Literature update week 24 (2019)

[1] *Simon A, Dezsi CA*. **Treatment of Hypertensive and Hypercholesterolaemic Patients with the Triple Fixed Combination of Atorvastatin, Perindopril and Amlodipine: The Results of the CORAL Study**. Adv Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31183780
ABSTRACT
INTRODUCTION: Hypertension and hypercholesterolaemia are important contributors to the development and progression of atherosclerosis. The coexistence of these two conditions is rather common: hypercholesterolaemia is present in 40-60% of hypertensive patients. Remarkably, patient compliance with antihypertensive regimens is better than with statin therapy. Thus, the inclusion of statins and blood pressure-lowering agents into a fixed combination might even double the effectiveness of statin therapy, and thereby achieve significantly greater reduction of cardiovascular risk. The CORAL study was a 3-month, prospective, multicentre, observational, non-interventional survey, which evaluated the blood pressure- and lipid-lowering efficacy of the triple fixed combination of atorvastatin/perindopril/amlodipine, administered in various dose combinations. METHODS: The efficacy of the triple fixed combination was reflected by the changes of the blood pressure readings taken in the office and during 24-h blood pressure monitoring (3 months elapsed between visits 1 and 3). The laboratory parameters obtained during data acquisition were also recorded. RESULTS: After 3 months of therapy, mean office blood pressure decreased from 158.5 +/- 16.7/91.7 +/- 9.4 to 132.2 +/- 8.3/80.1 +/- 6.8 mmHg ($p < 0.0001$), whereas mean 24-h blood pressure decreased from 146.0 +/- 14.5/82.5 +/- 12.1 to 132.1 +/- 13.2/75.6 +/- 9.9 mmHg. With regard to metabolic parameters, the inclusion of pre-existing statin therapy in the fixed combination led to further, significant reduction of lipid parameters as follows: total cholesterol level from 6.18 +/- 1.15 to 5.16 +/- 0.88 mmol/L, LDL-cholesterol from 3.41 +/- 1.01 to 2.80 +/- 0.82 mmol/L and triglyceride level from 2.26 +/- 1.17 to 1.82 +/- 0.83 mmol/L (all $p < 0.0001$). CONCLUSION: Treatment with the fixed triple combination of atorvastatin, perindopril and amlodipine might take us closer to the optimal therapy for hypertensive patients with hypercholesterolaemia. The expected improvement of patient adherence to treatment may result in an increase of the percentage patients who achieve both blood pressure control and the LDL-cholesterol targets recommended in guidelines. Moreover, this may translate into the further decline of the risk of prospective cardiovascular events. FUNDING: Egis Pharmaceuticals.

[2] *Vail D, Callaway NF, Ludwig CA et al.* **Lipid-Lowering Medications are Associated with Lower Risk of Retinopathy and Ophthalmic Interventions among U.S. Patients with Diabetes**. American journal of ophthalmology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31194953
ABSTRACT
PURPOSE: To evaluate the impact of lipid-lowering medications on diabetic retinopathy and diabetic complications requiring intervention in the U.S. POPULATION: DESIGN: Retrospective cohort analysis. SETTING: Administrative insurance claims drawn from the Truven MarketScan Commercial Claims and Encounters database. POPULATION: Beneficiaries with Type 2 diabetes mellitus (T2DM). MAIN OUTCOME MEASURE: Any signs of diabetic retinopathy, as measured by diagnosis codes for non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), and procedure codes for retinopathy

treatments (anti-VEGF injections, laser therapy, and vitrectomy). RESULTS: We analyzed a population of 269,782 patients diagnosed with T2DM between 2008 and 2015. 99,233 (37%) of patients were undergoing treatment with lipid-lowering medications. Approximately 6% of patients on lipid-lowering medications had a diagnosis code for NPDR, PDR, or DME, or a procedural code for intravitreal injections, PPV, or laser in their record following diagnosis with diabetes, compared to 6.5% of patients who did not take lipid-lowering medications ($p<0.01$). In adjusted time-to-event analyses, patients who took lipid-lowering medications prior to diagnosis with T2DM were less likely to progress to any retinopathy diagnosis (HR 0.60, 95% CI 0.55-0.65) and less likely to receive any treatment for retinopathy (HR 0.81, 95% CI 0.78-0.84). These findings were significant at the aggregate level, as well as at the level of individual diagnosis (NPDR HR 0.63, 95% CI 0.57-0.69; PDR HR 0.45, 95% CI 0.37-0.54; DME HR 0.39, 95% CI 0.33-0.45), and at the level of each treatment category (anti-VEGF injection HR 0.81, 95% CI 0.78-0.84; laser HR 0.62, 95% CI 0.47-0.81; vitrectomy HR 0.71, 95% CI 0.59-0.85). CONCLUSIONS: We find consistent evidence that patients on lipid-lowering medications are less likely to develop NPDR, PDR, or DME, and modest evidence that these patients are less likely to receive intravitreal injections of anti-VEGF medication, laser treatments, or vitrectomy. Our study validates the findings of studies that have used claims databases in East Asia in relatively homogeneous populations to estimate an association between statin use and retinopathy, replicating them in a U.S. context in a large commercial claims database.

[3] *Bartlett B, Ludewick HP, Misra A et al.* **Macrophages and T cells in atherosclerosis: a translational perspective**. American journal of physiology. Heart and circulatory physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31199186
ABSTRACT
Atherosclerosis is now considered chronic maladaptive inflammatory disease. The hallmark feature both in human and murine disease are atherosclerotic plaques. Macrophages and various T-cell lineages play a crucial role in atherosclerotic plaque establishment and disease progression. Humans and mice share many of the same processes that occur within atherogenesis. The various similarities enable considerable insight into disease mechanisms and those which contribute to cardiovascular complications. The apolipoprotein E and low-density lipoprotein receptor null mice have served as the foundation for further immunological pathway manipulation to identify pro- and anti-atherogenic pathways in attempt to reveal more novel therapeutic targets. In this review, we provide a translational perspective and discuss the roles of macrophages and various T cell lineages in contrasting pro-atherosclerotic and atheroprotective settings.

[4] *Di Ciaula A, Wang DQ, Molina-Molina E et al.* **Bile Acids and Cancer: Direct and Environmental-Dependent Effects**. Annals of hepatology 2017; 16 Suppl 1:S87-s105.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31196640
ABSTRACT
Bile acids (BAs) regulate the absorption of fat-soluble vitamins, cholesterol and lipids but have also a key role as signaling molecules and in the modulation of epithelial cell proliferation, gene expression and metabolism. These homeostatic pathways, when disrupted, are able to promote

local inflammation, systemic metabolic disorders and, ultimately, cancer. The effect of hydrophobic BAs, in particular, can be linked with cancer in several digestive (mainly oesophagus, stomach, liver, pancreas, biliary tract, colon) and extra-digestive organs (i.e. prostate, breast) through a complex series of mechanisms including direct oxidative stress with DNA damage, apoptosis, epigenetic factors regulating gene expression, reduced/increased expression of nuclear receptors (mainly farnesoid X receptor, FXR) and altered composition of gut microbiota, also acting as a common interface between environmental factors (including diet, lifestyle, exposure to toxics) and the molecular events promoting cancerogenesis. Primary prevention strategies (i.e. changes in dietary habits and lifestyle, reduced exposure to environmental toxics) mainly able to modulate gut microbiota and the epigenome, and the therapeutic use of hydrophilic BAs to counterbalance the negative effects of the more hydrophobic BAs might be, in the near future, part of useful tools for cancer prevention and management.

[5] *Mihailovic PM, Lio WM, Yano J et al.* **IL-7R blockade reduces post-myocardial infarction-induced atherosclerotic plaque inflammation in ApoE(-/-) mice**. Biochemistry and biophysics reports 2019; 19:100647.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31193072
ABSTRACT
Modulating inflammation by targeting IL-1beta reduces recurrent athero-thrombotic cardiovascular events without lipid lowering. This presents an opportunity to explore other pathways associated with the IL-1beta signaling cascade to modulate the inflammatory response post-myocardial infarction (MI). IL-7 is a mediator of the inflammatory pathway involved in monocyte trafficking into atherosclerotic plaques and levels of IL-7 have been shown to be elevated in patients with acute MI. Recurrent athero-thrombotic events are believed to be mediated in part by index MI-induced exacerbation of inflammation in atherosclerotic plaques. The objective of the study was to assess the feasibility of IL-7R blockade to modulate atherosclerotic plaque inflammation following acute MI in ApoE(-/-) mice. Mice were fed Western diet for 12 weeks and then subjected to coronary occlusion to induce an acute MI. IL-7 expression was determined using qRT-PCR and immuno-staining, and IL-7R was assessed using flow cytometry. Plaque inflammation was evaluated using immunohistochemistry. IL-7R blockade was accomplished with monoclonal antibody to IL-7R. IL-7 mRNA expression was significantly increased in the cardiac tissue of mice subjected to MI but not in controls. IL-7 staining was observed in the coronary artery. Plaque macrophage and lipid content were significantly increased after MI. IL-7R antibody treatment but not control IgG significantly reduced macrophage and lipid content in atherosclerotic plaques. The results show that IL-7R antibody treatment reduces monocyte/macrophage and lipid content in the atherosclerotic plaque following MI suggesting a potential new target to mitigate increased plaque inflammation post-MI.

[6] *Trakaki A, Sturm GJ, Pregartner G et al.* **Allergic rhinitis is associated with complex alterations in high-density lipoprotein composition and function**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019; 1864:1280-1292.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31185305

ABSTRACT
Despite strong evidence that high-density lipoproteins (HDLs) modulate the immune response, the role of HDL in allergies is still poorly understood. Many patients with allergic rhinitis (AR) develop a late-phase response, characterized by infiltration of monocytes and eosinophils into the nasal submucosa. Functional impairment of HDL in AR-patients may insufficiently suppress inflammation and cell infiltration, but the effect of AR on the composition and function of HDL is not understood. We used apolipoprotein (apo) B-depleted serum as well as isolated HDL from AR-patients (n=43) and non-allergic healthy controls (n=20) for detailed compositional and functional characterization of HDL. Both AR-HDL and apoB-depleted serum of AR-patients showed decreased anti-oxidative capacity and impaired ability to suppress monocyte nuclear factor-kappaB expression and pro-inflammatory cytokine secretion, such as interleukin (IL)-4, IL-6, IL-8, tumor necrosis factor alpha and IL-1 beta. Sera of AR-patients showed decreased paraoxonase and cholesteryl-ester transfer protein activities, increased lipoprotein-associated phospholipase A2 activity, while lecithin-cholesterol acyltransferase activity and cholesterol efflux capacity were not altered. Surprisingly, apoB-depleted serum and HDL from AR-patients showed an increased ability to suppress eosinophil effector responses upon eotaxin-2/CCL24 stimulation. Mass spectrometry and biochemical analyses showed reduced levels of apoA-I and phosphatidylcholine, but increased levels of apoA-II, triglycerides and lyso-phosphatidylcholine in AR-HDL. The changes in AR-HDL composition were associated with altered functional properties. In conclusion, AR alters HDL composition linked to decreased anti-oxidative and anti-inflammatory properties but improves the ability of HDL to suppress eosinophil effector responses.

[7] *Jiang H, Zheng H*. **Efficacy and adverse reaction to different doses of atorvastatin in the treatment of type II diabetes mellitus**. Bioscience reports 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31189741

ABSTRACT
BACKGROUND: Type II diabetes mellitus (T2DM), a persistent metabolic disorder, is primarily characterized by insulin resistance, relative insulin deficiency, and dyslipidemia. Here, we aimed to investigate whether different doses of atorvastatin (ATV) affect rats with T2DM. A total of 110 Sprague-Dawley rats were successfully established as T2DM models. METHODS: Firstly, the total cholesterol (TC), triglyceride (TG), high-/low-/very-low-density lipoprotein cholesterol (HDL-c/LDL-c/VLDL-c), alanine transaminase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (Cr), apolipoprotein Al (ApoA1) and apolipoprotein B (ApoB) levels in rat serum were analyzed. In addition, cholesteryl ester transfer protein (CETP) and retinol binding protein 4 (RBP4) were also measured. Then, the incidence of adverse reactions was noted. Finally, the pathological study of liver and pancreatic tissues was performed. RESULTS: Rats administered ATV at the doses of 40 and 80 mg/(kg.d) showed downregulated TG, LDL-c, ApoB, CETP and RBP4 levels yet upregulated HDL-c and ApoAl levels. Rats administered ATV at a dose of 80 mg/(kg.d) exhibited a higher incidence of adverse reactions and higher ALT and AST levels but lower BUN and Cr levels, which might affect liver and kidney function. Rats administered ATV at the doses of 40 and 80 mg/(kg.d) demonstrated significantly improved liver injury and pancreatic injury induced by T2DM. CONCLUSION: These data

revealed that ATV could improve the lipid metabolism in T2DM rats and 40 mg/(kg.d) may serve as the optimal dose for the reduction of lipid levels and the incidence of adverse effects.

[8] *Righolt CH, Zhang G, Ye X et al.* **Statin use and chronic lymphocytic leukemia incidence: A nested case-control study in Manitoba, Canada**. Cancer Epidemiol Biomarkers Prev 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31186266
ABSTRACT
BACKGROUND: Recent studies have reported reduced risk of chronic lymphocytic leukemia (CLL) among statin users. However, the possibility that the effect of statins may differ by their chemical or pharmacodynamic properties has not been investigated. METHODS: In this nested case-control study, all Manitobans aged >/= 40 years when diagnosed with CLL (as a first cancer) from 1999 to 2014 (n=1,385) were matched (on gender, age, residence, and duration of insurance coverage) to cancer-free controls (n=6,841). Using conditional logistic regression, statin use was analyzed by individual statins and groups: hydrophilic, low-potency lipophilic (fluvastatin and lovastatin) and high-potency lipophilic statins. RESULTS: Statin users constituted 27% and 28% of the CLL cases and controls. After adjusting for potential confounding by indication, patterns of healthcare utilization and use of other drugs, CLL incidence was not associated with use of hydrophilic (odds ratio: 1.08; 95% confidence interval: 0.86-1.34) or high-potency lipophilic statins (0.94; 0.79-1.11). Low-potency lipophilic statins were associated with a lower risk of CLL (0.64; 0.45-0.92), with stronger association (0.44; 0.22-0.88) observed with more regular use (half to full standard dose on average). CONCLUSIONS: We found an association between low-potency lipophilic statin use and reduced CLL risk, with a possible dose-response effect. IMPACT: While requiring replication in future studies, our findings suggest that the effect of statins on CLL risk may depend on their specific chemical or pharmacodynamic properties.

[9] *Huang A, Qi X, Wei L et al.* **Non-HDL-c/TC: A Novel Lipid-Related Marker in the Assessment of Severity of Coronary Artery Lesions and Cardiovascular Outcomes**. Cardiology research and practice 2019; 2019:5931975.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31179126
ABSTRACT
Background: Non-high-density lipoprotein cholesterol (non-HDL-c) predicts the severity of coronary artery lesions in patients not treated with statin. The association between non-HDL-c and severity of coronary artery lesions in patients treated with lipid-lowering therapy has been unknown. Hypothesis: We hypothesize a novel marker of non-HDL-c/TC predicts the severity of coronary artery lesions and clinical outcomes in 12 months in the patients treated with statin. Method: 473 subjects who met inclusion criteria were eligible for inclusion. Coronary artery angiography (CAG) was performed, and the Gensini score (GS) was calculated in all the subjects divided into three subgroups of low risk, medium risk, and high risk by the tertiles of GS. The non-HDL-c value was calculated as TC minus HDL-c, while non-HDL-c/TC was the ratio of non-HDL-c and TC. Results: The concentration of non-LDL-c differed between non-obstructive-CAD group and obstructive-CAD group ($P < 0.05$), and non-HDL-c/TC was elevated in the obstructive-CAD group ($P < 0.05$). Increased GS was associated with increasing non-HDL-c/TC ($P < 0.05$). Non-HDL-c/TC (OR: 108.50, 95% CI: 1.57-7520.28; P=0.030) remained as an independent

predicting factor of high risk under GS stratification. In unadjusted Cox model, high non-HDL-c/TC (RR: 1.976, 95% CI: 1.155-3.382; P=0.013) predicted the occurrence of adverse events. After multivariate adjustment, high non-HDL-c/TC (RR: 1.921, 95% CI: 1.105-3.339; P=0.021) was an independent predictor of poor outcomes. Conclusion: High level of non-HDL-c/TC presented an excellent prognostic value compared with other lipid-related markers in CAD patients treated with statin.

[10] *Vachiat A, McCutcheon K, Tsabedze N et al.* **Atherosclerotic plaque in HIV-positive patients presenting with acute coronary syndromes**. Cardiovasc J Afr 2019; 30:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31180115
ABSTRACT
AIM: This study aimed to characterise the atherosclerotic plaque and plaque burden in HIV-positive patients presenting with acute coronary syndromes (ACS), using intravascular ultrasound (IVUS) and virtual histology (VH). METHODS: This was a prospective study of 20 HIV-positive patients who presented with ACS. IVUS and VH were used to assess plaque burden and plaque characteristics in the culprit and non-culprit coronary arteries. RESULTS: HIV-positive patients with ACS had a mean age of 51.1 +/- 8.1 years. There were 13 (65%) male patients. ST-segment elevation myocardial infarction was the most common presentation of ACS (75%) with the left anterior descending artery being the most common culprit artery (60%). In 60% of patients, the total plaque burden was of moderate degree (40-70% stenosis) while it was of mild degree (< 40% stenosis) in 35%, and in 5% of patients it was severe (> 70% stenosis). A severe degree of total plaque burden was more commonly found in the culprit vessel (30%) than in the non-culprit vessels (5%). Furthermore, the plaque burden was found to be located predominantly in the proximal portion of the coronary arteries. The predominant plaque morphology consisted of fibrous plaque (55.4%) and fibro-fatty plaque (26.6%), while necrotic core was present in 13.3%. Dense calcium was present in only 4.7% of the cohort. CONCLUSIONS: IVUS and VH demonstrated a high burden of atherosclerosis in the left anterior descending artery and proximal vasculature of HIV-positive patients. The atherosclerotic plaque predominantly comprised non-calcified fibrous and fibro-fatty plaque.

[11] *Batrakoulis A, Fatouros IG, Chatzinikolaou A et al.* **Dose-response effects of high-intensity interval neuromuscular exercise training on weight loss, performance, health and quality of life in inactive obese adults: Study rationale, design and methods of the DoIT trial**. Contemporary clinical trials communications 2019; 15:100386.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31193901
ABSTRACT
Obesity is associated with high mortality and morbidity rates and low levels of quality of life among adults globally. It is critical to examine evidence-based practices for developing lifestyle behavioral changes such as physical movement and structured exercise training. The DoIT protocol, a high-intensity interval exercise training (HIIT) program, effectively reduces body mass, alters energy balance, and improves performance of obese adults with a high adherence rate. This study aims to determine the dose-response effects of the DoIT protocol on body composition, health, performance and quality of life in sedentary obese adults. This study will recruit 88 sedentary, obese males and females (BMI 25.0-34.9; 30-50 years) who will be

randomly assigned to one of four groups: (i) control (n=22), (ii) one session/week (n=22), (iii) two sessions/week (n=22) or (iv) three sessions/week (n=22). DoIT will use a supervised, circuit-type (1-3 rounds), functional/neuromotor and progressive exercise program for 12 months. DoIT incorporates 8-12 multi-planar, fundamental and complex, whole body movements and uses bodyweight and alternative exercise modes as a resistance. DoIT utilizes prescribed work-to-rest ratios which will be varied every four weeks. Each session will last less than 30min. DoIT will be implemented for a year and its effects on body mass and body composition, physical fitness, functional capacity, bone health, leptin, adiponectin, blood lipids, glycemic control, inflammation, oxidative stress and quality of life will be assessed. The outcomes of the proposed study will provide insight on optimal exercise prescription guidelines for such HIIT-type exercise protocols for overweight or obese individuals.

[12] *Stacy MR*. **Radionuclide Imaging of Atherothrombotic Diseases**. Current cardiovascular imaging reports 2019; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31191793
ABSTRACT
Purpose of Review: A variety of approaches and molecular targets have emerged in recent years for radionuclide-based imaging of atherosclerosis and vulnerable plaque using single photon emission computed tomography (SPECT) and positron emission tomography (PET), with numerous methods focused on characterizing the mechanisms underlying plaque progression and rupture. This review highlights the ongoing developments in both the preclinical and clinical environment for radionuclide imaging of atherosclerosis and atherothrombosis. Recent Findings: Numerous physiological processes responsible for the evolution of high-risk atherosclerotic plaque, such as inflammation, thrombosis, angiogenesis, and microcalcification, have been shown to be feasible targets for SPECT and PET imaging. For each physiological process, specific molecular markers have been identified that allow for sensitive non-invasive detection and characterization of atherosclerotic plaque. Summary: The capabilities of SPECT and PET imaging continue to evolve for physiological evaluation of atherosclerosis. This review summarizes the latest developments related to radionuclide imaging of atherothrombotic diseases.

[13] *Trzeciecka A, Stark DT, Kwong JMK et al.* **Comparative lipid profiling dataset of the inflammation-induced optic nerve regeneration**. Data in brief 2019; 24:103950.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31193141
ABSTRACT
In adult mammals, retinal ganglion cells (RGCs) fail to regenerate following damage. As a result, RGCs die after acute injury and in progressive degenerative diseases such as glaucoma; this can lead to permanent vision loss and, eventually, blindness. Lipids are crucial for the development and maintenance of cell membranes, myelin sheaths, and cellular signaling pathways, however, little is known about their role in axon injury and repair. Studies examining changes to the lipidome during optic nerve (ON) regeneration could greatly inform treatment strategies, yet these are largely lacking. Experimental animal models of ON regeneration have facilitated the exploration of the molecular determinants that affect RGC axon regeneration. Here, we analyzed lipid profiles of the ON and retina in an ON crush rat model using liquid

chromatography-mass spectrometry. Furthermore, we investigated lipidome changes after ON crush followed by intravitreal treatment with Zymosan, a yeast cell wall derivative known to enhance RGC regeneration. This data is available at the NIH Common Fund's Metabolomics Data Repository and Coordinating Center (supported by NIH grant, U01-DK097430) website, the Metabolomics Workbench, http://www.metabolomicsworkbench.org, where it has been assigned Project ID: PR000661. The data can be accessed directly via it's Project DOI: doi: 10.21,228/M87D53.

[14] *Basterra-Gortari FJ, Ruiz-Canela M, Martinez-Gonzalez MA et al.* **Effects of a Mediterranean Eating Plan on the Need for Glucose-Lowering Medications in Participants With Type 2 Diabetes: A Subgroup Analysis of the PREDIMED Trial**. Diabetes Care 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31182491
ABSTRACT
OBJECTIVE: To examine the effects of two Mediterranean eating plans (Med-EatPlans) versus a low-fat eating plan on the need for glucose-lowering medications. RESEARCH DESIGN AND METHODS: From the PREDIMED trial, we selected 3,230 participants with type 2 diabetes at baseline. These participants were randomly assigned to one of three eating plans: Med-EatPlan supplemented with extra virgin olive oil (EVOO), Med-EatPlan supplemented with mixed nuts, or a low-fat eating plan (control). In a subgroup (15%), the allocation was done in small clusters instead of using individual randomization, and the clustering effect was taken into account in the statistical analysis. In multivariable time-to-event survival models, we assessed two outcomes: 1) introduction of the first glucose-lowering medication (oral or injectable) among participants on lifestyle management at enrollment and 2) insulin initiation. RESULTS: After a median follow-up of 3.2 years, in multivariable analyses adjusting for baseline characteristics and propensity scores, the hazard ratios (HRs) of starting a first glucose-lowering medication were 0.78 (95% CI 0.62-0.98) for Med-EatPlan + EVOO and 0.89 (0.71-1.12) for Med-EatPlan + nuts, compared with the control eating plan. After a median follow-up of 5.1 years, the adjusted HRs of starting insulin treatment were 0.87 (0.68-1.11) for Med-EatPlan + EVOO and 0.89 (0.69-1.14) for Med-EatPlan + nuts compared with the control eating plan. CONCLUSIONS: Among participants with type 2 diabetes, a Med-EatPlan + EVOO may delay the introduction of new-onset glucose-lowering medications. The Med-EatPlan did not result in a significantly lower need for insulin.

[15] *Mantovani A, Altomari A, Lunardi G et al.* **Association between specific plasma ceramides and high-sensitivity C-reactive protein levels in postmenopausal women with type 2 diabetes**. Diabetes Metab 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31185304
ABSTRACT
AIM: Emerging evidence suggests that specific plasma ceramides are involved in the pathophysiology of cardiovascular disease (CVD) and other inflammation-associated diseases. However, scarce information is currently available on the association between distinct plasma ceramides (that have been associated with increased cardiovascular morbidity and mortality) and plasma high-sensitivity C-reactive protein (hs-CRP) concentrations in patients with type 2 diabetes mellitus (T2DM), a group of individuals at high risk of developing CVD and other

chronic inflammation-related conditions. METHODS: We measured six previously identified high-risk plasma ceramide species [Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/20:0), Cer(d18:1/22:0), Cer(d18:1/24:0), Cer(d18:1/24:1)] in 92 postmenopausal women with T2DM attending the diabetes outpatient service over a 3-month period. Plasma ceramide levels were measured using targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. RESULTS: Plasma hs-CRP levels were positively associated with all measured ceramides in univariable linear regression analyses. However, only plasma Cer(d18:1/16:0) (standard beta coefficient: 0.27, P=0.015), Cer(d18:1/22:0) (standard beta coefficient: 0.25, P=0.032) and Cer(d18:1/24:1) (standard beta coefficient: 0.30, P=0.007) remained significantly associated with increased plasma hs-CRP levels after adjusting for age, adiposity measures, diabetes duration, HbA1c, insulin resistance, smoking, hypertension, plasma LDL cholesterol, estimated glomerular filtration rate, preexisting ischaemic heart disease and use of lipid-lowering, antihypertensive, antiplatelet or hypoglycaemic drugs. CONCLUSION: In postmenopausal women with T2DM, elevated levels of specific plasma ceramides are associated with higher plasma hs-CRP levels independent of established cardiovascular risk factors, diabetes-related variables and other potential confounding factors.

[16] *Ghim JL, Phuong NTT, Kim MJ et al.* **Pharmacokinetics of fixed-dose combination of atorvastatin and metformin compared with individual tablets**. Drug design, development and therapy 2019; 13:1623-1632.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31190741
ABSTRACT
Purpose: The aims of this study was to investigate the mutual pharmacokinetic interactions between steady-state atorvastatin and metformin and the effect of food on the fixed-dose combined (FDC) tablet of atorvastatin and metformin extended release (XR). Subjects and methods: Study 1, an open-labeled, fixed sequence, multiple-dose pharmacokinetic drug-drug interaction study, was divided into 2 parts. Atorvastatin (40 mg) or metformin (1,000 mg) XR tablets were administered once daily via mono- or co-therapy for 7 days. Plasma levels of atorvastatin and 2-OH-atorvastatin, were quantitatively determined for 36 h in part A (n=50) while metformin plasma concentration was measured up to 24 h in part B (n=16) after the last dosing. Study 2, a randomized, open-labeled, single-dose, two-treatment, two-period, two-sequence crossover study, involved 27 healthy subjects to investigate the impact of food intake on the pharmacokinetics of a combined atorvastatin/metformin XR 20/500 mg (CJ-30056 20/500 mg) tablet. Results: After multiple doses of mono- or co-therapy of atorvastatin (40 mg) and metformin (1,000 mg) XR, the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) for the peak plasma concentration at steady state (Cmax,ss) and area under the plasma concentration-time curve during the dosing interval at steady state (AUCtau,ss) were 1.07 (0.94-1.22) and 1.05 (0.99-1.10) for atorvastatin, 1.06 (0.96-1.16) and 1.16 (1.10-1.21) for 2-OH-atorvastatin, and 1.00 (0.86-1.18) and 0.99 (0.87-1.13) for metformin, respectively. Food delayed time to reach maximum concentration (tmax), decreased atorvastatin Cmax by 32% with a GMR (90% CI) of 0.68 (0.59-0.78), and increased metformin AUCt by 56% with a GMR (90% CI) of 1.56 (1.43-1.69). Conclusion: No clinically relevant pharmacokinetic interaction was seen when atorvastatin was co-administered with metformin. Food appeared to change the

absorption of atorvastatin and metformin from an FDC formulation. These alterations were in accordance with those described with the single reference drugs when ingested with food.

[17] *Shu X, Chi L*. **Effect of pravastatin treatment on circulating adiponectin: a meta-analysis of randomized controlled trials**. Drug design, development and therapy 2019; 13:1633-1641.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31190742

ABSTRACT
Objective: Pravastatin has been suggested to increase circulating adiponectin in humans. However, results of randomized controlled trials (RCTs) are inconsistent. We aimed to systematically evaluate the influence of pravastatin on circulating adiponectin in humans by performing a meta-analysis of RCTs. Materials and methods: Studies were identified via systematic searching of PubMed, Embase, and Cochrane's Library databases. A random effect model was used to pool the results. Meta-regression and subgroup analyses were applied to explore the source of heterogeneity. Results: Eight RCTs with nine comparisons of 595 participants were included. Pravastatin treatment was associated with a significant increased level of circulating adiponectin as compared with controls (weighted mean difference [WMD] =0.63 microg/mL; 95% CI, 0.17-1.09 microg/mL; P=0.007) with moderate heterogeneity (I2=28%). These results were confirmed by meta-analysis of double-blinded placebo-controlled RCTs (WMD =0.82 microg/mL; P=0.01). Meta-regression analyses indicated that proportions of males in each study were positively correlated with the effect of pravastatin on adiponectin (coefficient: 0.015, P=0.03). Subgroup analyses confirmed that pravastatin significantly increased adiponectin in studies of males (WMD =1.41 microg/mL; P=0.008), but not in those of females (WMD =-0.04 microg/mL; P=0.94). Conclusion: Pravastatin treatment is associated with increased circulating adiponectin. Gender difference may exist regarding the effect of pravastatin treatment on adiponectin.

[18] *Andersson ML, Mannheimer B, Lindh JD*. **The effect of simvastatin on warfarin anticoagulation: a Swedish register-based nationwide cohort study**. Eur J Clin Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31201436

ABSTRACT
PURPOSE: Some data indicate that simvastatin may increase the anticoagulative effect in patients treated with warfarin, but the evidence is scarce. The aim of the present study was to investigate how the anticoagulative effect of warfarin is affected by the initiation of simvastatin in a very large patient sample. METHODS: In a retrospective cohort study, we included 5637 individuals on warfarin treatment initiating simvastatin. INR values and warfarin doses were calculated week-by-week during co-treatment. Data were obtained from two large Swedish warfarin registers and from the Swedish Prescribed Drug Register. RESULTS: INR increased from 2.43 at baseline to 2.58, 4 weeks after simvastatin initiation, and did not stabilize until the last quarter of the year studied. Consequently, the proportion of patients with an INR above 3 increased from around 8 to 15%. CONCLUSIONS: In conclusion, initiation of simvastatin resulted in moderately increased INR values and subsequent dose decreases in patients already on warfarin. In order to avoid the increased risk of bleeding, the initiation of simvastatin may be accompanied by closer INR monitoring.

Literature update week 24 (2019)

[19] *Conte MS, Bradbury AW, Kolh P et al.* **Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia**. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31182334
ABSTRACT
GUIDELINE SUMMARY: Chronic limb-threatening ischemia (CLTI) is associated with mortality, amputation, and impaired quality of life. These Global Vascular Guidelines (GVG) are focused on definition, evaluation, and management of CLTI with the goals of improving evidence-based care and highlighting critical research needs. The term CLTI is preferred over critical limb ischemia, as the latter implies threshold values of impaired perfusion rather than a continuum. CLTI is a clinical syndrome defined by the presence of peripheral artery disease (PAD) in combination with rest pain, gangrene, or a lower limb ulceration >2 weeks duration. Venous, traumatic, embolic, and nonatherosclerotic etiologies are excluded. All patients with suspected CLTI should be referred urgently to a vascular specialist. Accurately staging the severity of limb threat is fundamental, and the Society for Vascular Surgery Threatened Limb Classification system, based on grading of Wounds, Ischemia, and foot Infection (WIfI) is endorsed. Objective hemodynamic testing, including toe pressures as the preferred measure, is required to assess CLTI. Evidence-based revascularization (EBR) hinges on three independent axes: Patient risk, Limb severity, and ANatomic complexity (PLAN). Average-risk and high-risk patients are defined by estimated procedural and 2-year all-cause mortality. The GVG proposes a new Global Anatomic Staging System (GLASS), which involves defining a preferred target artery path (TAP) and then estimating limb-based patency (LBP), resulting in three stages of complexity for intervention. The optimal revascularization strategy is also influenced by the availability of autogenous vein for open bypass surgery. Recommendations for EBR are based on best available data, pending level 1 evidence from ongoing trials. Vein bypass may be preferred for average-risk patients with advanced limb threat and high complexity disease, while those with less complex anatomy, intermediate severity limb threat, or high patient risk may be favored for endovascular intervention. All patients with CLTI should be afforded best medical therapy including the use of antithrombotic, lipid-lowering, antihypertensive, and glycemic control agents, as well as counseling on smoking cessation, diet, exercise, and preventive foot care. Following EBR, long-term limb surveillance is advised. The effectiveness of nonrevascularization therapies (eg, spinal stimulation, pneumatic compression, prostanoids, and hyperbaric oxygen) has not been established. Regenerative medicine approaches (eg, cell, gene therapies) for CLTI should be restricted to rigorously conducted randomizsed clinical trials. The GVG promotes standardization of study designs and end points for clinical trials in CLTI. The importance of multidisciplinary teams and centers of excellence for amputation prevention is stressed as a key health system initiative.

[20] *Adorni MP, Ruscica M, Ferri N et al.* **Proprotein Convertase Subtilisin/Kexin Type 9, Brain Cholesterol Homeostasis and Potential Implication for Alzheimer's Disease**. Frontiers in aging neuroscience 2019; 11:120.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31178716
ABSTRACT

Alzheimer's disease (AD) has been associated with dysregulation of brain cholesterol homeostasis. Proprotein convertase subtilisin/kexin type 9 (PCSK9), beyond the known role in the regulation of plasma low-density lipoprotein cholesterol, was first identified in the brain with a potential involvement in brain development and apoptosis. However, its role in the central nervous system (CNS) and in AD pathogenesis is still far from being understood. While in vitro and in vivo evidence led to controversial results, genetic studies apparently did not find an association between PCSK9 loss of function mutations and AD risk or prevalence. In addition, a potential impairment of cognitive performances by the treatment with the PCSK9 inhibitors, alirocumab and evolocumab, have been excluded, although ongoing studies with longer follow-up will provide further insights. PCSK9 is able to affect the expression of neuronal receptors involved in cholesterol homeostasis and neuroinflammation, and higher PCSK9 concentrations have been found in the cerebrospinal fluid (CSF) of AD patients. In this review article, we critically examined the science of PCSK9 with respect to its modulatory role of the mechanisms underlying the pathogenesis of AD. In addition, based on literature data, we made the hypothesis to consider brain PCSK9 as a negative modulator of brain cholesterol homeostasis and neuroinflammation and a potential pharmacological target for treatment.

[21] *Hagemann PM, Nsiah-Dosu S, Hundt JE et al.* **Modulation of Mast Cell Reactivity by Lipids: The Neglected Side of Allergic Diseases**. Frontiers in immunology 2019; 10:1174.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31191542
ABSTRACT
Mast cells (MCs) have long been mainly regarded as effector cells in IgE-associated allergic disorders with potential immunoregulatory roles. Located close to the allergen entry sites in the skin and mucosa, MCs can capture foreign substances such as allergens, toxins, or noxious substances and are exposed to the danger signals produced by epithelial cells. MC reactivity shaped by tissue-specific factors is crucial for allergic responses ranging from local skin reactions to anaphylactic shock. Development of Th2 response leading to allergen-specific IgE production is a prerequisite for MC sensitization and induction of FcepsilonRI-mediated MC degranulation. Up to now, IgE production has been mainly associated with proteins, whereas lipids present in plant pollen grains, mite fecal particles, insect venoms, or food have been largely overlooked regarding their immunostimulatory and immunomodulatory properties. Recent studies, however, have now demonstrated that lipids affect the sensitization process by modulating innate immune responses of epithelial cells, dendritic cells, and NK-T cells and thus crucially contribute to the outcome of sensitization. Whether and how lipids affect also MC effector functions in allergic reactions has not yet been fully clarified. Here, we discuss how lipids can affect MC responses in the context of allergic inflammation. Direct effects of immunomodulatory lipids on MC degranulation, changes in local lipid composition induced by allergens themselves and changes in lipid transport affecting MC reactivity are possible mechanisms by which the function of MC might be modulated.

[22] *Gupta M, Nikolic A, Ng D et al.* **Colchicine Myopathy: A Case Series Including Muscle MRI and ABCB1 Polymorphism Data**. Frontiers in neurology 2019; 10:553.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31178824
ABSTRACT

Colchicine is a medication most commonly used in the treatment of gout and familial mediterannean fever. A rare complication of therapy is toxicity causing proximal myopathy and polyneuropathy. Colchicine myopathy has been associated with the coadministration of other medications with colchicine, such as statins or tacrolimus, and is more common in patients with renal impairment. Otherwise, it is unclear which patients are at greatest risk of developing this adverse drug reaction. ABCB1 is important to the metabolism of colchicine, so we speculated that it was possible that colchicine myopathy patients may have a particular genotype that is associated with this side effect. We describe two cases of colchicine myopathy which occurred with co-administration of rosuvastatin. From one case, we present the first published data on muscle MRI in this condition. We additionally present an analysis of four genetic polymorphisms in ABCB1 and transcript levels in muscle tissue, and demonstrate the descriptive finding of reduced ABCB1 transcript levels in the colchicine myopathy patients.

[23] *Chaiyasothi T, Nathisuwan S, Dilokthornsakul P et al.* **Effects of Non-statin Lipid-Modifying Agents on Cardiovascular Morbidity and Mortality Among Statin-Treated Patients: A Systematic Review and Network Meta-Analysis**. Frontiers in pharmacology 2019; 10:547.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31191304
ABSTRACT
Background: Currently, there is a lack of information on the comparative efficacy and safety of non-statin lipid-lowering agents (NST) in cardiovascular (CV) disease risk reduction when added to background statin therapy (ST). This study determine the relative treatment effects of NST on fatal and non-fatal CV events among statin-treated patients. Methods: A network meta-analysis based on a systematic review of randomized controlled trials (RCTs) comparing non-statin lipid-modifying agents among statin-treated patients was performed. PubMed, EMBASE, CENTRAL, and Clinicaltrial.gov were searched up to April 10, 2018. The primary outcomes were CV and all-cause mortalities. Secondary CV outcomes were coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), any stroke, and coronary revascularization. Risks of discontinuations were secondary safety outcomes. Results: Sixty-seven RCTs including 259,429 participants with eight interventions were analyzed. No intervention had significant effects on the primary outcomes (CV mortality and all-cause mortality). For secondary endpoints, proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK) plus statin (PCSK/ST) significantly reduced the risk of non-fatal MI (RR 0.82, 95% CI 0.72-0.93, p = 0.003), stroke (RR 0.74, 95% CI 0.65-0.85, p < 0.001), coronary revascularization (RR 0.84, 95% CI 0.75-0.94, p = 0.003) compared to ST. Combinations of ST and all NST except PCSK and ezetimibe showed higher rate of discontinuation due to adverse events compared to ST. Conclusions: None of NST significantly reduced CV or all-cause death when added to ST. PCSKs and to a lesser extent, ezetimibe may help reduce cardiovascular events with acceptable tolerability profile among broad range of patients.

[24] *van der Vorst EPC, Peters LJF, Muller M et al.* **G-Protein Coupled Receptor Targeting on Myeloid Cells in Atherosclerosis**. Frontiers in pharmacology 2019; 10:531.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31191301
ABSTRACT

Atherosclerosis, the underlying cause of the majority of cardiovascular diseases (CVDs), is a lipid-driven, inflammatory disease of the large arteries. Gold standard therapy with statins and the more recently developed proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have improved health conditions among CVD patients by lowering low density lipoprotein (LDL) cholesterol. Nevertheless, a substantial part of these patients is still suffering and it seems that 'just' lipid lowering is insufficient. The results of the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) have now proven that inflammation is a key driver of atherosclerosis and that targeting inflammation improves CVD outcomes. Therefore, the identification of novel drug targets and development of novel therapeutics that block atherosclerosis-specific inflammatory pathways have to be promoted. The inflammatory processes in atherosclerosis are facilitated by a network of immune cells and their subsequent responses. Cell networking is orchestrated by various (inflammatory) mediators which interact, bind and induce signaling. Over the last years, G-protein coupled receptors (GPCRs) emerged as important players in recognizing these mediators, because of their diverse functions in steady state but also and specifically during chronic inflammatory processes - such as atherosclerosis. In this review, we will therefore highlight a selection of these receptors or receptor sub-families mainly expressed on myeloid cells and their role in atherosclerosis. More specifically, we will focus on chemokine receptors, both classical and atypical, formyl-peptide receptors, the chemerin receptor 23 and the calcium-sensing receptor. When information is available, we will also describe the consequences of their targeting which may hold promising options for future treatment of CVD.

[25] *Kim JS, Turbov J, Rosales R et al.* **Combination simvastatin and metformin synergistically inhibits endometrial cancer cell growth**. Gynecologic oncology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31178149
ABSTRACT
OBJECTIVE: Recent data show that simvastatin (SIM) and metformin (MET) have anti-proliferative effects in endometrial cancer cells. The combination (MET+SIM) inhibits tumor growth and metastasis in prostate cancer cells which possess similar molecular alterations to many early endometrial cancers. We tested the hypothesis that the anti-proliferative effects of MET+SIM in endometrial cancer cells would be greater than the effects of each agent alone. METHODS: RL95-2, HEC1B, and Ishikawa endometrial cancer cell lines were treated with MET and/or SIM. Growth inhibition was measured by MTS cell proliferation assays. Apoptosis was evaluated by caspase-3, Annexin V, and TUNEL assays and by apoptosis markers (BAX, Bcl-2, Bim) using western blot. Bim was silenced using Bim siRNA to confirm this apoptotic pathway. Treatment effects on the mTOR pathway were investigated by western blot using antibodies to phosphorylated (phospho)-AMPK and phospho-S6. RESULTS: MET+SIM synergistically inhibited growth in all three cell lines. The combination induced apoptosis as measured by TUNEL, Annexin V, and caspase-3 assays. Bim siRNA transfection abrogated this effect-silencing Bim in MET+SIM-treated RL95-2 cells rescued cell viability in MTS assays and reduced caspase-3 activity compared with control siRNA-transfected cells. Combination treatment upregulated phosphorylated AMPK and downregulated downstream phosphorylated S6, suggesting mTOR inhibition as a mechanism for these anti-proliferative effects. CONCLUSIONS: MET+SIM treatment synergistically inhibits endometrial cancer cell viability. This may be mediated by

apoptosis and mTOR pathway inhibition. Our results provide preclinical evidence that the combination of these well-tolerated drugs may warrant further clinical investigation for endometrial cancer treatment.

[26] *Yan R, Gu HQ, Wang W et al.* **Health-related quality of life in blood pressure control and blood lipid-lowering therapies: results from the CHIEF randomized controlled trial**. Hypertension research : official journal of the Japanese Society of Hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31197264

ABSTRACT

Our study aimed to explore changes in health-related quality of life (HRQoL) during blood pressure control and blood lipid-lowering therapies. We conducted a 2 x 2 factorial-designed randomized controlled trial in 180 clinical centers in China. At baseline, participants were randomly assigned to an amlodipine + amiloride/hydrochlorothiazide group or an amlodipine + telmisartan group for the blood pressure control treatment and to a statin group or a routine intervention group for the blood lipid-lowering treatment. The allocation ratio was 1:1 for both treatments. Follow-up lasted for 4 years. HRQoL was assessed using the EuroQol five dimensions three levels (EQ-5D-3L) questionnaire every year. Of 13,542 hypertensive patients enrolled in the clinical trial, 9885 were eligible for the analysis. The problems for all dimensions of the EQ-5D-3L descriptive system were slight at baseline and were well preserved in the follow-up period. The EuroQol visual analog scale (EQ VAS) score and the EQ-5D-3L index improved over time (Ptrend < 0.001), with improvements similar among interventions but different between patients who reached the treatment targets or not. Decreases in systolic/diastolic blood pressure and low-density lipoprotein cholesterol and increases in high-density lipoprotein cholesterol were independently correlated with increases in the EQ VAS score and the EQ-5D-3L index. In conclusion, HRQoL is associated with blood pressure/lipid levels but not with specific antihypertensive or lipid-lowering interventions. Blood pressure control and blood lipid-lowering therapies should not be denied to Chinese patients in consideration of their negative effects on quality of life.

[27] *Farrah TE, Anand A, Gallacher PJ et al.* **Endothelin Receptor Antagonism Improves Lipid Profiles and Lowers PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) in Patients With Chronic Kidney Disease**. Hypertension 2019:Hypertensionaha11912919.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31177906

ABSTRACT

Dyslipidemia is common in chronic kidney disease (CKD). Despite statins, many patients fail to adequately lower lipids and remain at increased risk of cardiovascular disease. Selective ETA (endothelin-A) receptor antagonists reduce cardiovascular disease risk factors. Preclinical data suggest that ETA antagonism has beneficial effects on circulating lipids. We assessed the effects of selective ETA antagonism on circulating lipids and PCSK9 (proprotein convertase subtilisin/kexin type 9) in CKD. This was a secondary analysis of a fully randomized, double-blind, 3-phase crossover study. Twenty-seven subjects with predialysis CKD on optimal cardio- and renoprotective treatment were randomly assigned to receive 6 weeks dosing with placebo, the selective ETA receptor antagonist, sitaxentan, or long-acting nifedipine. We measured circulating lipids and PCSK9 at baseline and then after 3 and 6 weeks. Baseline lipids and PCSK9

did not differ before each study phase. Whereas placebo and nifedipine had no effect on lipids, 6 weeks of ETA antagonism significantly reduced total (-11+/-1%) and low-density lipoprotein-associated (-20+/-3%) cholesterol, lipoprotein (a) (-16+/-2%) and triglycerides (-20+/-4%); high-density lipoprotein-associated cholesterol increased (+14+/-2%), P<0.05 versus baseline for all. Additionally, ETA receptor antagonism, but neither placebo nor nifedipine, reduced circulating PCSK9 (-19+/-2%; P<0.001 versus baseline; P<0.05 versus nifedipine and placebo). These effects were independent of statin use and changes in blood pressure or proteinuria. Selective ETA antagonism improves lipid profiles in optimally-managed patients with CKD, effects that may occur through a reduction in circulating PCSK9. ETA receptor antagonism offers a potentially novel strategy to reduce cardiovascular disease risk in CKD. Clinical Trial Registration- URL: http://www.clinicaltrials.gov . Unique identifier: NCT00810732.

[28] *Chen H, Li Z, Dong L et al.* **Lipid metabolism in chronic obstructive pulmonary disease**. International journal of chronic obstructive pulmonary disease 2019; 14:1009-1018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31190786

ABSTRACT

Dysregulated lipid metabolism plays crucial roles in various diseases, including diabetes mellitus, cancer, and neurodegeneration. Recent studies suggest that alterations in major lipid metabolic pathways contribute to pathogenesis of lung diseases, including chronic obstructive pulmonary disease (COPD). These changes allow lung tissue to meet the energy needs and trigger anabolic pathways that initiate the synthesis of active molecules directly involved in the inflammation. In this review, we summarize the changes of catabolism and anabolism of lipids, lipid molecules including lipid mediators, lipid synthesis transcription factors, cholesterol, and phospholipids, and how those lipid molecules participate in the initiation and resolution of inflammation in COPD.

[29] *Kuniyoshi N, Miyakawa H, Matsumoto K et al.* **Detection of Anti-mitochondrial Antibodies Accompanied by Drug-induced Hepatic Injury due to Atorvastatin**. Intern Med 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31178503

ABSTRACT

A 44-year-old Japanese woman was admitted to our hospital with fatigue and an altered liver function. She had been receiving atorvastatin treatment for 10 months. Although no jaundice was seen, the patient's serum alkaline phosphatase and gamma-glutamyl transpeptidase levels were markedly elevated. Based on the results of a drug-induced lymphocyte-stimulation test, her liver disease was diagnosed as atorvastatin-induced hepatic injury. Subsequently, anti-mitochondrial antibodies (AMAs) were detected in her serum; however, a liver biopsy specimen did not show the characteristic features of primary biliary cholangitis. We herein report the detection of AMAs accompanied by drug-induced hepatic injury caused by atorvastatin.

[30] *Charytan DM, Sabatine MS, Pedersen TR et al.* **Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial**. Journal of the American College of Cardiology 2019; 73:2961-2970.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31196453

ABSTRACT

BACKGROUND: Data on PCSK9 inhibition in chronic kidney disease (CKD) is limited. OBJECTIVES: The purpose of this study was to compare outcomes with evolocumab and placebo according to kidney function. METHODS: The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial randomized individuals with clinically evident atherosclerosis and low-density lipoprotein cholesterol (LDL-C) >/=70 mg/dl or non-high-density lipoprotein cholesterol >/=100 mg/dl to evolocumab or placebo. The primary endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization), key secondary endpoint (cardiovascular death, myocardial infarction, or stroke), and safety were analyzed according to chronic kidney disease (CKD) stage estimated from CKD-epidemiology estimated glomerular filtration rate. RESULTS: There were 8,077 patients with preserved kidney function, 15,034 with stage 2 CKD, and 4,443 with >/=stage 3 CKD. LDL-C reduction with evolocumab compared with placebo at 48 weeks was similar across CKD groups at 59%, 59%, and 58%, respectively. Relative risk reduction for the primary endpoint was similar for preserved function (hazard ratio [HR]: 0.82; 95% CI: 0.71 to 0.94), stage 2 (HR: 0.85; 95% CI: 0.77 to 0.94), and stage >/=3 CKD (HR: 0.89; 95% CI: 0.76 to 1.05); pint = 0.77. Relative risk reduction for the secondary endpoint was similar across CKD stages (pint = 0.75)-preserved function (HR: 0.75; 95% CI: 0.62 to 0.90), stage 2 (HR: 0.82; 95% CI: 0.72 to 0.93), stage >/=3 (HR: 0.79; 95% CI: 0.65 to 0.95). Absolute RRs at 30 months for the secondary endpoint were -2.5% (95% CI: -0.4% to -4.7%) for stage >/=3 CKD compared with -1.7% (95% CI: 0.5% to -2.8%) with preserved kidney function. Adverse events, including estimated glomerular filtration rate decline, were infrequent and similar regardless of CKD stage. CONCLUSIONS: LDL-C lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistent across CKD groups. Absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was numerically greater with more advanced CKD. (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk [FOURIER]; NCT01764633).

[31] *Jin Y, Fu J*. **Novel Insights Into the NLRP 3 Inflammasome in Atherosclerosis**. Journal of the American Heart Association 2019; 8:e012219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31184236
ABSTRACT

[32] *Raggi P, Gadiyaram V, Zhang C et al.* **Statins Reduce Epicardial Adipose Tissue Attenuation Independent of Lipid Lowering: A Potential Pleiotropic Effect**. Journal of the American Heart Association 2019; 8:e013104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31190609
ABSTRACT
Background High epicardial adipose tissue (EAT) attenuation (Hounsfield units [HUs]) on computed tomography is considered a marker of inflammation and is associated with an increased risk of cardiovascular events. Statins reduce the volume of EAT , but it is unknown whether they affect EAT HUs . Methods and Results We reviewed the chest computed tomographic scans of 420 postmenopausal women randomized to either 80 mg of atorvastatin or 40 mg of pravastatin daily and rescanned after 1 year to measure change in coronary artery calcium score. EAT HUs were measured near the proximal right coronary artery and remote

from any area of coronary artery calcium. Computed tomographic images were also queried for subcutaneous adipose tissue (SubQ) attenuation (HUs) change over time. The mean patients' age was 65+/-6 years. The baseline EAT HU value was higher than the SubQ HU value (-89.4+/-24.0 HU versus -123.3+/-30.4 HU ; P<0.001). The EAT HU value decreased significantly in the entire cohort (-5.4+/-29.7 HU [-6% change]; P<0.001), but equally in the patients given atorvastatin and pravastatin (-6.35+31 HU and -4.55+28 HU ; P=0.55). EAT HU change was not associated with change in total cholesterol, low-density lipoprotein cholesterol, coronary artery calcium, and EAT volume (all P=not significant). Change in high-density lipoprotein cholesterol was marginally associated with EAT HU change (P=0.07). Statin treatment did not induce a change in SubQ HUs . Conclusions Statins induced a decrease in EAT HUs over time, independent of intensity of low-density lipoprotein cholesterol lowering. The positive effect on EAT and the neutral effect on SubQ suggest that statins induced a decrease in metabolic activity in EAT by reduction in cellularity, vascularity, or inflammation. The clinical significance of the observed change in EAT HUs remains to be demonstrated.

[33] *Park JH, Ovbiagele B*. **Association of Non-LDL Indices with Recurrent Stroke Risk while on Lipid-Modifying Therapy**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31189759
ABSTRACT
AIMS: Low-density lipoprotein (LDL)-lowering statin therapy is an established secondary stroke prevention strategy. However, the differential impact of key non-LDL levels on recurrent stroke risk, while on lipid-modifying therapy (LT), remains unclear. METHODS: We analyzed the dataset of a multicenter trial involving 3640 recent (4 months) noncardioembolic stroke patients followed for 2 years. Participants were categorized into four groups of presumed improving lipid profile: level 0, no LT prescribed; level I, LT use with low high-density lipoprotein cholesterol (HDL-C) (40 mg/dL for men; 50 mg/dL for women); level II, LT use with high HDL-C (>/= 40 mg/dL and >/= 50 mg/dL, respectively); and level III, level II with low triglycerides (150 mg/dL). Independent associations of LT category with stroke, major vascular events (MVEs; stroke/coronary heart disease/vascular death), and all-cause death were assessed. RESULTS: LTs were mostly statins (95%). The unadjusted recurrent stroke rate declined with LT category level (9.2% for level 0; 8.4% for level I; 7.5% for level II; and 5.7% for level III). Compared with level 0, the adjusted hazard ratio of stroke for level I was 0.78 (95% confidence interval (CI), 0.59-1.03), level II 0.80 (0.54-1.18), and level III 0.63 (0.43-0.91). Multivariable analyses of MVEs and all-cause death followed a similar pattern of declining risk with higher LT category level. CONCLUSIONS: Compared with the nonuse of LT, there may be a hierarchy of residual vascular risk after stroke by non-LDL type and target, while on LT. Particularly, stroke patients with low HDL-C levels on LT may benefit from additional therapeutic strategies to improve their outcomes.

[34] *Choi SSS, Lashkari B, Mandelis A et al.* **Frequency-domain differential photoacoustic radar: theory and validation for ultrasensitive atherosclerotic plaque imaging**. Journal of biomedical optics 2019; 24:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31197987
ABSTRACT

Lipid composition of atherosclerotic plaques is considered to be highly related to plaque vulnerability. Therefore, a specific diagnostic or imaging modality that can sensitively evaluate plaques' necrotic core is desirable in atherosclerosis imaging. In this regard, intravascular photoacoustic (IVPA) imaging is an emerging plaque detection technique that provides lipid-specific chemical information from an arterial wall with great optical contrast and long acoustic penetration depth. While, in the near-infrared window, a 1210-nm optical source is usually chosen for IVPA applications since lipids exhibit a strong absorption peak at that wavelength, the sensitivity problem arises in the conventional single-ended systems as other arterial tissues also show some degree of absorption near that spectral region, thereby generating undesirably interfering photoacoustic (PA) signals. A theory of the high-frequency frequency-domain differential photoacoustic radar (DPAR) modality is introduced as a unique detection technique for accurate and molecularly specific evaluation of vulnerable plaques. By assuming two low-power continuous-wave optical sources at approximately 1210 and approximately 970 nm in a differential manner, DPAR theory and the corresponding simulation/experiment studies suggest an imaging modality that is only sensitive and specific to the spectroscopically defined imaging target, cholesterol.

[35] *Allah EA, Kamel EZ, Osman HM et al.* **Could Short-Term Perioperative High-Dose Atorvastatin Offer Antiarrhythmic and Cardio-Protective Effects in Rheumatic Valve Replacement Surgery?** Journal of cardiothoracic and vascular anesthesia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31178259

ABSTRACT

OBJECTIVES: To evaluate the role of prophylactic high-dose atorvastatin for prevention of postoperative atrial fibrillation (POAF), inflammatory response attenuation, and myocardial protection after valve replacement cardiac surgery. DESIGN: Randomized controlled trial. SETTING: Assiut University Hospitals. PARTICIPANTS: Sixty-four adult patients undergoing cardiac valve replacement surgery. INTERVENTIONS: The participants were equally divided into 2 groups. Group S received 80 mg of atorvastatin (oral tablets), 12 and 2 hours preoperatively, and on the 2nd, 3rd, 4th, and 5th postoperative days. Control group C received placebo at the same time periods. MEASUREMENTS: The incidence of POAF, postoperative white blood cell count, serum C-reactive protein, interleukin 6, and troponin I. MAIN RESULTS: Group S patients showed a lower incidence of POAF compared with the placebo group (p=0.031). The white blood cell count showed significant reductions in group S compared with group C on the second, third, fourth, and fifth postoperative days. The C-reactive protein level showed significant reductions on the third, fourth, and fifth postoperative days in group S compared with group C (p=0.001, 0.001, and 0.001, respectively). The serum level of interleukin 6 showed a significant reduction on the fifth postoperative day in group S compared with group C (p=0.001). There was no significant difference between the 2 groups regarding the troponin I level and inotropic score. CONCLUSION: Prophylactic use of high dose atorvastatin can decrease the incidence of POAF and attenuate the inflammatory process in adult patients undergoing isolated rheumatic cardiac valve replacement surgery.

[36] *Vallee A, Lelong H, Lopez-Sublet M et al.* **Association between different lipid parameters and aortic stiffness: clinical and therapeutic implication perspectives**. Journal of hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31188165
ABSTRACT
INTRODUCTION: Recommendations about lipid parameters varied from different guidelines. Aortic stiffness is a marker of vascular aging and may reflect occurrence of cardiovascular diseases. Aortic pulse wave velocity (PWV), a marker of aortic stiffness, can be measured by applanation tonometry. The purpose of our study was to test the associations between lipid parameters and aortic stiffness. METHODS: A cross-sectional study was conducted from 2012 to 2017, 603 participants were included: 517 patients and 86 'healthy' individuals used to calculate the theoretical PWV. Lipid parameters, including total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), non-HDL, total cholesterol/HDL ratio, triglycerides/HDL ratio and LDL/HDL ratio were measured. Theoretical PWV can be calculated according to age, sex, mean blood pressure and heart rate, allowing to form an individual PWV index [(measured PWV - theoretical PWV)/theoretical PWV]. PWV index [(measured PWV - theoretical PWV)/theoretical PWV] greater than 0 defined aortic stiffness. RESULTS: In multiple linear regression analyses, total cholesterol (P = 0.03), LDL (P = 0.04), non-HDL (P = 0.03), total cholesterol/HDL (P = 0.01) and LDL/HDL (P = 0.03) were significantly correlated with PWV. In multiple logistic regression analyses, non-HDL [OR = 1.12 (1.04-1.20), P = 0.01, R value: 0.224], total cholesterol/HDL [OR = 1.12 (1.02-1.22), P = 0.03, R value: 0.219] and total cholesterol [OR = 1.11 (1.01-1.23), P = 0.03, R value: 0.209] were significantly associated with aortic stiffness. CONCLUSION: Non-HDL, total cholesterol and total cholesterol/HDL were significantly associated with aortic stiffness than others and especially individually lipid parameters. This result should be considered in future clinical lipid-lowering trials.

[37] *Almeciga-Diaz CJ, Hidalgo OA, Olarte-Avellaneda S et al.* **Identification of Ezetimibe and Pranlukast as Pharmacological Chaperones for the Treatment of the Rare Disease Mucopolysaccharidosis Type IVA**. Journal of medicinal chemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31188588
ABSTRACT
Mucopolysaccharidosis type IVA (MPS IVA) is a rare disease caused by mutations in the gene encoding the lysosomal enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS). We report here two GALNS pharmacological chaperones, ezetimibe and pranlukast, identified by molecular docking-based virtual screening. These compounds bound to the active cavity of GALNS and increased its thermal stability as well as the production of recombinant GALNS in bacteria, yeast, and HEK293 cells. MPS IVA fibroblasts treated with these chaperones exhibited increases in GALNS protein and enzyme activity and reduced the size of enlarged lysosomes. Abnormalities in autophagy markers p62 and LC3B-II were alleviated by ezetimibe and pranlukast. Combined treatment of recombinant GALNS with ezetimibe or pranlukast produced an additive effect. Altogether, the results demonstrate that ezetimibe and pranlukast can increase the yield of recombinant GALNS and be used as a monotherapy or combination therapy to improve the therapeutic efficacy of MPS IVA enzyme replacement therapy.

[38] *Guan X, Liu Z, Zhao Z et al.* **Emerging roles of low-density lipoprotein in the development and treatment of breast cancer**. Lipids in health and disease 2019; 18:137.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31182104
ABSTRACT
Breast cancer is a heterogeneous disease with increasing incidence and mortality and represents one of the most common cancer types worldwide. Low-density lipoprotein (LDL) is a complex particle composed of several proteins and lipids, which carries cholesterol into peripheral tissues and also affects the metabolism of fatty acids. Recent reports have indicated an emerging role of LDL in breast cancer, affecting cell proliferation and migration, thereby facilitating disease progression. However, controversy still exists among distinct types of breast cancer that can be affected by LDL. Classical therapeutic approaches, such as radiotherapy, chemotherapy, and lipid-lowering drugs were also reported as affecting LDL metabolism and content in breast cancer patients. Therefore, in this review we summarized and discussed the role of LDL in the development and treatment of breast cancer.

[39] *Hristov I, Mocanu V, Zugun-Eloae F et al.* **Association of intracellular lipid accumulation in subcutaneous adipocyte precursors and plasma adipokines in bariatric surgery candidates**. Lipids in health and disease 2019; 18:141.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31189474
ABSTRACT
BACKGROUND: The adipocyte expansion is a critical process with implications in the pathogenesis of obesity associated metabolic syndrome. Impaired adipogenesis leads to dysfunctional, hypertrophic adipocytes, local inflammation and peripheric insulin resistance. METHODS: We assessed the relationship between the adipogenic differentiation capacity of the subcutaneous adipose derived stem cells (ASCs), evaluated by total lipid accumulation, and the metabolic and hormonal profile in a group of obese female patients proposed for bariatric surgery (N = 20) versus normal weight female controls (N = 7). RESULTS: The lipid accumulation (measured as optical density at 492 nm) of ASCs during their differentiation to adipocytes was significantly lower in ASCs isolated from obese patients as compared to ASCs isolated from normal weight patients (0.49 +/- 0.1 vs. 0.71 +/- 0.1, $p < 0.001$). Significant negative correlations between lipid accumulation in adipogenic differentiated ASCs and plasma concentrations of triglycerides ($p < 0.01$), insulin ($p < 0.001$), HOMA-IR ($p < 0.01$), adiponectin ($p < 0.05$) and leptin/adiponectin ratio ($p < 0.05$) were found in obese group. CONCLUSIONS: In severely obese female patients, the abnormal adipogenesis is related to insulin resistance and leptin/adiponectin ratio. The abnormal lipid accumulation in the mature adipocyte derived from obese ASCs could possible predict the further development of type 2 diabetes mellitus in severely obese patients and influence the selection of patients for bariatric surgery.

[40] *Villani R, Navarese EP, Cavallone F et al.* **Risk of Statin-Induced Hypertransaminasemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Mayo Clinic proceedings. Innovations, quality & outcomes 2019; 3:131-140.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31193835
ABSTRACT

Objective: To assess the effect of statins compared with placebo on the risk of developing hypertransaminasemia. Patients and Methods: We performed a systematic review of electronic databases and included articles published between January 1, 1965, and April 10, 2017. Randomized clinical trials (RCTs) comparing statins vs placebo were included. Odds ratios (ORs) were pooled in random-effect meta-analyses according to established methods recommended by the Cochrane Collaboration. Results: Seventy-three eligible RCTs, comprising 123,051 patients, were identified. Statins associated with a significantly risk of hypertransaminasemia (OR 1.45; 95% confidence interval [CI], 1.24-1.69; P<.001). Atorvastatin showed the highest odds (OR 2.66; 95% CI, 1.74-4.06; P<.001) followed by rosuvastatin (OR 1.35; 95% CI, 1.06-1.70; P=.01) and lovastatin (OR 1.53; 95% CI, 1.03-2.28; P=.04). Pravastatin, fluvastatin, and simvastatin yielded no statistically different odds compared with placebo. Conclusions: A dose-dependent risk of developing hypertransaminasemia occurs in patients taking atorvastatin, rosuvastatin, and lovastatin.

[41] *Schmit D, Fliser D, Speer T*. **Proprotein convertase subtilisin/kexin type 9 in kidney disease**. 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=31190079
ABSTRACT
Chronic kidney disease (CKD) is associated with a substantially increased risk for the development of atherosclerotic cardiovascular (CV) disease. Accordingly, CV mortality is increased even in the earliest stages of CKD. In the general population and in CKD patients, high plasma levels of low-density lipoprotein cholesterol (LDL-C) are crucially involved in the initiation and progression of atherosclerotic vascular lesions. Lowering LDL-C by use of statins and/or ezetimibe represents the gold standard of lipid-lowering therapy, with a great body of evidence from several large clinical trials. Statin therapy reduces CV events in patients with normal and impaired kidney function alike, while the evidence for patients on maintenance haemodialysis is weaker. The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease represents a novel lipid-lowering tool. Currently the monoclonal antibodies evolocumab and alirocumab are the approved PCSK9 inhibitors. Despite maximum-tolerated statin therapy, they efficiently further reduce LDL-C plasma levels without any major adverse effects. Moreover, in large clinical outcome trials, both antibodies have been proven to lower CV events. Notably, the LDL-lowering capacity was independent of baseline kidney function and also efficient in patients with moderate CKD. However, patients with severely impaired kidney function, that is, the population at the highest CV risk, have been excluded from those trials. The relevance of the LDL-independent effects of PCSK9 inhibitors, such as lowering lipoprotein(a) or ameliorating dyslipidaemia in patients with nephrotic syndrome, has to be determined. Therefore further specific studies assessing the effects and outcomes of PCSK9-inhibiting treatment in CKD patients are warranted.

[42] *Lutz MW, Casanova R, Saldana S et al.* **Analysis of pleiotropic genetic effects on cognitive impairment, systemic inflammation, and plasma lipids in the Health and Retirement Study**. Neurobiology of aging 2019; 80:173-186.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31201950

ABSTRACT
Variants associated with modulation of c-reactive protein (CRP) and plasma lipids have been investigated for polygenic overlap with Alzheimer's disease risk variants. We examined pleiotropic genetic effects on cognitive impairment conditioned on genetic variants (SNPs) associated with systemic inflammation as measured by CRP and with plasma lipids using data from the Health and Retirement Study. SNP enrichment was observed for cognitive impairment conditioned on the secondary phenotypes of plasma CRP and lipids. Fold enrichment of 100%-800% was observed for increasingly stringent p-value thresholds for SNPs associated with cognitive impairment conditional on plasma CRP, 80%-800% for low-density lipoprotein, and 80%-600% for total cholesterol. Significant associations (false discovery rate Q </= 0.05) between cognitive impairment, conditional with either CRP, low-density lipoprotein, or total cholesterol, were found for the locus on chromosome 19 that contains the APOE, TOMM40, APOC1, and PVRL2 genes. Relative numbers of significant SNPs in each of the genes differed by the conditional associations with the secondary phenotypes. Biological interpretation of both the genetic pleiotropy results and the individual genome-wide association results showed that the variants and proximal genes identified are involved in multiple pathological processes including cholesterol metabolism, inflammation, and mitochondrial transport. These findings are potentially important for Alzheimer's disease risk prediction and development of novel therapeutic approaches.

[43] *Stevenson JC*. **BMS consensus statement for primary prevention of coronary heart disease in women**. Post reproductive health 2019; 25:64-69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31192759
ABSTRACT

[44] *Poller B, Woessner R, Barve A et al.* **Fevipiprant has a low risk of influencing co-medication pharmacokinetics: Impact on simvastatin and rosuvastatin in different SLCO1B1 genotypes**. Pulmonary pharmacology & therapeutics 2019:101809.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31195091
ABSTRACT
Fevipiprant, a prostaglandin D2 receptor 2 antagonist, is in clinical development as a treatment for asthma. The goal of this study was to assess the potential of fevipiprant to cause drug-drug interactions (DDI) as a perpetrator, that is, by altering the pharmacokinetics (PK) of co-medications. In vitro drug interaction studies of clinically relevant drug metabolizing enzymes and transporters were conducted for fevipiprant and its acyl glucuronide (AG) metabolite. Comparison of Ki values with unbound systemic or portal vein steady-state plasma exposure of fevipiprant and its AG metabolite revealed the potential for inhibition of organic anion transporting polypeptide 1B1 (OATP1B1) transporters (R-value of 5.99), while other targets including cytochrome P450 enzymes were not, or only marginally, inhibited. Consequently, an open-label, two-part, two-period, single-sequence clinical study assessed the effect of fevipiprant 450mg QD on the pharmacokinetics of simvastatin 20mg and rosuvastatin 20mg, two statins with different dependency in OATP1B1-mediated hepatic uptake, in healthy adult volunteers. The study also assessed the pharmacogenetics of the SLCO1B1 gene, which encodes OATP1B1. Clinically, fevipiprant 450mg QD showed a low potential for interaction and

increased the peak concentrations of simvastatin acid and rosuvastatin by 2.23- and 1.87-fold, respectively, with little or no impact on total exposure. Genotype analysis confirmed that SLCO1B1 genotype influences statin pharmacokinetics to a similar extent either with or without fevipiprant co-administration. In summary, fevipiprant at 450mg QD has only minor liabilities as a perpetrator for DDI.

[45] *Djekic D, Pinto R, Repsilber D et al.* **Serum untargeted lipidomic profiling reveals dysfunction of phospholipid metabolism in subclinical coronary artery disease**. Vascular health and risk management 2019; 15:123-135.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31190850
ABSTRACT
Purpose: Disturbed metabolism of cholesterol and triacylglycerols (TGs) carries increased risk for coronary artery calcification (CAC). However, the exact relationship between individual lipid species and CAC remains unclear. The aim of this study was to identify disturbances in lipid profiles involved in the calcification process, in an attempt to propose potential biomarker candidates. Patients and methods: We studied 70 patients at intermediate risk for coronary artery disease who had undergone coronary calcification assessment using computed tomography and Agatston coronary artery calcium score (CACS). Patients were divided into three groups: with no coronary calcification (NCC; CACS: 0; n=26), mild coronary calcification (MCC; CACS: 1-250; n=27), or severe coronary calcification (SCC; CACS: >250; n=17). Patients' serum samples were analyzed using liquid chromatography-mass spectrometry in an untargeted lipidomics approach. Results: We identified 103 lipids within the glycerolipid, glycerophospholipid, sphingolipid, and sterol lipid classes. After false discovery rate correction, phosphatidylcholine (PC)(16:0/20:4) in higher levels and PC(18:2/18:2), PC(36:3), and phosphatidylethanolamine(20:0/18:2) in lower levels were identified as correlates with SCC compared to NCC. There were no significant differences in the levels of individual TGs between the three groups; however, clustering the lipid profiles showed a trend for higher levels of saturated and monounsaturated TGs in SCC compared to NCC. There was also a trend for lower TG(49:2), TG(51:1), TG(54:5), and TG(56:8) levels in SCC compared to MCC. Conclusion: In this study we investigated the lipidome of patients with coronary calcification. Our results suggest that the calcification process may be associated with dysfunction in autophagy. The lipidomic biomarkers revealed in this study may aid in better assessment of patients with subclinical coronary artery disease.

[46] *Purnamasari D, Abdaly MS, Azizi MS et al.* **Carotid intima-media thickness among normoglycemia and normotension first-degree relatives of type 2 diabetes mellitus**. Vascular health and risk management 2019; 15:101-107.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31190848
ABSTRACT
Introduction: Theoretically, first-degree relatives (FDRs) of type 2 diabetes mellitus (T2DM) are predisposed to have earlier and more severe atherosclerosis than non-FDR due to hereditary insulin resistance. A previous study reported that atherosclerotic plaques were found in 45.2% of young adults FDR of T2DM, but the study did not include non-FDR as control group. The aim of this study was to compare subclinical atherosclerosis (carotid intima-media thickness, CIMT)

between FDR of T2DM and non-FDR. Method: This was a cross-sectional study involving 16 FDR subjects and 16 age-sex matched non-FDR subjects, aged 19-40 years, with normal glucose tolerance and no hypertension. Collected data included demographic characteristic, anthropometric measurement (BMI and waist circumference), laboratory analysis (fasting blood glucose, HbA1c, lipid profile), and CIMT examination (using B-mode ultrasound). Results: The mean of CIMT in the FDR group was higher than that in the non-FDR group (0.44 mm vs 0.38 mm, p=0.005). After adjusting for waist circumference, BMI, low-density lipoprotein cholesterol, and triglyceride, CIMT maintained significant difference between FDR and non-FDR subjects. BMI and waist circumference showed moderate correlation with CIMT. Conclusion: CIMT in young adult FDR of T2DM is thicker than that in age-and sex-matched non-FDR population.