $p < 0.02$); this reduction was not significantly different from glimepiride. oxLDL showed a slight, but not significant increase in both treatment groups. Regression analysis showed a correlation between DeltaoxApoA-I and DeltaAGE ($r = 0.30$; $p = 0.007$) in all patients, while both of these parameters were unrelated to changes in HbA1c, HDL-C, duration of illness, or use of statins. CONCLUSIONS: Long-term treatment with pioglitazone was effective in reducing the oxidation of HDL, but not LDL in patients with DM2, while glimepiride didn't. This finding seems to be associated to the change of glyco-oxidation status, not to any improvement in glycemic control or lipid profile. TRIAL REGISTRATION: NCT00700856, ClinicalTrials.gov Registered June 18, 2008.

[2] *Petrov I, Dumitrescu A, Snejdrlova M et al.* **Clinical Management of High and Very High Risk Patients with Hyperlipidaemia in Central and Eastern Europe: An Observational Study**. Adv Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30758746
ABSTRACT
INTRODUCTION: A retrospective/prospective observational study was conducted to explore the current management of hyperlipidaemia in high-risk (HR) and very high risk (VHR) patients in central/eastern Europe and Israel. METHODS: The study enrolled adult patients who were receiving lipid-lowering therapy and attending a specialist (cardiologist/diabetologist/lipidologist) or internist for a routine visit at 57 sites (including academic/specialist/internal medicine centres) across Bulgaria, Croatia, Czech Republic, Israel, Poland, Romania and Slovakia. Data were collected from medical records, for the 12 months before enrolment, with/without </= 6 months' additional prospective follow-up. RESULTS: A total of 1244 patients, mean (SD) age 63.3 (11.3) years were included (307 with familial hypercholesterolaemia (FH), 943 secondary prevention patients). Almost all patients (98.1%) were receiving statins (76.7% monotherapy/21.4% combined therapy), with 53.1% receiving high-intensity statin therapy: 127 patients (10.2%) had adverse events attributed to statin intolerance. Mean (SD) low density lipoprotein cholesterol (LDL-C) levels were 3.3 (1.7) mmol/L at the first, and 2.7 (1.3) mmol/L at the last, visit of the retrospective phase of observation, with little change during the prospective phase. Less than one-quarter (23.8%; 95% CI 17.29-31.45%)

of HR patients and less than half (42.0%; 39.05-44.98%) of VHR patients achieved their risk-based LDL-C targets of < 2.5 and < 1.8 mmol/L, respectively. Less than 15% of FH patients reached these targets (10.9% (5.6-18.7%) of HR and 12.1% (8.0-17.4%) of VHR patients). The revised 2016 ESC/EAS target for HR patients (2.6 mmol/L) was met by 28.5% (21.44-36.38%) of HR patients overall. Almost one-half of patients (42.1%) experienced one or more cardiovascular events during observation. CONCLUSION: Our findings confirm that, despite widespread statin use, a substantial proportion of patients treated for hyperlipidaemia in central/eastern Europe and Israel, particularly those with FH, do not reach recommended LDL-C targets, thus remaining at risk of cardiovascular events. FUNDING: Amgen (Europe) GmbH.

[3] *Sharma A, Sun JL, Lokhnygina Y et al.* **Patient Phenotypes, Cardiovascular Risk, and Ezetimibe Treatment in Patients After Acute Coronary Syndromes (from IMPROVE-IT)**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30739657
ABSTRACT
Risk prediction following acute coronary syndrome (ACS) remains challenging. Data-driven machine-learning algorithms can potentially identify patients at high risk of clinical events. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial randomized 18,144 post-ACS patients to ezetimibe+simvastatin or placebo+simvastatin. We performed hierarchical cluster analysis to identify patients at high risk of adverse events. Associations between clusters and outcomes were assessed using Cox proportional hazards models. The primary outcome was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina hospitalization, or coronary revascularization >/=30 days after randomization. We evaluated ezetimibe's impact on outcomes across clusters and the ability of the cluster analysis to discriminate for outcomes compared with the Global Registry of Acute Coronary Events (GRACE) score. Five clusters were identified. In cluster 1 (n=13,252), most patients experienced a non-STEMI (54.8%). Cluster 2 patients (n=2,719) had the highest incidence of unstable angina (n=83.3%). Cluster 3 patients (n=782) all identified as Spanish descent, whereas cluster 4 patients (n=803) were primarily from South America (56.2%). In cluster 5 (n=587), all patients had ST elevation. Cluster analysis identified patients at high risk of adverse outcomes (log-rank p <0.0001); Cluster 2 (vs 1) patients had the highest risk of outcomes (hazards ratio 1.33, 95% confidence interval 1.24 to 1.43). Compared with GRACE risk, cluster analysis did not provide superior outcome discrimination. A consistent ezetimibe treatment effect was identified across clusters (interaction p=0.882). In conclusion, cluster analysis identified significant difference in risk of outcomes across cluster groups. Data-driven strategies to identify patients who may differentially benefit from therapies and for risk stratification require further evaluation.

[4] *Baer DJ, Novotny JA*. **Consumption of cashew nuts does not influence blood lipids or other markers of cardiovascular disease in humans: a randomized controlled trial**. The American journal of clinical nutrition 2019; 109:269-275.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30753323
ABSTRACT
Background: The US Food and Drug Administration (FDA) approved a qualified health claim for tree nuts and reduction of cardiovascular disease. However, cashews are excluded from that

claim due to their content of saturated fats, which is predominantly stearic acid. Because stearic acid is neutral with respect to blood lipids, several studies have been conducted to test the effect of cashew nuts on blood lipids, and these studies have produced conflicting results. Objectives: The aim of this study was to conduct a highly controlled intervention to determine the effect of cashews fed at the amount specified in the health claim on risk factors for cardiovascular disease. Methods: A total of 42 adults participated in a controlled-feeding study conducted as a randomized crossover trial with 2 treatment phases. The volunteers were provided the same base diet in both treatment phases, with no additions during the control phase and with the addition of 1.5 servings (42 g) of cashews/d for the cashew nut phase. During the cashew nut phase, the amount of all foods was decreased proportionally to achieve isocaloric overall diets in the 2 phases. After 4 wk of intervention, assessments included blood lipids, blood pressure, central (aortic) pressure, augmentation index, blood glucose, endothelin, proprotein convertase subtilisin/kexin type 9 (PCSK9), adhesion molecules, and clotting and inflammatory factors. Results: There were no significant differences in blood lipids, blood pressure, augmentation index, blood glucose, endothelin, adhesion molecules, or clotting factors in this weight-stable cohort. PCSK9 was significantly decreased after cashew consumption, although there was no change in LDL cholesterol. Conclusions: Consumption of 1.5 servings of cashew nuts/d, the amount associated with the FDA qualified health claim for tree nuts and cardiovascular disease, did not positively or adversely affect any of the primary risk factors for cardiovascular disease. This trial was registered at clinicaltrials.gov as NCT02628171.

[5] *Li B, Salata K, de Mestral C et al.* **Perceptions of Canadian vascular surgeons toward pharmacologic risk reduction in patients with peripheral artery disease: 2018 update**. Annals of vascular surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30771465
ABSTRACT
BACKGROUND: Vascular surgeons have a central role in managing peripheral artery disease (PAD). This study assessed their knowledge, attitudes, and behaviours regarding pharmacologic risk reduction in PAD and results were compared to a similar 2004 survey conducted by our group. METHODS: An online questionnaire was administered to 161 active members of the Canadian Society for Vascular Surgery. RESULTS: Forty-eight participants (30%) completed the survey. Recommended targets for LDL cholesterol, blood pressure, and glucose were known by 52%, 38%, and 50% of vascular surgeons, respectively. Almost all participants recognized antiplatelet dosages and statin indications, but less than half could identify indications (29%) and precautions (44%) for angiotensin converting enzyme (ACE) inhibitor therapy. A majority (58%) routinely evaluate risk factors in < 50% of their patients. Most vascular surgeons regularly provide risk reduction counselling, but less than 10% initiate or modify antihypertensive or ACE inhibitor therapy. Compared to 2004, knowledge of targets and indications/precautions for common cardiovascular medications and frequency of risk factor assessment have not changed. Rates of counselling for diabetes control and statin prescription have improved, but remain suboptimal. Regarding newer medications with cardiovascular benefit, under 10% would prescribe PCSK9 and SGLT2 inhibitors if they were available. The majority of vascular surgeons rate their PAD risk reduction knowledge as average and support an up-to-date Canadian PAD

guideline. Most participants believe that risk reduction therapy is best provided by family physicians and internists, but also acknowledge that vascular surgeons should be well-versed in assessing and managing risk factors in PAD. CONCLUSIONS: Significant knowledge and action gaps exist amongst Canadian vascular surgeons with regards to pharmacologic cardiovascular risk reduction in PAD. Although there is recognition that vascular surgeons are central to the medical management of patients with PAD, few routinely evaluate risk factors and prescribe medications. There is little evidence of sufficient improvement since 2004. New educational and clinical strategies are needed to improve PAD risk reduction pharmacotherapy amongst Canadian vascular surgeons.

[6] *Garcia R, Burkle J*. **New and Future Parenteral Therapies for the Management of Lipid Disorders**. Arch Med Res 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30739730
ABSTRACT
Cardiovascular disease (CVD) is the leading cause of death in the world. According to the World Health Organization, an estimated 17.9 million people died from CVD in 2016, representing 31% of all global deaths. Of these deaths, 5% are due to myocardial infarction and stroke. Dyslipidemia is known as the major risk factor of atherosclerotic cardiovascular disease. With current therapies, about 60% of high-risk CVD patients do not achieve LDL-C goals, and in patients with familiar hypercholesterolemia (FH) at maximum intensity statin treatment, only 20% achieve LDL-C goals. We discuss new and future parenteral therapies for the management of lipid disorders.

[7] *Hajhosseiny R, Bahaei TS, Prieto C, Botnar RM*. **Molecular and Nonmolecular Magnetic Resonance Coronary and Carotid Imaging**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118311754.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30760017
ABSTRACT
Atherosclerosis is the leading cause of cardiovascular morbidity and mortality. Over the past 2 decades, increasing research attention is converging on the early detection and monitoring of atherosclerotic plaque. Among several invasive and noninvasive imaging modalities, magnetic resonance imaging (MRI) is emerging as a promising option. Advantages include its versatility, excellent soft tissue contrast for plaque characterization and lack of ionizing radiation. In this review, we will explore the recent advances in multicontrast and multiparametric imaging sequences that are bringing the aspiration of simultaneous arterial lumen, vessel wall, and plaque characterization closer to clinical feasibility. We also discuss the latest advances in molecular magnetic resonance and multimodal atherosclerosis imaging.

[8] *Miki T, Miyoshi T, Kotani K et al.* **Decrease in oxidized high-density lipoprotein is associated with slowed progression of coronary artery calcification: Subanalysis of a prospective multicenter study**. Atherosclerosis 2019; 283:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30769272
ABSTRACT

BACKGROUND AND AIMS: Oxidized high-density lipoprotein (oxHDL) is characterized by reduced anti-inflammatory properties compared with HDL. However, the role of oxHDL in the pathogenesis of coronary artery calcification (CAC), a marker of subclinical atherosclerosis, remains unclear. We prospectively investigated the association between the change in oxHDL and progression of CAC in a substudy of a multicenter study. METHODS: In the principal study, patients with a CAC score of 1-999 were treated with pitavastatin with/without eicosapentaenoic acid. Measurement of CAC with multidetector-row computed tomography and a blood test were performed at baseline and at the 1-year follow-up. In the principal study, the increase in CAC did not differ among treatment groups. In this substudy, patients were divided into two groups: CAC progression (change in Agatston score of >0) and no CAC progression. RESULTS: In total, 140 patients were analyzed. The oxHDL level significantly decreased from 167 (132-246) at baseline to 122 (103-149) after treatment (median [25(th)-75th percentile], U/ml) ($p < 0.001$). The annual change in CAC was significantly positively associated with changes in oxHDL ($r=0.17$, $p=0.04$), triglycerides ($r=0.17$, $p=0.04$), and high-sensitivity C-reactive protein ($r=0.22$, $p=0.01$) but was not associated with changes in low-density lipoprotein cholesterol or HDL-cholesterol. Multiple logistic analysis demonstrated that the decrease in oxHDL per 10 U/ml was independently associated with CAC progression (odds ratio, 0.95; 95% confidence interval, 0.90-0.99; $p=0.04$). CONCLUSIONS: The decrease in oxHDL is associated with the attenuation of CAC progression, suggesting that oxHDL is a potential target for atherosclerosis prevention.

[9] *Husain MI, Chaudhry IB, Khoso AB et al.* **Adjunctive simvastatin for treatment-resistant depression: study protocol of a 12-week randomised controlled trial**. BJPsych open 2019; 5:e13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30762508
ABSTRACT
BACKGROUND: A third of patients diagnosed with major depressive disorder (MDD) experience treatment-resistant depression (TRD). Relatively few pharmacological agents have established efficacy for TRD. Therefore, the evaluation of novel treatments for TRD is a pressing priority. Statins are pleiotropic agents and preclinical studies as well as preliminary clinical trials have suggested that these drugs may have antidepressant properties.AimsTo report on a protocol for a 12-week, randomised, double-blind, placebo-controlled trial of add-on treatment with simvastatin for patients meeting DSM-5 criteria for MDD who have failed to respond to at least two adequate trials with approved antidepressants. The trial has been registered with Clinicaltrials.gov in (ClinicalTrials.gov identifier: NCT03435744). METHOD: After screening and randomisation to the two parallel arms of the trial, 75 patients will receive simvastatin and 75 patients will receive placebo as adjuncts to treatment as usual. The primary outcome is change in Montgomery-Asberg Depression Rating Scale scores from baseline to week 12 and secondary outcomes include changes in scores on the 24-item Hamilton Rating Scale for Depression, the Clinical Global Impression scale, the 7-item Generalized Anxiety Disorder scale and change in body mass index from baseline to week 12. Assessments will take place at screening, baseline, and weeks 2, 4, 8 and 12. Checklists for adverse effects will be undertaken at each visit. Simvastatin (20 mg) will be given once daily. Other secondary outcomes include C-reactive protein and plasma lipids measured at baseline and week 12. RESULTS: This trial will assess

simvastatin's efficacy and tolerability as an add-on treatment option for patients with TRD and provide insights into its putative mechanisms of action. CONCLUSIONS: As the first trial investigating the use of simvastatin as an augmentation strategy in patients with TRD, if the results indicate that adjuvant simvastatin is efficacious in reducing depressive symptoms, it will deliver immediate clinical benefit.Declaration of interestI.B.C. and N.H. have given lectures and advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, Astra Zeneca and Janssen pharmaceuticals for which they or their employing institution have been reimbursed. R.R. and M.M.H. have received educational grants and support for academic meetings from Pfizer, Roche, Novartis and Nabiqasim. A.H.Y. has been commissioned to provide lectures and advice to all major pharmaceutical companies with drugs used in affective and related disorders. A.H.Y. has undertaken investigator-initiated studies from Astra Zeneca, Eli Lilly, Lundbeck and Wyeth. None of the companies have a financial interest in this research.

[10] *Yang J, Dou G, Tesche C et al.* **Progression of coronary atherosclerotic plaque burden and relationship with adverse cardiovascular event in asymptomatic diabetic patients**. BMC cardiovascular disorders 2019; 19:39.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30744612
ABSTRACT
BACKGROUND: The heterogeneity of risk in patients with diabetes mellitus (DM) is acknowledged in new guidelines promulgating different treatment recommendations for diabetics at low cardiac risk. We performed a retrospective longitudinal follow-up study to evaluate coronary plaque progression and its impact on cardiac events in asymptomatic diabetic patients. METHODS: Data of 197 asymptomatic patients (63.1 +/- 17 years, 60% males) with DM and suspected coronary artery disease (CAD) who underwent clinically indicated dual-source cardiac computed tomography (CT) were retrospectively analyzed. Patients with DM received standard of care treatment. Patients were classified into two groups based on CT coronary artery calcium scores (CACS): A, CACS> 10; B, CACS</=10. Progression of coronary plaque burden in both groups was evaluated and compared by baseline and follow-up coronary CT angiography (CCTA) using semi-automated plaque analysis and quantification software. Follow-up data were retrospectively gathered from medical records and endpoints of cardiac events were recorded via prospective phone-calls. The impacts of plaque composition and progression on cardiac events were specifically assessed. RESULTS: Patients with CACS> 10 showed an increase in dense coronary calcium volume, while patients with CACS</=10 had a more pronounced increase in the volume of low-attenuation "lipid-rich" plaque components between CCTA acquisitions. The composite endpoint occurred in 20 patients (10.2%) after a median follow-up period of 41.8 months. Furthermore, at follow-up CCTA, the presence of CACS> 10 (adjusted odds ratio, 0.701; 95% CI, 0.612-0.836), increase of dense calcium volume (OR, 0.860 95% CI, 0.771-0.960), and lipid volume (OR, 1.013; 95% CI, 1.007-1.020) were all independent predictors of cardiac events. CONCLUSION: Asymptomatic patients with DM experienced plaque progression as well as progression to "overt or silent CAD". The relative increase in plaque volume was associated with subsequent cardiac events, and the coronary calcification seemed to be inversely related to the outcome in asymptomatic diabetic patients.

[11] *Fan L, Wang Y, Liu X, Guan X*. **Association between statin use and herpes zoster: systematic review and meta-analysis**. BMJ open 2019; 9:e022897.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30765397
ABSTRACT
OBJECTIVE: Statins are commonly prescribed worldwide. In addition to being potent lipid-lowering agents, statins have immunomodulating properties that may increase the risk of varicella zoster virus reactivation. This adverse effect may have substantial public health implications. DESIGN: We performed a meta-analysis of observational studies to assess the association between statin use and the risk of herpes zoster infection. We searched PubMed, Embase, Web of Science and Cochrane databases to identify studies published from 1980 to 2018. The multivariate-adjusted ORs were pooled using random-effect models, and subgroup and sensitivity analyses were performed to examine the source of heterogeneity. RESULT: Six studies were analysed, with a total of more than two million participants. We determined if the use of statins might increase the risk of infection of herpes zoster (OR 1.18, 95% CI 1.11 to 1. 25). We detected significant heterogeneity (I(2)=91.2%; p<0.000), and determined that the heterogeneity arises from regional differences. CONCLUSION: The use of statins may increase the risk of herpes zoster infection. Because the studies included are limited and there may be potential bias, further studies are warranted.

[12] *Colantonio LD, Monda KL, Rosenson RS et al.* **Characteristics and Cardiovascular Disease Event Rates among African Americans and Whites Who Meet the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial Inclusion Criteria**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30746585
ABSTRACT
PURPOSE: Determine the risk for cardiovascular disease (CVD) events among adults with clinically evident CVD who meet the inclusion criteria for the FOURIER clinical trial on PCSK9 inhibition in a real-world database. METHODS: We analyzed data from 2072 African American and 2972 white REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants 45-85 years of age with clinically evident CVD. Study participants meeting the FOURIER inclusion criteria (one major or two minor cardiovascular risk factors, fasting LDL cholesterol >/= 70 mg/dL or non-HDL cholesterol >/= 100 mg/dL, triglycerides </= 400 mg/dL, and taking statin) were followed for CVD events (myocardial infarction, stroke, coronary revascularization, and CVD death) from baseline in 2003-2007 through 2014. RESULTS: Overall, 771 (37.2%) African Americans and 1200 (40.4%) whites met the FOURIER inclusion criteria. The CVD event rate per 1000 person years was 60.6 (95% CI 53.6-67.6) among African Americans and 63.5 (95% CI 57.7-69.3) among whites. The risk for CVD events among adults meeting the FOURIER inclusion criteria was higher for those with a history of multiple cardiovascular events (hazard ratios among African Americans and whites 1.34 [95% CI 1.05-1.71] and 1.34 [1.10-1.63], respectively), a prior coronary revascularization (1.44 [1.13-1.84] and 1.23 [1.00-1.52], respectively), diabetes (1.38 [1.08-1.76] and 1.41 [1.15-1.72], respectively), reduced glomerular filtration rate (1.63 [1.26-2.11] and 1.29 [1.03-1.62], respectively), and albuminuria (1.77 [1.37-2.27] and 1.33 [1.07-1.65], respectively). CONCLUSIONS: The CVD event rate is high among

African Americans and whites meeting the FOURIER inclusion criteria. Characteristics associated with a higher CVD risk may inform the decision to initiate PCSK9 inhibition.

[13] *Nakamura M, Liu T, Husain S et al.* **Glycogen Synthase Kinase-3alpha Promotes Fatty Acid Uptake and Lipotoxic Cardiomyopathy**. Cell Metab 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30745182
ABSTRACT
Obesity induces lipotoxic cardiomyopathy, a condition in which lipid accumulation in cardiomyocytes causes cardiac dysfunction. Here, we show that glycogen synthase kinase-3alpha (GSK-3alpha) mediates lipid accumulation in the heart. Fatty acids (FAs) upregulate GSK-3alpha, which phosphorylates PPARalpha at Ser280 in the ligand-binding domain (LBD). This modification ligand independently enhances transcription of a subset of PPARalpha targets, selectively stimulating FA uptake and storage, but not oxidation, thereby promoting lipid accumulation. Constitutively active GSK-3alpha, but not GSK-3beta, was sufficient to drive PPARalpha signaling, while cardiac-specific knockdown of GSK-3alpha, but not GSK-3beta, or replacement of PPARalpha Ser280 with Ala conferred resistance to lipotoxicity in the heart. Fibrates, PPARalpha ligands, inhibited phosphorylation of PPARalpha at Ser280 by inhibiting the interaction of GSK-3alpha with the LBD of PPARalpha, thereby reversing lipotoxic cardiomyopathy. These results suggest that GSK-3alpha promotes lipid anabolism through PPARalpha-Ser280 phosphorylation, which underlies the development of lipotoxic cardiomyopathy in the context of obesity.

[14] *Kanigur Sultuybek G, Soydas T, Yenmis G*. **NF-kappaB as the mediator of metformin's effect on aging and age-related diseases**. Clinical and experimental pharmacology & physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30754072
ABSTRACT
Aging can be defined as the progressive failure of repair and maintenance systems with a consequent accumulation of cellular damage in nucleic acids, proteins, and lipids. These various types of damage promote aging by driving cellular senescence and apoptosis. NF-kB (nuclear factor-kappa B) pathway is one of the key mediators of aging and this pathway is activated by genotoxic, oxidative and inflammatory stress, and regulates expression of cytokines, growth factors, and genes that regulate apoptosis, cell cycle progression, and inflammation. Therefore, NF-kB is increased in a variety of tissues with aging, thus the inhibition of NF-kB leads to delayed onset of aging-related symptoms and pathologies such as diabetes, atherosclerosis, and cancer. Metformin is often used as an anti-diabetic medication in type 2 diabetes throughout the world and appears to be a potential anti-aging agent. Owing to its antioxidant, anticancer, cardio-protective and anti-inflammatory properties, metformin has become a potential candidate drug, improving in the context of aging and aging-related diseases. An inappropriate NF-kB activation is associated with diseases and pathologic conditions which can impair the activity of genes involved in cell senescence, apoptosis, immunity, and inflammation. Metformin, inhibiting the expression of NF-kB gene, eliminates the susceptibility to common diseases. This review underlines the pleiotropic effects of metformin in aging and different

aging-related diseases and attributes its effects to the modulation of NF-kB. This article is protected by copyright. All rights reserved.

[15] *Marco-Benedi V, Jarauta E, Perez-Calahorra S et al.* **Treatment of a high cardiovascular risk patient with McArdle's disease with PCSK9 inhibitors**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30738610

ABSTRACT

A 60-year-old male with familial combined hyperlipidemia, ischemic heart disease and type 2 diabetes. Since childhood, intolerance to intense exercise. The patient was diagnosed of McArdle's disease after an episode of rhabdomyolysis associated with statins as treatment after a myocardial infarction. Since then, he had been treated with diet, fibrates and ezetimibe with good tolerance, despite this, LDL cholesterol (cLDL) remained >180mg/dl. He started to be treated with alirocumab 150mg/sc every 14 days, with excellent clinical response and a decrease in cLDL to 15mg/dl. Our case shows that PCSK9 inhibitors are effective and safe in patients with muscle diseases who have statin contraindication, and they are a good therapeutic tool for these patients.

[16] *Altunkeser BB, Tuncez A, Ozturk B et al.* **Comparative effects of high-dose atorvastatin versus rosuvastatin on lipid parameters, oxidized low-density lipoprotein, and proprotein convertase subtilisin kexin 9 in acute coronary syndrome**. Coronary artery disease 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30741744

ABSTRACT

AIM: Current guidelines recommend administration of high-dose statins in acute coronary syndrome (ACS). It has been reported that statins upregulate proprotein convertase subtilisin kexin 9 (PCSK9) mRNA expression and increase circulating PCSK9 levels. We aimed to compare the effects of high-dose atorvastatin and rosuvastatin on serum oxidized low-density lipoprotein (oxidized-LDL) and PCSK9 levels in statin-naive patients with ACS. PATIENTS AND METHODS: One hundred and six patients with ACS were enrolled in this study. The patients were assigned randomly to receive atorvastatin (80 mg/day) or rosuvastatin (40 mg/day) by using a ratio of 1 : 1 in randomization. The levels of total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol, LDL-cholesterol, oxidized-LDL, and PCSK9 were compared between groups after a 4-week treatment. RESULTS: Our study population included 53 patients in the atorvastatin group (age: 58.13+/-11.30 years, 11.32% female) and 53 patients in the rosuvastatin group (age: 59.08+/-12.44 years, 15.09% female). In both groups, lipid parameters, oxidized-LDL, and PCSK9 values changed significantly according to the baseline following treatment. High-dose atorvastatin and rosuvastatin induced similar decreases in LDL-cholesterol, oxidized-LDL, and triglyceride levels and similarly increased in high-density lipoprotein cholesterol and PCSK9 levels (P>0.05). CONCLUSION: We showed that atorvastatin and rosuvastatin treatment regimens have comparable effects on lipid parameters and PCSK9 levels in ACS patients.

[17] *Zhang L, Hussain Z, Ren Z.* **Structure and function of proprotein convertase subtilisin/kexin type 9 (PCSK9) in atherosclerosis**. Current drug targets 2019.

Literature update week 07 (2019)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30767742

ABSTRACT

BACKGROUND: Normal pressure hydrocephalus (NPH) is a critical brain disorder in which excess cerebrospinal fluid (CSF) is accumulated in the brain's ventricles causing damage or disruption of the brain tissues. Amongst various signs and symptoms, difficulty in walking, blurred speech, impaired decision making and critical thinking, and loss of bladder and bowl control are considered the hallmark features of NPH. OBJECTIVE: The current review was aimed to present a comprehensive overview and critical appraisal of majorly employed neuroimaging techniques for rational diagnosis and effective monitoring of effectiveness of employed therapeutic intervention for NPH. Moreover, a critical overview of recent developments and utilization of pharmacological agents for treatment of hydrocephalus has also been appraised. RESULTS: Considering the complications associated with the shunt-based surgical operations, consistent monitoring of shunting via neuroimaging techniques hold greater clinical significance. Despite having extensive applicability of MRI and CT scan, these conventional neuroimaging techniques are associated with misdiagnosis or several health risks to patients. Recent advances in MRI (i.e., Sagittal-MRI, coronal-MRI, Time-SLIP (time-spatial-labeling-inversion-pulse), PC-MRI and diffusion-tensor-imaging (DTI)) have shown promising applicability in diagnosis of NPH. Having associated with several adverse effects with surgical interventions, non-invasive approaches (pharmacological agents) have earned greater interest of scientists, medical professional, and healthcare providers. Amongst pharmacological agents, diuretics, isosorbide, osmotic agents, carbonic anhydrase inhibitors, glucocorticoids, NSAIDs, digoxin, and gold-198 have been employed for management of NPH and prevention of secondary sensory/intellectual complications. CONCLUSION: Employment of rational diagnostic tool and therapeutic modalities avoids misleading diagnosis and sophisticated management of hydrocephalus by efficient reduction of cerebrospinal fluid (CSF) production, reduction of fibrotic and inflammatory cascades secondary to meningitis and hemorrhage, and protection of brain from further deterioration.

[18] *Nestel PJ*. **Dietary Fat and Blood Pressure**. Curr Hypertens Rep 2019; 21:17.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30747320

ABSTRACT

PURPOSE OF REVIEW: Do dietary fats lower blood pressure? This review covers total fats, individual fatty acids and foods that provide specific fats. RECENT FINDINGS: Evidence for blood pressure lowering is stronger for supplements providing individual marine fatty acids than for fish intake since data on fish consumption are scarce. Such effects are more readily apparent in hypertensive than normal subjects. Biological mechanisms to support linkage between dietary fish oils and blood pressure are plausible. Information on other dietary fatty acids (saturates, linoleic acid, alpha-linolenic acid) is mostly less robust and therefore inconclusive. However, findings with respect to consumption of dairy foods especially of the low-fat variety do suggest association with lower blood pressures. Apart from marine fatty acids which have mostly been significantly associated with clinically modest blood pressure-lowering, the effects of other dietary fatty acids are inconsistent or clinically minor. Consumption of dairy especially of yoghurt has been linked with lower blood pressure despite the relatively high saturated fat content but the mechanism is unclear.

[19] *Rao X, Zhao S, Braunstein Z et al.* **Oxidized LDL upregulates macrophage DPP4 expression via TLR4/TRIF/CD36 pathways**. EBioMedicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30738832
ABSTRACT
BACKGROUND: We and others have shown that dipeptidyl peptidase-IV (DPP4) expression is increased in obesity/atherosclerosis and is positively correlated with atherosclerotic burden. However, the mechanism by which DPP4 expression is regulated in obesity remains unclear. In this study, we investigated the pathways regulating the expression of DPP4 on macrophages. METHODS: Flowsight(R) Imaging Flow Cytometry was employed for the detection of DPP4 and immunophenotyping. DPP4 enzymatic activity was measured by a DPPIV-Glo Protease Assay kit. FINDINGS: Human monocytes expressed a moderate level of membrane-bound DPP4. Obese patients with body mass index (BMI)>/=30 had a higher level of monocyte DPP4 expression, in parallel with higher levels of HOMA-IR, blood glucose, triglycerides, and non-HDL cholesterol, compared to those in the non-obese (BMI<30) patients. Oxidized low-density lipoprotein (oxLDL), but not native LDL, up-regulated DPP4 expression on macrophages with a preferential increase in CD36(+) cells. OxLDL mediated DPP4 up-regulation was considerably diminished by Toll-like receptor-4 (TLR4) knockdown and CD36 deficiency. TRIF deficiency, but not MyD88 deficiency, attenuated oxLDL-induced DPP4 increase. INTERPRETATION: Our study suggests a key role for oxLDL and downstream CD36/TLR4/TRIF in regulating DPP4 expression. Increased DPP4 in response to oxidized lipids may represent an integrated mechanism linking post-prandial glucose metabolism to lipoprotein abnormality-potentiated atherosclerosis.

[20] *Garber AJ, Abrahamson MJ, Barzilay JI et al.* **CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2019 EXECUTIVE SUMMARY**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2019; 25:69-100.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30742570
ABSTRACT
ABBREVIATIONS: A1C = hemoglobin A1C; AACE = American Association of Clinical Endocrinologists; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACCORD BP = Action to Control Cardiovascular Risk in Diabetes Blood Pressure; ACE = American College of Endocrinology; ACEI = angiotensin-converting enzyme inhibitor; AGI = alpha-glucosidase inhibitor; apo B = apolipoprotein B; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrant; BMI = body mass index; BP = blood pressure; CCB = calcium channel blocker; CGM = continuous glucose monitoring; CHD = coronary heart disease; CKD = chronic kidney disease; DKA = diabetic ketoacidosis; DPP4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; ER = extended release; FDA = Food and Drug Administration; GLP1 = glucagon-like peptide 1; HDL-C = high-density-lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density-lipoprotein cholesterol; LDL-P = low-density-lipoprotein particle; Look AHEAD = Look Action for Health in Diabetes; NPH = neutral protamine Hagedorn; OSA = obstructive sleep apnea; PCSK9 = proprotein convertase subtilisin-kexin type 9

serine protease; RCT = randomized controlled trial; SU = sulfonylurea; SGLT2 = sodium-glucose cotransporter 2; SMBG = self-monitoring of blood glucose; T2D = type 2 diabetes; TZD = thiazolidinedione.

[21] *Ruiz-Bustillo S, Ivern C, Badosa N et al.* **Efficacy of a nurse-led lipid-lowering secondary prevention intervention in patients hospitalized for ischemic heart disease: A pilot randomized controlled trial**. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology 2019:1474515119831511.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30757908
ABSTRACT
BACKGROUND AND AIMS:: Lack of achievement of secondary prevention objectives in patients with ischaemic heart disease remains an unmet need in this patient population. We aimed at evaluating the six-month efficacy of an intensive lipid-lowering intervention, coordinated by nurses and implemented after hospital discharge, in patients hospitalized for an ischaemic heart disease event. METHODS:: Randomized controlled trial, in which a nurse-led intervention including periodic follow-up, serial lipid level controls, and subsequent optimization of lipid-lowering therapy, if appropriate, was compared with standard of care alone in terms of serum lipid-level control at six months after discharge. RESULTS:: The nurse-led intervention was associated with an improved management of low-density lipoprotein (LDL) cholesterol levels compared with standard of care alone: LDL cholesterol levels 100 mg/dL were achieved in 97% participants in the intervention arm as compared with 67% in the usual care arm (p value <0.001), the LDL cholesterol 70 mg/dL target recommended by the 2016 European Society of Cardiology guidelines was achieved in 62% vs. 37% participants (p value 0.047) and the LDL cholesterol reduction of 50% recommended by the American College of Cardiology/American Heart Association in 2013 was achieved in 25.6% of participants in the intervention arm as compared with 2.6% in the usual care arm (p value 0.007). The intervention was also associated with improved blood pressure control among individuals with hypertension. CONCLUSIONS:: Our findings highlight the opportunity that nurse-led, intensive, post-discharge follow-up plans may represent for achieving LDL cholesterol guideline-recommended management objectives in patients with ischaemic heart disease. These findings should be replicated in larger cohorts.

[22] *Vesza Z, Pires C, da Silva PM*. **Statin-related Lichenoid Dermatosis: An Uncommon Adverse Reaction to a Common Treatment**. European journal of case reports in internal medicine 2018; 5:000844.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30756034
ABSTRACT
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are generally safe and well-tolerated drugs that are extensively used for the primary and secondary prevention of atherosclerotic cardiovascular events. Muscle and liver adverse reactions are the best recognized, while cutaneous side effects are exceedingly rare. We present the case of a 65-year-old woman with severe hypercholesterolemia, who developed generalized erythematous cutaneous lesions with pruritus, resembling lichen planus, months after starting treatment with

simvastatin. The symptoms disappeared on withdrawal of simvastatin and reappeared within 3 months upon rechallenge with rosuvastatin. In addition to describing a rare adverse effect of statins, the authors also discuss the nutraceutical approach to the management of a statin-intolerant patient. LEARNING POINTS: Lichenoid drug eruption is an uncommon cutaneous adverse effect of several drugs, with very few cases associated with statins.A temporal relationship, dechallenge/rechallenge information, and the lack of confounding factors or alternative explanations support the suggestion of causality.Due to the lack of optimized alternative treatment options for statin-intolerant patients, the nutraceutical approach should be considered.

[23] *Wojcicka G, Zareba M, Warpas A et al.* **The effect of exenatide (a GLP-1 analog) and sitagliptin (a DPP-4 inhibitor) on plasma platelet-activating factor acetylhydrolase (PAF-AH) activity and concentration in normal and fructose-fed rats**. European journal of pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30768981
ABSTRACT
Inflammation and oxidative stress are the two processes crucial in atherogenesis. Platelet-activating factor acetylhydrolase (PAF-AH), a plasma lipoprotein-associated enzyme, degrades pro-inflammatory lipids generated within oxidatively modified lipoproteins. Extensive evidence shows that incretin-based drugs, a new class of anti-diabetic agents, can provide cardiovascular protection that cannot be attributed to their glucose-lowering effects. The present study was undertaken to determine whether the antiatherogenic effects of the GLP-1(glucagon-like peptide-1) receptor agonist (exenatide) and DPP-4(dipeptidyl peptidase-4) inhibitors (sitagliptin) may occur via the regulation of platelet-activating factor acetylhydrolase (PAF-AH) activity/mass and inhibition of low-density lipoprotein (LDL) oxidation in the fructose-fed rats. Normal and fructose-fed rats (8 wk) were treated (4 wk) with sitagliptin (5 and 10 mg/kg p.o.) or with exenatide (5 and 10 microg/kg, s.c.). Plasma PAF-AH activity and phosphatidylcholine (PC) concentration were measured colorimetrically. Plasma PAF-AH concentration, oxidized LDL (oxLDL), hexanoyl-Lys adduct (HEL), lyso-PC, apolipoprotein A-I (apoA-I), apoB, platelet-activating factor (PAF), monocyte chemoattractant protein-1 (MCP-1) and endothelin-1 (ET-1) were measured by ELISA. The four-week exenatide (5 microg/kg, sc.) treatment of fructose fed-rats significantly increased plasma PAF-AH activity (+33%, P<0.001) and decreased the level of circulating oxLDL (-42%, P<0.05) and MCP-1 (-23%, P<0.01). These changes were accompanied by the decrease in plasma PC/lyso-PC (-47%, P<0.001) and apoB/apoA-I ratio (-75%, P<0.001). The effect of exenatide on enzyme activity was associated with only a minor effect on metabolic parameters and was independent of weight reduction. Exenatide but not sitagliptin inhibits oxidative modification of LDL probably due to favorable effect on plasma PAF-AH activity.

[24] *Lee S, Akioyamen LE, Aljenedil S et al.* **Genetic testing for familial hypercholesterolemia: Impact on diagnosis, treatment and cardiovascular risk**. European journal of preventive cardiology 2019:2047487319829746.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30755017
ABSTRACT

AIMS: Familial hypercholesterolemia (FH) is the most common genetic disorder in medicine, with a prevalence of 1/250. Affected individuals have elevated low-density lipoprotein cholesterol (LDL-C) and an increased lifetime risk of atherosclerotic cardiovascular disease (ASCVD). The diagnosis of FH is based on algorithms that include LDL-C levels, physical manifestations, family history of high LDL-C and premature ASCVD, and, more recently, genetic testing. We sought to determine the impact of genetic testing on the: 1) diagnosis of 'definite familial hypercholesterolemia', 2) initiation and adherence of lipid-lowering therapy and 3) risk of ASCVD. METHODS: We performed a systematic review and meta-analysis, pooling odds ratios and 95% confidence intervals for ASCVD from studies comparing risk estimates in individuals harboring FH-causing variants and unaffected individuals. RESULTS: After screening 3304 unique publications, 56 studies were included in the analysis. 1) Genetic testing provided confirmation of FH in 28-80%, over clinical criteria alone, depending on the diagnostic algorithm and the method of analysis. In two large population-based studies comprising 76,751 individuals, an FH-causing variant was identified in only 1.7-2.5% of subjects with an LDL-C > 4.9 mmol/L (190 mg/dL). 2) A confirmed molecular diagnosis increased lipid-lowering therapy adherence (five studies, n = 4181 definite FH). 3) Loss-of-function variant of the LDLR were at a markedly increased risk of myocardial infarction (odds ratio 6.77, 95% confidence interval 4.75-9.66), and patients with a milder (hypomorphic) pathogenic LDLR change had a 4.4-fold increase in risk (odds ratio 4.4, 95% confidence interval 2.34-8.26), compared with controls. CONCLUSION: DNA sequencing confirms the diagnosis of FH but has a poor yield in unselected patients whose sole criterion is an elevated LDL-C. Initiation and adherence to treatment is improved. The risk of ASCVD is 4.4- to 6.8-fold increased in patients with an FH-causing variant compared with controls, depending on the severity of the DNA change.

[25] *Kim JH, Chung BI*. **Re: Timu J. Murtola, Hemo Syvala, Teemu Tolonen, et al. Atorvastatin Versus Placebo for Prostate Cancer Before Radical Prostatectomy-A Randomized, Double-blind, Placebo-controlled Clinical Trial. Eur Urol 2018;74:697-701**. European urology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30738708
ABSTRACT

[26] *Murtola TJ, Syvala H, Riikonen J*. **Reply to Jae Heon Kim and Benjamin I. Chung's Letter to the Editor re: Teemu J. Murtola, Heimo Syvala, Teemu Tolonen, et al. Atorvastatin Versus Placebo for Prostate Cancer Before Radical Prostatectomy-A Randomized, Double-blind, Placebo-controlled Clinical Trial. Eur Urol 2018;74:697-701**. European urology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30738709
ABSTRACT

[27] *Kumar S*. **Cardiometabolic risk factors and their treatment in patients with Type 2 diabetes**. Expert review of endocrinology & metabolism 2007; 2:331-339.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30743808
ABSTRACT
The prevalence of obesity-associated diabetes is increasing dramatically in the UK and worldwide. Obesity, particularly abdominal obesity, is not only associated with other cardiovascular risk factors, but is an independent cardiometabolic risk factor for diabetes and

cardiovascular disease. Thus, the focus of obesity management, especially in patients with prediabetes and Type 2 diabetes, should encompass cardiometabolic risk reduction as well as weight loss. Lifestyle and diet modification should form the basis of all effective strategies for weight reduction. Pharmacotherapy provides an additional option that is appropriate in some individuals, alongside lifestyle modification, to improve cardiometabolic risk. Drugs currently available include antidiabetic agents, statins, fibrates, antihypertensives and weight-loss drugs.

[28] *Bentz AJ, Netland PJ, Newman WP et al.* **Comparison of Cardiovascular Outcomes Between Statin Monotherapy and Fish Oil and Statin Combination Therapy in a Veteran Population**. Federal practitioner : for the health care professionals of the VA, DoD, and PHS 2018; 35:26-31.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30766323
ABSTRACT
A study that compared the use of statin therapies with and without fish oil in a veteran population found an insignificant difference between the 2 arms.

[29] *Dowd CM, Tillmann JJ*. **Therapeutic Interchange From Rosuvastatin to Atorvastatin in a Veteran Population**. Federal practitioner : for the health care professionals of the VA, DoD, and PHS 2015; 32:20-24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30766035
ABSTRACT
A change in formulary statins was not associated with any differences in liver enzymes or lipid control for patients but did result in significant cost savings at the North Florida/South Georgia Veterans Health System.

[30] *Drake B, Grimm DL, Allman J, 2nd*. **Treatment Failure With Atorvastatin After Change From Rosuvastatin to Atorvastatin**. Federal practitioner : for the health care professionals of the VA, DoD, and PHS 2015; 32:25-29.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30766036
ABSTRACT
Lipid levels remained largely unchanged, and patients experienced few adverse events following the conversion of patients from rosuvastatin to atorvastatin therapy at the Huntington VAMC.

[31] *Felicetta JV*. **Did Niacin Get a Bum Rap?** Federal practitioner : for the health care professionals of the VA, DoD, and PHS 2015; 32:6-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30766053
ABSTRACT

[32] *Sharpton RA, Laucka PJ, McKeller RN et al.* **The Impact of Obesity on the Efficacy of Simvastatin for Lowering Low-Density Lipoprotein Cholesterol in a Veteran Population**. Federal practitioner : for the health care professionals of the VA, DoD, and PHS 2017; 34:41-44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30766266
ABSTRACT

A retrospective review found that obesity did not impact the lipid-lowering effectiveness of simvastatin therapy.

[33] *Phillips B, Szostak J, Titz B et al.* **A six-month systems toxicology inhalation/cessation study in ApoE(-/-) mice to investigate cardiovascular and respiratory exposure effects of modified risk tobacco products, CHTP 1.2 and THS 2.2, compared with conventional cigarettes**. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30763686
ABSTRACT
Smoking is one of the major modifiable risk factors in the development and progression of chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). Modified-risk tobacco products (MRTP) are being developed to provide substitute products for smokers who are unable or unwilling to quit, to lessen the smoking-related health risks. In this study, the ApoE(-/-) mouse model was used to investigate the impact of cigarette smoke (CS) from the reference cigarette 3R4F, or aerosol from two potential MRTPs based on the heat-not-burn principle, carbon-heated tobacco product 1.2 (CHTP1.2) and tobacco heating system 2.2 (THS 2.2), on the cardiorespiratory system over a 6-month period. In addition, cessation or switching to CHTP1.2 after 3 months of CS exposure was assessed. A systems toxicology approach combining physiology, histology and molecular measurements was used to evaluate the impact of MRTP aerosols in comparison to CS. CHTP1.2 and THS2.2 aerosols, compared with CS, demonstrated lower impact on the cardiorespiratory system, including low to absent lung inflammation and emphysematous changes, and reduced atherosclerotic plaque formation. Molecular analyses confirmed the lower engagement of pathological mechanisms by MRTP aerosols than CS. Both cessation and switching to CHTP1.2 reduced the observed CS effects to almost sham exposure levels.

[34] *Nishikido T, Ray KK.* **Non-antibody Approaches to Proprotein Convertase Subtilisin Kexin 9 Inhibition: siRNA, Antisense Oligonucleotides, Adnectins, Vaccination, and New Attempts at Small-Molecule Inhibitors Based on New Discoveries**. Frontiers in cardiovascular medicine 2018; 5:199.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30761308
ABSTRACT
Low-density lipoprotein (LDL) is one of the principal risk factors for atherosclerosis. Circulating LDL particles can penetrate into the sub-endothelial space of arterial walls. These particles undergo oxidation and promote an inflammatory response, resulting in injury to the vascular endothelial wall. Persistent elevation of LDL-cholesterol (LDL-C) is linked to the progression of fatty streaks to lipid-rich plaque and thus atherosclerosis. LDL-C is a causal factor for atherosclerotic cardiovascular disease and lowering it is beneficial across a range of conditions associated with high risk of cardiovascular events. Therefore, all guidelines-recommended initiations of statin therapy for patients at high cardiovascular risk is irrespective of LDL-C. In addition, intensive LDL-C lowering therapy with statins has been demonstrated to result in a greater reduction of cardiovascular event risk in large clinical trials. However, many high-risk patients receiving statins fail to achieve the guideline-recommended reduction in LDL-C levels in

routine clinical practice. Moreover, low levels of adherence and often high rates of discontinuation demand the need for further therapies. Ezetimibe has typically been used as a complement to statins when further LDL-C reduction is required. More recently, proprotein convertase subtilisin kexin 9 (PCSK9) has emerged as a novel therapeutic target for lowering LDL-C levels, with PCSK9 inhibitors offering greater reductions than feasible through the addition of ezetimibe. PCSK9 monoclonal antibodies have been shown to not only considerably lower LDL-C levels but also cardiovascular events. However, PCSK9 monoclonal antibodies require once- or twice-monthly subcutaneous injections. Further, their manufacturing process is expensive, increasing the cost of therapy. Therefore, several non-antibody treatments to inhibit PCSK9 function are being developed as alternative approaches to monoclonal antibodies. These include gene-silencing or editing technologies, such as antisense oligonucleotides, small interfering RNA, and the clustered regularly interspaced short palindromic repeats/Cas9 platform; small-molecule inhibitors; mimetic peptides; adnectins; and vaccination. In this review, we summarize the current knowledge base on the role of PCSK9 in lipid metabolism and an overview of non-antibody approaches for PCSK9 inhibition and their limitations. The subsequent development of alternative approaches to PCSK9 inhibition may give us more affordable and convenient therapeutic options for the management of high-risk patients.

[35] *Sarraju A, Knowles JW*. **Genetic Testing and Risk Scores: Impact on Familial Hypercholesterolemia**. Frontiers in cardiovascular medicine 2019; 6:5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30761309
ABSTRACT
Familial Hypercholesterolemia (FH) is an inherited lipid disorder affecting 1 in 220 individuals resulting in highly elevated low-density lipoprotein levels and risk of premature coronary disease. Pathogenic variants causing FH typically involve the LDL receptor (LDLR), apolipoprotein B-100 (APOB), and proprotein convertase subtulisin/kexin type 9 genes (PCSK9) and if identified convey a risk of early onset coronary artery disease (ASCVD) of 3- to 10-fold vs. the general population depending on the severity of the mutation. Identification of monogenic FH within a family has implications for family-based testing (cascade screening), risk stratification, and potentially management, and it has now been recommended that such testing be offered to all potential FH patients. Recently, robust genome wide association studies (GWAS) have led to the recognition that the accumulation of common, small effect alleles affecting many LDL-c raising genes can result in a clinical phenotype largely indistinguishable from monogenic FH (i.e., a risk of early onset ASCVD of ~3-fold) in those at the extreme tail of the distribution for these alleles (i.e., the top 8% of the population for a polygenic risk score). The incorporation of these genetic risk scores into clinical practice for non-FH patients may improve risk stratification but is not yet widely performed due to a less robust evidence base for utility. Here, we review the current status of FH genetic testing, potential future applications as well as challenges and pitfalls.

[36] *Zaki Husain Rizvi S, Ali Shah F, Khan N et al.* **Simvastatin-loaded solid lipid nanoparticles for enhanced anti-hyperlipidemic activity in hyperlipidemia animal model**. Int J Pharm 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30753932

ABSTRACT
The objective of current study was to develop solid lipid nanoparticles-loaded with simvastatin (SIM-SLNs) and investigate their in vivo anti-hyperlipidemic activity in poloxamer-induced hyperlipidemia model. Nano-template engineering technique was used to prepare SIM-SLNs with palmityl alcohol as lipid core and a mixture of Tween 40/Span 40/Myrj 52 to stabilize the core. The prepared SIM-SLNs were evaluated for physicochemical parameters including particle diameter, surface charge, morphology, incorporation efficiency, thermal behaviour and crystallinity. In vitro release profile of SIM-SLNs in simulated gastric and intestinal fluids was evaluated by using dialysis bag technique and anti-hyperlipidemic activity was assessed in hyperlipidemia rat model. SIM-SLNs revealed uniform particle size with spherical morphology, zeta potential of -24.9 mV and high incorporation efficiency (approximately 85%). Thermal behaviour and crystallinity studies demonstrated successful incorporation of SIM in the lipid core and its conversion to amorphous form. SIM-SLNs demonstrated a sustained SIM release from the lipid core of nanoparticles. SIM-SLNs significantly reduced the elevated serum lipids as indicated by approximately 3.9 and approximately 1.5-times decreased total cholesterol compared to those of untreated control and SIM dispersion treated hyperlipidemic rats. In conclusion, SIM-SLNs showed a great promise for improving the therapeutic outcomes of SIM via its effective oral delivery.

[37] *Nenna A, Spadaccio C, Lusini M et al.* **Preoperative atorvastatin reduces bleeding and blood transfusions in patients undergoing elective isolated aortic valve replacement**. Interact Cardiovasc Thorac Surg 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30753487

ABSTRACT
OBJECTIVES: Minimization of bleeding to reduce the use of blood products is of utmost importance in cardiac surgery. Statins are known for their pleiotropic effects beyond lipid-lowering properties, and the use of atorvastatin preoperatively is associated with reduced risk of bleeding and blood product use after coronary surgery. However, no studies have investigated if this beneficial effect also extends to aortic valve surgery. METHODS: In this retrospective cohort study, 1145 consecutive patients undergoing elective primary isolated aortic valve replacement meeting the inclusion and exclusion criteria were selected from January 2009 to December 2017 (547 in the atorvastatin group, 598 in the control group). Postoperative bleeding, blood product use, and complications were monitored during hospitalization. RESULTS: Postoperative bleeding was significantly lower in the atorvastatin group compared with the controls in the first 12 h after surgery (372 +/- 137 vs 561 +/- 219 ml; P = 0.001) and considering overall bleeding (678 +/- 387 vs 981 +/- 345 ml, P = 0.001). A total of 32.3% of controls and 26.3% of atorvastatin users received packed red blood cells (P = 0.027), and major surgical complications were similar between the groups. Postoperative length of stay was shorter in the atorvastatin group with an average reduction of 1 day of hospitalization (6.0 +/- 1.4 vs 6.9 +/- 2.1 days; P = 0.001). Postoperative bleeding among the atorvastatin-treated patients was significantly greater in those taking lower doses compared to those taking higher doses of atorvastatin with a 20% between-group difference (P = 0.001). CONCLUSIONS: Preoperative treatment with atorvastatin might reduce postoperative bleeding and transfusion

of packed red blood cells in patients undergoing elective isolated aortic valve replacement. This result might translate into faster recovery after surgery and reduced hospitalization costs.

[38] *Shapiro MD, Minnier J, Tavori H et al.* **Relationship Between Low-Density Lipoprotein Cholesterol and Lipoprotein(a) Lowering in Response to PCSK9 Inhibition With Evolocumab**. Journal of the American Heart Association 2019; 8:e010932.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30755061
ABSTRACT
Background Beyond their potent LDL (low-density lipoprotein) cholesterol (LDL -C)-lowering efficacy (50-60%), PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors also reduce Lp(a) (lipoprotein[a]) levels by 25% to 30%, suggesting a 2:1 response ratio. We aimed to characterize the relationship between LDL -C and Lp(a) lowering by evolocumab, a PCSK 9 inhibitor, in a large clinical trial population and to determine the prevalence of concordant/discordant LDL -C and Lp(a) responses to PCSK 9 inhibition. Methods and Results Data were analyzed from 4 randomized, 12-week, multicenter, phase 3 evolocumab trials. Patients with familial hypercholesterolemia, nonfamilial hypercholesterolemia, or statin intolerance participated in the trials. The main measure was the degree of concordance or discordance of LDL -C and Lp(a) in response to PCSK 9 inhibition; concordant response was defined as LDL -C reduction >35% and Lp(a) reduction >10%. The study cohort comprised 895 patients (438 female; median age: 59.0 years [interquartile range: 51-66 years]). Baseline mean level of LDL -C was 133.6 mg/dL (SE: 1.7) and median Lp(a) level was 46.4 mg/dL (interquartile range: 18.4-82.4 mg/dL). A discordant response was observed in 165 (19.7%) patients. With these cutoffs, the prevalence of discordance was higher when considering baseline Lp(a) concentrations >30 mg/dL (26.5%) or >50 mg/dL (28.6%). Conclusions We demonstrate high prevalence of discordance in LDL -C and Lp(a) reduction in response to evolocumab, particularly when considering higher baseline Lp(a) concentrations, indicating the possibility of alternative pathways beyond LDLR (LDL receptor)-mediated clearance involved in Lp(a) reduction by evolocumab. Clinical Trial Registration URL : http://www.clinicaltrials.gov . Unique identifiers: NCT 01763827, NCT 01763866, NCT 01763905, NCT 01763918.

[39] *Al'Aref SJ, Su A, Gransar H et al.* **A cross-sectional survey of coronary plaque composition in individuals on non-statin lipid lowering drug therapies and undergoing coronary computed tomography angiography**. Journal of cardiovascular computed tomography 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30745132
ABSTRACT
INTRODUCTION: Non-statin therapy (NST) is used as second-line treatment when statin monotherapy is inadequate or poorly tolerated. OBJECTIVE: To determine the association of NST with plaque composition, alone or in combination with statins, in patients undergoing coronary computed tomography angiography (coronary CTA). METHODS: From the multicenter CONFIRM registry, we analyzed individuals who underwent coronary CTA with known lipid-lowering therapy status and without prior coronary artery disease at baseline. We created a propensity score for being on NST, followed by stepwise multivariate linear regression, adjusting for the propensity score as well as risk factors, to determine the association between NST and the number of coronary artery segments with each plaque type (non-calcified (NCP),

partially calcified (PCP) or calcified (CP)) and segment stenosis score (SSS). RESULTS: Of the 27,125 subjects in CONFIRM, 4,945 met the inclusion criteria; 371 (7.5%) took NST. At baseline, patients on NST had more prevalent risk factors and were more likely to be on concomitant cardiac medications. After multivariate and propensity score adjustment, NST was not associated with plaque composition: NCP (0.07 increase, 95% CI: -0.05, 0.20; p=0.26), PCP (0.10 increase, 95% CI: -0.10, 0.31; p=0.33), CP (0.18 increase, 95% CI: -0.10, 0.46; p=0.21) or SSS (0.45 increase, 95% CI: -0.02,0.93; p=0.06). The absence of an effect of NST on plaque type was not modified by statin use (p for interaction>0.05 for all). CONCLUSION: In this cross-sectional study, non-statin therapy was not associated with differences in plaque composition as assessed by coronary CTA.

[40] *Yaribeygi H, Atkin SL, Simental-Mendia LE et al.* **Anti-inflammatory effects of resolvins in diabetic nephropathy: Mechanistic pathways**. Journal of cellular physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30746696
ABSTRACT
The incidence of diabetes mellitus is growing rapidly. The exact pathophysiology of diabetes is unclear, but there is increasing evidence of the role of the inflammatory response in both developing diabetes as well as its complications. Resolvins are naturally occurring polyunsaturated fatty acids that are found in fish oil and sea food that have been shown to possess anti-inflammatory actions in several tissues including the kidneys. The pathways by which resolvins exert this anti-inflammatory effect are unclear. In this review we discuss the evidence showing that resolvins can suppress inflammatory responses via at least five molecular mechanisms through inhibition of the nucleotide-binding oligomerization domain protein 3 inflammasome, inhibition of nuclear factor kappaB molecular pathways, improvement of oxidative stress, modulation of nitric oxide synthesis/release and prevention of local and systemic leukocytosis. Complete understanding of these molecular pathways is important as this may lead to the development of new effective therapeutic strategies for diabetes and diabetic nephropathy.

[41] *Zheng S, Zhao J, Xing H, Xu S*. **Oxidative stress, inflammation, and glycometabolism disorder-induced erythrocyte hemolysis in selenium-deficient exudative diathesis broilers**. Journal of cellular physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30741419
ABSTRACT
Selenium (Se) deficiency causes injury of diversified tissues and cells, including livers, hearts, skeletal muscles, and erythrocytes. The aim of the present study is to explore the molecular mechanism of erythrocyte hemolysis due to Se deficiency in broilers. One hundred and eighty broilers (male/female, 1 day old) were randomly divided into two groups and fed with either a normal Se content diet (C group, 0.2 mg Se/kg) or a Se-deficient diet (ED group, 0.008 mg Se/kg) for 45 days. During the trial period of 15-30 days, biological properties such as osmotic fragility, fluidity, phospholipid components of cell membrane, adenosine triphosphatase activities, and antioxidant function of erythrocytes in broilers were examined. Moreover, the messenger RNA (mRNA) expressions of genes associated with inflammation, glycometabolism, and avian uncoupling protein (avUCP) were detected. We found that compared with the C

group, hemolysis rate, degree of polarization, and microviscosity of erythrocytes were increased in broilers of the ED group. The composition of erythrocyte membrane lipids was changed. Meanwhile, the antioxidant function of erythrocytes was weakened and mRNA levels of inflammatory genes were stimulated by Se deficiency ($p < 0.05$). In addition, mRNA expressions of rate-limiting enzymes in glycometabolism were effected and avUCP mRNA level was downregulated ($p < 0.05$) in the ED group. It has been concluded from the results that oxidative stress, inflammatory response, and glycometabolism disorder lead to erythrocyte hemolysis by changing the structure and function of erythrocyte membrane in ED broilers suffered from Se deficiency.

[42] *Hori M, Miyauchi E, Son C, Harada-Shiba M*. **Detection of the benign c.2579C>T (p.A860V) variant of the LDLR gene in a pedigree-based genetic analysis of familial hypercholesterolemia**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30745271
ABSTRACT
BACKGROUND: More than 2500 variants of the low-density lipoprotein receptor (LDLR) gene have been reported in familial hypercholesterolemia (FH). However, the effects of these variants on the pathophysiology of FH have not been fully clarified. OBJECTIVE: Our aim was to examine whether the c.2579C>T (p.A860V) variant of the LDLR gene affects the phenotype of FH. We present 2 index cases harboring biallelic LDLR variants, including the c.2579C>T (p.A860V) variant, which is defined as having uncertain significance in ClinVar. METHODS: Genetic analysis was performed for coding regions of the LDLR and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes in 2 families. Detailed clinical and biochemical data were gathered from family members. RESULTS: In one family, the index case involved a patient who harbored biallelic A860V and c.1528-1529insA (p.T510Nfs) LDLR variants and had 8 children; the affected children had the p.T510Nfs variant, and the unaffected children had the A860V variant. In another family, the patient involved in the index case and his sister had biallelic A860V and c.1845+2T>C LDLR variants. There was no difference in FH phenotype between these siblings and their relatives who were heterozygous for the c.1845+2T>C variant. In addition, the allele frequency of the A860V variant (0.0062/0.0095) in the Japanese population, as indicated by 2 databases, was higher than expected based on the prevalence of heterozygous FH in the Japanese population (0.002-0.005). CONCLUSIONS: This is the first report to show using pedigree-based genetic analysis that the A860V variant of the LDLR gene is a benign variant.

[43] *Knickelbine T, Jia L, White SK et al.* **A systematic approach for successful PCSK9 inhibitor prescribing in clinical practice**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30745203
ABSTRACT
BACKGROUND: Despite patient and provider interest, the use of PCSK9i therapy remains limited in clinical practice. High annual listed prices have created intense payer scrutiny and frequent health plan denials, with national approval rates in the range of 30% to 40%. OBJECTIVE: Our goal was to validate the strategies for increasing PCSK9i approval rates and to present a framework for successful PCSK9i prescribing in clinical practice. METHODS: In Sept 2015, a systematic team-based approach was developed and implemented at our institution. The

approach centered on a preventive team of 3 senior staff cardiologists, 1 nurse practitioner, 1 physician assistant, 1 care coordinator, 1 pharmacist, and 1 pharmacy technician. The team was responsible for gathering and compiling the required documents to support an approval, as well as collaborating with the in-house pharmacy to complete PA and appeals processes. RESULTS: In the total study population, 141 (71.9%) were approved for PCSK9i therapy at first submission and 55 (28.1%) were rejected. Of those initially rejected, 48 (85.7%) appealed and all 48 who appealed (100.0%) were ultimately approved. The final coverage decision was 189 (96.4%) approved and 7 (3.6%) rejected. CONCLUSION: Our study highlights the presence of modifiable barriers in the PCSK9i approval process. Given the crucial role of health care teams in overcoming these modifiable barriers, we developed a simple stepwise algorithm for navigating the PCSK9i approval process. Our algorithm can help relieve busy providers of heavy administrative burdens and facilitate greater accuracy, standardization, and efficiency in documentation.

[44] *Reynolds VW, Chinn ME, Jolly JA et al.* **Integrated specialty pharmacy yields high PCSK9 inhibitor access and initiation rates**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30745204
ABSTRACT
BACKGROUND: Access to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors that lower low-density lipoprotein cholesterol in patients at high risk of atherosclerotic cardiovascular disease events has proven challenging. Methods to overcome access barriers are needed to fully realize the benefits of these novel agents. OBJECTIVE: This study evaluated medication access rates in patients prescribed a PCSK9 inhibitor at a health care system with integrated specialty pharmacy services. METHODS: We performed a single-center, ambispective cohort study of patients prescribed a PCSK9 inhibitor between September 2015 and December 2016 at Vanderbilt University Medical Center outpatient clinics. The primary end point was the percentage of PCSK9 inhibitor prescriptions resulting in access of the total prescriptions triaged to Vanderbilt Specialty Pharmacy. Secondary end points assessed among patients approved for therapy included time between benefits investigation and insurance approval, financial assistance use, and treatment initiation rates. RESULTS: Two hundred ninety-nine patients met inclusion criteria (average age = 63 years). Forty-six percent were female, 57% held commercial insurance, and 70% had an atherosclerotic cardiovascular disease indication. Overall, 96% of prescriptions resulted in access to a PCSK9 inhibitor. Most patients were approved with an initial prior authorization (58%) or after one appeal (29%). The median time to approval was 8 days. Among patients approved for therapy, 53% received financial assistance and 94% initiated therapy. CONCLUSION: An integrated specialty pharmacy service model in outpatient clinics produced high rates of PCSK9 inhibitor therapy access and initiation. This high level of access supports this model as a best practice for prescribing PCSK9 inhibitor therapy.

[45] *Lee S, Lee HJ, Kang H et al.* **Trastuzumab Induced Chemobrain, Atorvastatin Rescued Chemobrain with Enhanced Anticancer Effect and without Hair Loss-Side Effect**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30754707
ABSTRACT

The authors identified that chemo-brain was induced after trastuzumab (TZB) therapy. In addition, atorvastatin (ATV) could rescue chemo-brain during trastuzumab (TZB) therapy. Enhanced therapeutic effect of TZB was confirmed after ATV therapy. We also investigated that there was no hair loss side effect due to ATV therapy. In an animal model, 150 mug TZB and five serial doses of 20 mg/kg ATV were administered. (18)F-fluorodeoxyglucose Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) data were acquired. Statistical parametric mapping analysis and voxel-based morphometry analysis were performed to identify differences in glucose metabolism and gray matter concentration. The enhanced therapeutic efficacy of TZB after ATV treatment was assessed using a human epidermal growth factor receptor 2-positive gastric cancer model. We found a decrease in cerebral glucose metabolism and gray matter concentration in the frontal lobe following TZB therapy ($p < 0.005$). After subsequent ATV administration, glucose metabolism and regional gray matter concentration were rescued ($p < 0.005$). Cognitive impairment due to TZB and the rescue effect of ATV were confirmed using a passive avoidance test and quantitative real-time reverse transcription PCR. Furthermore, the penetration and accumulation of TZB in tumors increased by 100% after ATV co-administration, which resulted in an enhanced anti-cancer effect. Our study collectively demonstrates that ATV co-administration with TZB rescued the TZB-induced chemo-brain and enhances the therapeutic efficacy of TZB in tumors. We also showed that there was no hair loss during ATV therapy.

[46] *Dicembrini I, Giannini S, Ragghianti B et al.* **Effects of PCSK9 inhibitors on LDL cholesterol, cardiovascular morbidity and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials**. Journal of endocrinological investigation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30762200

ABSTRACT

BACKGROUND AND AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors determine a wide reduction of LDL cholesterol, greater than other lipid-lowering agents. The present meta-analysis is aimed at the assessment of PCSK9 inhibitors effect on LDL Cholesterol, cardiovascular morbidity and all-cause mortality. METHODS AND RESULTS: A Medline and Clinicaltrials.gov search for eligible studies until December 1, 2017, was performed. All randomized trials (> 12 weeks) comparing PCSK-9 inhibitors with placebo or active drugs were retrieved. Primary endpoints: (a) LDL cholesterol at endpoint; (b) Major cardiovascular events (MACE); (c) All-cause mortality. Data extraction was performed independently by two of the authors, and conflicts resolved by a third investigator. A total of 38 trials fulfilling the inclusion criteria were identified, with mean duration of 36.4 weeks. The reduction of LDL cholesterol at endpoint, versus placebo, ezetimibe, and high-dose statins was - 65.3 [- 69.6, - 60.9]%, - 57.7 [- 68.3;- 47.0]%, and - 34.5 [- 40.8;- 28.1]%, respectively, with alirocumab possibly showing a smaller effect than the other drugs of the class. Treatment with PCSK9 inhibitors was associated with a reduction in the incidence of MACE (Mantel-Haenszel Odds Ratio [MH-OR] 0.83 [0.78, 0.88]), with significant effects of alirocumab and evolocumab only. The number needed to treat for 2 years for preventing one event was 89. All-cause mortality and cardiovascular mortality were not reduced by treatment with PCSK-9 inhibitors (MH-OR 0.94 [0.84, 1.04] and 0.97[0.86;1.09]). CONCLUSIONS: PCSK-9 inhibitors are effective in reducing LDL cholesterol and

the incidence of major cardiovascular events in high-risk patients. Bococizumab does not show significant effects on MACE. REGISTRATION NUMBER: PROSPERO-CRD42018087640.

[47] *Ramirez JL, Gasper WJ, Khetani SA et al.* **Fish Oil Increases Specialized Pro-resolving Lipid Mediators in PAD (The OMEGA-PAD II Trial)**. J Surg Res 2019; 238:164-174.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30771686
ABSTRACT
BACKGROUND: N-3 polyunsaturated fatty acid (PUFA) supplementation has been associated with reduced mortality and inflammation in patients with cardiovascular disease. There are limited data on the effects of n-3 PUFA supplementation in patients with peripheral artery disease (PAD). MATERIALS AND METHODS: The OMEGA-PAD II trial was a double-blinded, randomized, placebo-controlled trial to assess the effect of 3 mo of high-dose oral n-3 PUFA supplementation on inflammation, endothelial function, and walking ability in patients with PAD. RESULTS: Twenty-four patients with claudication received 4.4 g/d of fish oil or placebo for 3 mo. Outcomes measured included high-sensitivity C-reactive protein levels, the omega-3 index, endothelial function as measured via flow-mediated vasodilation, walking impairment questionnaire, and a 6-min walk test. Plasma levels of specialized pro-resolving lipid mediators (SPMs) were measured by liquid-chromatography-tandem mass spectrometry. In patients treated with fish oil, the absolute mean omega-3 index significantly increased from baseline (fish oil: 7.2 +/- 1.2%, P < 0.001; placebo: -0.4 +/- 0.9%, P = 0.31; between-group P < 0.001). Furthermore, there were significant increases in several pathway markers of SPM biosynthesis, including several mono-hydroxyeicosapentaenoic acids and mono-hydroxydocosahexaenoic acids. We also observed significant increases in the SPM lipoxin A5 (fish oil: 0.57 +/- 0.70 pg/mL, P = 0.05; placebo: 0.01 +/- 0.38 pg/mL, P = 0.93; between-group P = 0.04) and resolvin E3 (fish oil: 154 +/- 171 pg/mL, P = 0.04; placebo: 32 +/- 54 pg/mL, P = 0.08; between-group P = 0.04). There were no significant changes in high-sensitivity C-reactive protein, flow-mediated vasodilation, walking impairment questionnaire, or 6-min walk test in the fish oil group. CONCLUSIONS: Fish oil increases SPMs in plasma of patients with PAD. Further studies are required to determine whether these early changes translate to clinical improvements in patients with PAD.

[48] *Lee S, Kim DH, Youn YN et al.* **Rosuvastatin attenuates bioprosthetic heart valve calcification**. The Journal of thoracic and cardiovascular surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30738596
ABSTRACT
OBJECTIVE: There are pathophysiologic similarities between calcification and atherosclerosis because both are the product of an active inflammatory process. The aim of the study was to examine the effects of statin treatment on calcification in commercially available bioprosthetic heart valves. METHODS: Twenty Sprague-Dawley rats were fed a high-fat diet to induce hypercholesterolemia during 4 weeks. They were randomly divided into 2 groups according to statin intake (control, n = 10: high-fat diet/statin; n = 10: high-fat diet with statin). Four commercially available tissue valve (Magna Perimount, Carpentier-Edwards, Irvine, Calif; Hancock, Medtronic, Minneapolis, Minn; Mitroflow, LivaNova, London, England; and Trifecta, St Jude Medical, St Paul, Minn) cusp samples (total 320) were implanted in rat dorsal subcutis at 4

weeks. After implantation, rosuvastatin was administered daily to the statin group. The cusps were explanted at 12 weeks, and calcium levels were determined by atomic absorption spectroscopy. Western blotting, histologic, and immunohistochemical analyses were conducted to identify the anticalcification mechanism of the statin. RESULTS: The mean calcium level in the control group was significantly higher than in the statin group (P < .01) for all tissue valves (Magna Perimount: 2.67 +/- 0.26 mg/g vs 1.31 +/- 0.40 mg/g; Hancock: 2.70 +/- 0.57 mg/g vs 1.53 +/- 0.34 mg/g; Mitroflow: 2.39 +/- 0.71 mg/g vs 1.26 +/- 0.38 mg/g; Trifecta: 2.54 +/- 0.42 mg/g vs 1.63 +/- 0.72 mg/g). Inflammatory cell infiltration and interleukin-6 and bone morphogenetic protein 2 expressions were significantly reduced in the statin group. CONCLUSIONS: Statin treatment significantly attenuated bioprosthetic heart valve calcification associated with decreasing the levels of interleukin-6 and bone morphogenetic protein 2. Thus, statin treatment might be helpful for the longevity of bioprosthetic heart valves.

[49] *Wang X, Luo S, Gan X et al.* **Safety and efficacy of ETC-1002 in hypercholesterolemic patients: a meta-analysis of randomized controlled trials**. Kardiol Pol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30740643
ABSTRACT
BACKGROUND: Due to the myopathic adverse events of statins, safer alternatives are being studied. ETC-1002 is a novel low-density lipoprotein cholesterol (LDL-C)-lowering agent, currently under trial in hypercholesterolemic patients. AIM: To investigate the tolerability and efficacy of ETC-1002 in hypercholesterolemic patients through systematic review of published randomized controlled trials (RCTs). METHODS: We searched five databases for RCTs that investigated the safety and efficacy of ETC-1002 in hypercholesterolemic patients. The retrieved search results were screened, and then data were extracted and analyzed (as mean difference [MD] or odds ratio [OR]) using RevMan software. RESULTS: Five RCTs (625 hypercholesterolemic patients) were identified. ETC-1002 was superior to placebo in terms of percent changes from baseline in LDL-C (MD = -26.58, CI = [-35.50, -17.66], p < 0.0001), non-HDL-C (MD = -21.54, CI = [-28.48, -14.6], p < 0.00001), and apolipoprotein-B (MD=-15.97, CI= [-19.36, -12.57], p < 0.0001) serum levels. When compared to ezetimibe, ETC-1002 was superior in reducing LDL-C (-30.1+/-1.3 vs -21.1+/-1.3). Regarding safety, ETC-1002 did not increase the risk of all adverse events (OR=0.58, CI= [0.37, 0.91], p=0.02) and arthralgia (OR = 0.32, CI = [0.13, 0.81], p = 0.02) compared to placebo. All other adverse events including myalgia, headache, and urinary tract infections were similar between ETC-1002 and placebo groups. The evidence certainty in the assessed outcomes was moderate to high except lipoprotein(a), free fatty acids, and VLDL particle number (very low certainty). CONCLUSION: ETC-1002 is a safe and effective lipid-lowering agent and may be a suitable alternative in statin-intolerant patients. Well-designed studies are needed to explore the long-term safety and efficacy of ETC-1002 in these patients.

[50] *Acharya P, Talahalli RR*. **n-3 Fatty Acids Abrogate Dyslipidemia-Induced Changes in Bile Acid Uptake, Synthesis, and Transport in Young and Aged Dyslipidemic Rats**. Lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30740707
ABSTRACT

In this study, the effect of n-3 fatty acids (FA) [alpha-linolenic acid (ALA) and eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)] on the intestinal bile acid (BA) uptake, hepatic BA synthesis, and enterohepatic bile acid transporters (BAT) was assessed in young and aged dyslipidemic rats. Dyslipidemia was induced in young and aged rats by feeding a high-fat (HF) diet. Experimental groups received diets containing canola oil (HF + CNO) and fish oil (HF + FO) as a source of ALA and EPA + DHA, respectively. After 60 days of feeding, intestinal BA uptake and expression of apical sodium-dependent bile acid transporter (Asbt), organic solute transporter-alpha/beta (Osta/b) messenger RNA (mRNA), and hepatic expression of Na(+) taurocholate cotransporting polypeptide (Ntcp), bile salt export pump (Bsep), cholesterol 7-alpha hydroxylase A1 (Cyp7a1), Farnesoid X receptor (Fxr), small heterodimer partner-1 (Shp), liver receptor homolog-1 (Lrh-1), and hepatic nuclear factor-4 alpha (Hnf4a) mRNA were measured. Hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity and total BA in serum, liver, and feces were assessed. The dyslipidemic HF group had: (1) increased intestinal BA uptake and Asbt and Osta/b mRNA expression, (2) increased BA in serum, (3) decreased hepatic expression of Ntcp, Bsep, and Cyp7a1 mRNA, (4) increased activity of HMG-CoA reductase, (5) increased hepatic expression of Fxr and Shp mRNA, (6) decreased hepatic expression of Lrh-1 and Hnf4a mRNA, and (7) decreased BA in feces, when compared to control, HF + CNO, and HF + FO groups. Immunostaining revealed increased expression of intestinal Asbt and hepatic Ntcp protein in the HF group when compared to control, HF + CNO, and HF + FO groups. n-3 FA abrogated dyslipidemia-induced changes in the intestinal uptake, hepatic synthesis, and enterohepatic transporters of BA in both young and aged rats. EPA + DHA was more effective than ALA in modulating dyslipidemia-induced changes.

[51] *Feillet-Coudray C, Fouret G, Vigor C et al.* **Long-Term Measures of Dyslipidemia, Inflammation, and Oxidative Stress in Rats Fed a High-Fat/High-Fructose Diet**. Lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30767221

ABSTRACT

Inflammation and oxidative stress are thought to be involved in, or associated with, the development of obesity, dyslipidemia, hepatic steatosis, and insulin resistance. This work was designed to determine the evolution of inflammation and oxidative stress during onset and progression of hepatic steatosis and glucose intolerance. Seventy-five male Wistar rats were divided to control and high-fat high-fructose (HFHFr) groups. A subgroup of each group was sacrificed at 4, 8, 12, 16, and 20 weeks. HFHFr-fed rats exhibited overweight, glucose intolerance, and hepatic steatosis with increased contents of hepatic diacylglycerols and ceramides. The HFHFr diet increased hepatic interleukin 6 (IL-6) protein and adipose tissue CCL5 gene expression and hepatic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity but not mitochondrial reactive oxygen species (ROS) production. The HFHFr diet decreased plasma and liver levels of isoprostanoid metabolites as well as plasma thiobarbituric acid-reactive substance (TBARS) levels. Hepatic glutathione content was decreased with a moderate decrease in superoxide dismutase (SOD) and glutathione peroxidase (GPx) with the HFHFr diet. Overall, HFHFr diet led to hepatic lipid accumulation and glucose intolerance, which were accompanied by only moderate inflammation and oxidative stress. Most of these changes occurred at the same time and as early as 8 or 12 weeks of diet treatment. This implies that oxidative stress may be the result, not the cause, of these metabolic alterations, and suggests

that marked hepatic oxidative stress should probably occur at the end of the steatotic stage to result in frank insulin resistance and steatohepatitis. These findings need to be further evaluated in other animal species as well as in human studies.

[52] *Wang M, Zhao D, Xu L et al.* **Role of PCSK9 in PCOS**. Metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30768966
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin / kexin type 9 (PCSK9) plays a critical role in the cholesterol metabolism by negatively regulating the low-density lipoprotein receptor (LDLR). Lipid metabolic and ovarian disorders are the common clinical manifestation of polycystic ovary syndrome (PCOS). Here, we intended to elucidate the role of PCSK9 in the pathogenesis of PCOS conducted on a human population in case-control design and animal part in an interventional study. METHODS: We firstly investigated the serum levels of PCSK9 in 46 PCOS patients compared with 49 healthy women as controls, and then developed a PCOS mouse model induced by dehydroepiandrosterone (DHEA) and a high-fat diet (HFD) to determine the role of PCSK9 in abnormal lipid metabolism and ovarian dysfunction of PCOS in four groups (n=40 per group): control, PCOS mice, PCOS plus alirocumab group, and PCOS plus vehicle group. The expression of PCSK9 in their serum, hepatic and ovarian tissues, serum lipid profiles and hormones were measured. Additionally, Furthermore, mRNA and protein expression levels of LDLR in hepatic and ovarian tissues, ovarian morphology and function were determined. Finally, we used freshly isolated theca-interstitial cells (TICs) and granulosa cells (GCs) from prepubertal normal mice to explore the effect of PCSK9 on LDL uptake of the cells. RESULTS: Serum PCSK9 concentrations were higher in PCOS patients than normal controls ($P<0.05$). The PCOS model mice exhibited significantly increased serum levels of total cholesterol (TC), LDL-C and high-density lipoprotein-cholesterol (HDLC; $P<0.001$, $P<0.001$, $P=0.0004$, respectively). Moreover, the serum PCSK9 protein level was significantly increased in PCOS mice ($P=0.0002$), which positively correlated with serum LDL-C ($r=0.5279$, $P=0.0004$) and TC ($r=0.4151$, $P=0.035$). In both liver and ovary of PCOS mice, PCSK9 mRNA and protein levels were significantly increased ($P<0.05$), but LDLR levels were significantly decreased ($P<0.05$). Furthermore, alirocumab inhibiting PCSK9 partly increased in LDLR expression in both liver and ovary in PCOS mice, also ameliorated the lipid metabolic disorders and pathological changes of ovarian morphology and function and serum reproductive hormones but not in the PCOS plus vehicle group. In vitro experiment, recombinant PCSK9 decreased LDL uptake in TICs and GCs ($P<0.001$, $P=0.0011$, respectively), which were partly reversed by alirocumab ($P<0.001$, $P=0.012$, respectively). CONCLUSION: Abnormal high expression of PCSK9 in the blood, liver and ovary may be involved in the pathogenesis of PCOS by affecting lipid metabolism and ovarian function, and the inhibition of PCSK9 may partly reverse the pathological changes of PCOS. Our research suggests a possibility of PCSK9 as a new attractive target for diagnosis and treatment of PCOS.

[53] *Rajaraman B, Ramadas N, Krishnasamy S et al.* **Hyperglycaemia cause vascular inflammation through advanced glycation end products/early growth response-1 axis in gestational diabetes mellitus**. Molecular and cellular biochemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30767098

ABSTRACT
Hyperglycaemia during pregnancy is the main reason for developing diabetes mediated vascular complications. Advanced glycation end products (AGEs) are formed due to non-enzymatic glycation of proteins, lipids and nucleic acids during hyperglycaemia. It has the potential to damage vasculature by modifying the substrate or by means of AGEs and receptor of AGE (RAGE) interaction. It has been linked with the pathogenesis of various vascular diseases including coronary heart disease, atherosclerosis, restenosis etc. This study was carried out to investigate the role of AGEs-EGR-1 pathway in gestational diabetes mellitus (GDM) vascular inflammation. Human umbilical vein endothelial cells (HuVECs) isolated from normal glucose tolerant mothers were subjected to various treatments including high glucose, silencing of early growth response (EGR)-1, blockade of protein kinase C (PKC) beta, blocking extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), and treatment with AGEs and assayed for EGR-1, tissue factor (TF) and soluble intercellular adhesion molecule (sICAM)-1. Similarly, umbilical vein endothelial cells isolated from normal and GDM mothers were assayed for EGR-1, TF, and sICAM-1. There was a significant increase in EGR-1 and TF levels in HuVECs isolated form GDM mother's umbilical cord and normal HuVECs treated with high glucose condition. This was accompanied by elevated levels of sICAM-1 in high glucose treated cells. Our results revealed AGE-mediated activation of EGR-1 and its downstream genes via PKC betaII and ERK1/2 signaling pathway. The present study demonstrated a novel mechanism of AGEs/ PKC betaII/ ERK1/2/EGR-1 pathway in inducing vascular inflammation in GDM.

[54] *Del Vecchio L, Baragetti I, Locatelli F*. **New agents to reduce cholesterol levels: implications for nephrologists**. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30753594
ABSTRACT
Statins and ezetimibe effectively reduce the burden of cardiovascular (CV) disease in patients with chronic kidney disease (CKD). Unfortunately, many subjects still die or have CV events despite cholesterol-lowering therapy. This is particularly true in patients with more advanced CKD. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that induces the degradation of the low-density lipoprotein receptor by targeting it for lysosomal destruction. Its inhibition causes a dramatic fall in cholesterol levels on top of maximized statin therapy. This goal is obtained with different therapeutic approaches, spanning from monoclonal antibodies to non sense oligonucleotides and silencing RNA (siRNA). Two human, monoclonal antibodies are approved for clinical use; they are still very expensive. Both agents significantly lower cholesterol levels. Evolocumab and alirocumab reduce significantly the risk for CV disease without relevant safety issues. Inclisiran is an siRNA molecule that produces PCSK9-specific RNA silencing. Data from a Phase II study showed significant cholesterol-lowering efficacy. The experience accumulated so far is limited in the CKD population. PCSK9 inhibition also has the potential to reduce the burden of CV in this subset by obtaining a much greater decrease in serum cholesterol compared with statin therapy or ezetimibe. Doubts exist that this approach will improve the outcome of dialysis patients, in whom vascular calcifications predominate.

[55] *Weylandt KH, Schmocker C, Ostermann AI et al.* **Activation of Lipid Mediator Formation Due to Lipoprotein Apheresis**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30744123
ABSTRACT
Lipoprotein apheresis reliably reduces low-density lipoprotein (LDL) cholesterol in patients with atherosclerotic disease and therapy-refractory hypercholesterolemia or elevated lipoprotein (a) (Lp(a)). Besides lowering lipoproteins and triglycerides, apheresis also decreases levels of essential omega-6 and omega-3 polyunsaturated fatty acids (n-6 and n-3 PUFAs) in blood plasma. In contrast, heparin-induced extracorporeal low-density lipoprotein precipitation (HELP) lipid apheresis might increase the formation of potentially pro-inflammatory and pro-thrombotic lipid mediators derived from n-6 and n-3 PUFAs. The study presented here analyzed lipid mediator profiles in the plasma of patients with hyperlipidemia treated by one of three different apheresis methods, either HELP, direct absorption (DA), or membrane filtration (MDF), in a direct pre- and post-apheresis comparison. Using gas chromatography and liquid chromatography tandem mass spectrometry (LC-MS/MS) we were able to analyze fatty acid composition and the formation of lipid mediators called oxylipins. Our data illustrate-particularly in HELP-treated patients-significant decreases of essential omega-6 and omega-3 polyunsaturated fatty acids in blood plasma but significant increases of PUFA-derived lipoxygenase-, as well as cyclooxygenase- and cytochrome P450-derived lipid mediators. Given that n-3 PUFAs in particular are presumed to be cardioprotective and n-3 PUFA-derived lipid mediators might limit inflammatory reactions, these data indicate that n-3 PUFA supplementation in the context of lipid apheresis treatment might have additional benefits through apheresis-triggered protective n-3 PUFA-derived lipid mediators.

[56] *Trong HN, Tat TN, Anh TTN et al.* **Efficacy of Adding Oral Simvastatin to Topical Therapy for Treatment of Psoriasis: The Vietnamese Experience**. Open access Macedonian journal of medical sciences 2019; 7:237-242.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30745969
ABSTRACT
BACKGROUND: Psoriasis, the prevalence of which ranges from 2% to 3% of the general population, has been recently recognised as not only a chronic inflammatory skin disorder but also an immunometabolic systemic disease. Dyslipidemia is one of the most important comorbidities of psoriasis. Statins, frequently used as anti-hyperlipidemic agents, may be beneficial in the treatment of several autoimmune diseases, including psoriasis, due to their anti-inflammatory and immunomodulatory characteristics. Hence, we hypothesised that using this medication was not only beneficial for reducing hyperlipidemia but also improving psoriatic conditions. AIM: We conducted a study to determine the prevalence of dyslipidemia in psoriatic patients as well as whether the addition of statins (simvastatin prescribed forms) to standard topical antipsoriatic treatment can improve skin lesions in psoriatic patients. METHODS: A group of 128 psoriatic patients and 128 healthy controls who were matched with the patients regarding ethnicity, age, and sex were enrolled, and their lipid concentrations were determined. Furthermore, sixty patients were randomly selected from the former group and divided into two treatment subgroups to evaluate the effect of statins on the severity of psoriasis using the PASI score. RESULTS: We found that the rate of dyslipidemia in the patient

group was significantly higher than in the healthy group (53.9% versus 21.9%, p < 0.001), particularly the triglyceride concentration (1.86 +/- 1.17 versus 1.43 +/- 0.79 mg/dL, p < 0.001). Also, the PASI score reduction in the simvastatin-treated subgroup was significantly different from that in the placebo-treated one after eight weeks of therapy (8.63 +/- 4.78 versus 5.34 +/- 3.59, p < 0.01). CONCLUSION: This study showed that simvastatin might play a role in controlling hyperlipidemia and in turn decrease the PASI score in psoriatic patients.

[57] *Chan BD, Wong WY, Lee MM et al.* **Exosomes in inflammation and inflammatory disease**. Proteomics 2019:e1800149.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30758141
ABSTRACT
Exosomes are a subset of extracellular vesicles released by all cell types and involved in local and systemic intercellular communication. In the past decade, research into exosomes has swelled as their important role in the mediation of health and disease has been increasingly established and acknowledged. Exosomes carry a diverse range of cargo including proteins, nucleic acids and lipids derived from their parental cell that, when delivered to the recipient cell, can confer pathogenic or therapeutic effects through modulation of immunity and inflammation. In this review, we will discuss of the role of exosomes on mediation of immune and inflammatory responses, and their participation in diseases with a significant inflammatory component. The considerable potential for exosomes in therapy and diagnosis of inflammatory diseases will also be highlighted. This article is protected by copyright. All rights reserved.

[58] *Petrenya N, Lamberg-Allardt C, Melhus M et al.* **Vitamin D status in a multi-ethnic population of northern Norway: the SAMINOR 2 Clinical Survey**. Public health nutrition 2019:1-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30767841
ABSTRACT
OBJECTIVE: To investigate serum 25-hydroxyvitamin D (S-25(OH)D) concentration in a multi-ethnic population of northern Norway and determine predictors of S-25(OH)D, including Sami ethnicity. DESIGN: Cross-sectional data from the second survey of the Population-based Study on Health and Living Conditions in Regions with Sami and Norwegian Populations (the SAMINOR 2 Clinical Survey, 2012-2014). S-25(OH)D was measured by the IDS-iSYS 25-Hydroxy Vitamin D assay. Daily dietary intake was assessed using an FFQ. BMI was calculated using weight and height measurements. SETTING: Ten municipalities of northern Norway (latitude 68 degrees -70 degrees N).ParticipantsMales (n 2041) and females (n 2424) aged 40-69 years. RESULTS: Mean S-25(OH)D in the study sample was 64.0 nmol/l and median vitamin D intake was 10.3 microg/d. The prevalence of S-25(OH)D<30 nmol/l was 1.9 % and <50 nmol/l was 24.7 %. In sex-specific multivariable linear regression models, older age, blood sample collection in September-October, solarium use, sunbathing holiday, higher alcohol intake (in females), use of cod-liver oil/fish oil supplements, use of vitamin/mineral supplements and higher intakes of vitamin D were significantly associated with higher S-25(OH)D, whereas being a current smoker and obesity were associated with lower S-25(OH)D. These factors explained 21-23 % of the variation in S-25(OH)D. CONCLUSIONS: There were many modifiable risk factors related to S-25(OH)D, however no clear ethnic differences were found. Even in winter, the low

prevalence of vitamin D deficiency found among participants with non-Sami, multi-ethnic Sami and Sami self-perceived ethnicity was likely due to adequate vitamin D intake.

[59] *Masajtis-Zagajewska A, Nowicki M*. **Effect of atorvastatin on iron metabolism regulation in patients with chronic kidney disease - a randomized double blind crossover study**. Renal failure 2018; 40:700-709.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30741616
ABSTRACT
INTRODUCTION: To determine the effect of 6-month administration of atorvastatin on hepcidin and hemojuvelin levels, inflammatory parameters and iron metabolism in patients with chronic kidney disease (CKD) stages 3 and 4. METHODS: Thirty six statin- and erythropoiesis-stimulating agent-naive patients with CKD stages 3 and 4 and LDL cholesterol >/=100 mg/dl received atorvastatin or placebo for two 6-month periods in a double blind, randomized crossover study. Hepcidin, hemojuvelin, hsCRP, IL-6, hemoglobin, red blood cell distribution width, iron, total iron binding capacity (TIBC), and unsaturated iron binding capacity (UIBC) were measured before and after each treatment period. RESULTS: Hepcidin decreased (from 102 [307] to 63 [170] pg/ml (p > .001)) in the course of statin therapy but remained unchanged after placebo administration (173 [256] to 153 [204] pg/ml, respectively). Hemojuvelin did not change after either part of the study. Both IL-6 and hsCRP decreased following statin therapy (from 8.7 [12.0] to 8.1 [13.9] pg/ml; p = .04 and from 4.7 [4.0] to 4.0 [3.6] mg/l; p = .4, respectively), but did not change after placebo administration. Blood hemoglobin increased slightly but significantly after 6-month statin therapy (from 11.6 +/- 1.6 to 11.9 +/- 1.5 g/dl, p = .002), and was unchanged after placebo treatment. TIBC and UIBC increased significantly after 6-month statin therapy, and serum iron also tended to increase. The change of eGFR during the study did not differ between the two treatment periods. CONCLUSIONS: Statin may have a small but potentially beneficial effect on serum hepcidin, which may lead to improvement of anemia control in CKD patients.

[60] *Lagraauw HM, Wezel A, van der Velden D et al.* **Stress-induced mast cell activation contributes to atherosclerotic plaque destabilization**. Scientific reports 2019; 9:2134.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30765859
ABSTRACT
Mast cells accumulate in the perivascular tissue during atherosclerotic plaque progression and contribute to plaque destabilization. However, the specific triggers for mast cell activation in atherosclerosis remain unresolved. We hypothesized that psychological stress-induced activation of mast cells may contribute to plaque destabilization. To investigate this, apoE(-/-) mice on Western-type diet were exposed to 120' restraint stress. A single episode of restraint caused a significant increase in mast cell activation in the heart. In addition to a rise in serum corticosterone and changes in circulating leukocyte populations, we observed an increase in the circulating pro-inflammatory cytokine interleukin (IL)-6 in the stressed mice. Subsequent characterization of the atherosclerotic plaques revealed a high incidence and larger size of intraplaque hemorrhages in stressed mice. In mast cell-deficient apoE(-/-) mice, restraint stress affected circulating leukocyte levels, but did not increase plasma IL-6 levels. Furthermore, we did not observe any intraplaque hemorrhages in these mice upon stress, strongly indicating the

involvement of a mast cell-dependent response to stress in atherosclerotic plaque destabilization. In conclusion, we demonstrate that acute stress activates mast cells, which induces the incidence of intraplaque hemorrhage in vivo, identifying acute stress as a risk factor for atherosclerotic plaque destabilization.

[61] *Guillamat-Prats R, Rami M, Herzig S, Steffens S*. **Endocannabinoid Signalling in Atherosclerosis and Related Metabolic Complications**. Thrombosis and haemostasis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30769363
ABSTRACT
Endocannabinoids are a group of arachidonic acid-derived lipid mediators binding to cannabinoid receptors CB1 and CB2. An overactivity of the endocannabinoid system plays a pathophysiological role in the development of visceral obesity and insulin resistance. Moreover, elevated circulating endocannabinoid levels are also prevalent in atherosclerosis. The pathophysiological increase of endocannabinoid levels is due to an altered expression of endocannabinoid synthesizing and degrading enzymes induced by inflammatory mediators such as cytokines or lipids. Emerging experimental evidence suggests that enhanced endocannabinoid signalling affects atherosclerosis via multiple effects, including a modulation of vascular inflammation, leukocyte recruitment, macrophage cholesterol metabolism and consequently atherosclerotic plaque stability. In addition, recent findings in various metabolic disease models highlight the relevance of peripheral CB1 cannabinoid receptors in adipose tissue, liver and pancreas, which crucially regulate lipid and glucose metabolism as well as macrophage properties in these organs. This suggests that targeting the endocannabinoid system in the vasculature and peripheral organs might have a therapeutic potential for atherosclerosis by inhibiting vascular inflammation and improving metabolic risk factors. This review will provide a brief update on the effects of endocannabinoid signalling in atherosclerosis and related metabolic complications.

[62] *Sakellarios AI, Fotiadis DI*. **The pleiotropic effect of statins on the atherosclerotic plaque and coronary heart disease**. Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30770174
ABSTRACT