Literature update week 21 (2019)

[1] *Nguyen MA, Wyatt H, Susser L et al.* **Delivery of microRNAs by Chitosan Nanoparticles to Functionally Alter Macrophage Cholesterol Efflux In Vitro and In Vivo**. ACS nano 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31125197

ABSTRACT

The prevention and treatment of cardiovascular diseases (CVD) has largely focused on lowering circulating LDL cholesterol, yet a significant burden of atherosclerotic disease remains even when LDL is low. Recently, microRNAs (miRNAs) have emerged as exciting therapeutic targets for cardiovascular disease. miRNAs are small noncoding RNAs that post-transcriptionally regulate gene expression by degradation or translational inhibition of target mRNAs. A number of miRNAs have been found to modulate all stages of atherosclerosis, particularly those that promote the efflux of excess cholesterol from lipid laden macrophages in the vessel wall to the liver. However, one of the major challenges of miRNA-based therapy is to achieve tissue-specific, efficient and safe delivery of miRNAs in vivo. We sought to develop chitosan nanoparticles (chNPs) that can deliver functional miRNA mimics to macrophages and to determine if these nanoparticles can alter cholesterol efflux and reverse cholesterol transport in vivo. We developed chNPs with a size range of 150-200nm via ionic gelation method using tripolyphosphate (TPP) as a crosslinker. In this method, negatively charged miRNAs were encapsulated in the nanoparticles by ionic interactions with polymeric components. We then optimized the efficiency of intracellular delivery of different formulations of chitosan/TPP/miRNA to mouse macrophages. Using a well-defined miRNA with roles in macrophage cholesterol metabolism, we tested whether chNPs could deliver functional miRNAs to macrophages. We find chNPs can transfer exogenous miR-33 to naive macrophages and reduce the expression of ABCA1, a potent miR-33 target gene, both in vitro and in vivo, confirming that miRNAs delivered via nanoparticles can escape the endosomal system and function in the RISC complex. Because miR-33 and ABCA1 play a key role in regulating the efflux of cholesterol from macrophages, we also confirmed that macrophages treated with miR-33-loaded chNPs exhibited reduced cholesterol efflux to apolipoprotein A1, further confirming functional delivery of the miRNA. In vivo, mice treated with miR33-chNPs showed decreased reverse cholesterol transport (RCT) to the plasma, liver, and feces. In contrast, when efflux-promoting miRNAs were delivered via chNPs, ABCA1 expression and cholesterol efflux into the RCT pathway was improved. Over all, miRNAs can be efficiently delivered to macrophages via nanoparticles where they can function to regulate ABCA1 expression and cholesterol efflux, suggesting that these miRNA nanoparticles can be used in vivo to target atherosclerotic lesions.

[2] *Seong SJ, Ohk B, Kang WY et al.* **Pharmacokinetic Drug Interactions Between Amlodipine, Valsartan, and Rosuvastatin in Healthy Volunteers**. Adv Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31119689

ABSTRACT

INTRODUCTION: Amlodipine, valsartan, and rosuvastatin are among the medications widely coadministered for the treatment of hyperlipidemia accompanied by hypertension. The aim of this study was to investigate the possible pharmacokinetic drug-drug interactions between amlodipine, valsartan, and rosuvastatin in healthy Korean male volunteers. METHODS: In this phase 1, open-label, multiple-dose, two-part, two-period, fixed-sequence study, the enrolled subjects were randomized into two parts (A and B). In part A (n = 32), each subject received one

fixed-dose combination (FDC) tablet of amlodipine/valsartan 10 mg/160 mg alone for 10 consecutive days in period I, and the same FDC for 10 days with concomitant 7-day administration of 20 mg rosuvastatin in period II. In part B (n = 25), each subject received rosuvastatin alone for 7 days in period I, and the FDC for 10 days with concomitant 7-day administration of rosuvastatin in period II. In both parts, there was a 12-day washout between periods. Serial blood samples were collected for up to 72 h for amlodipine and rosuvastatin, and for up to 48 h for valsartan after the last dose of each period. The plasma concentrations of amlodipine, valsartan, and rosuvastatin were determined by using liquid chromatography-tandem mass spectrometry. RESULTS: Fifty-seven subjects were enrolled; 30 and 25 subjects completed part A and part B, respectively. The geometric mean ratios and 90% confidence intervals for the maximum plasma concentration at steady state (Cmax,ss) and the area under the plasma concentration-time curve over the dosing interval at steady state (AUCtau,ss) were 0.9389 (0.9029-0.9763) and 0.9316 (0.8970-0.9675) for amlodipine, 0.7698 (0.6503-0.9114) and 0.7888 (0.6943-0.8962) for valsartan, and 0.9737 (0.8312-1.1407) and 0.9596 (0.8826-1.0433) for rosuvastatin, respectively. Of the 57 subjects enrolled in this study, 10 subjects experienced 13 adverse events (AEs); no severe or serious AEs were reported. CONCLUSION: When amlodipine, valsartan, and rosuvastatin were coadministered to healthy volunteers, the pharmacokinetic exposure to valsartan was decreased, but no change in exposure to amlodipine and rosuvastatin occurred. All treatments were well tolerated. CLINICAL TRIAL REGISTRATION: https://cris.nih.go.kr CRIS KCT0001660. FUNDING: KyungDong Pharmaceutical Corp. Ltd., Seoul, Republic of Korea.

[3] *Maggi P, De Socio GV, Cicalini S et al.* **Statins and aspirin in the prevention of cardiovascular disease among HIV-positive patients between controversies and unmet needs: review of the literature and suggestions for a friendly use**. AIDS research and therapy 2019; 16:11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31126301

ABSTRACT

BACKGROUND: As in non-infected subjects, statins and aspirin have a pivotal preventive role in reducing the cardiovascular related morbidity and mortality in HIV infected patients. The persistence of immune activation in these subjects, could contribute to accelerate atherosclerosis, therefore, these treatments that reduce inflammation could provide additional cardiovascular protection. However the current guidelines for the use of these drugs in general population are dissimilar, with important differences between American and European ones. Aim of the present position paper is to provide recommendations aimed to overcome the actual differences and limitations among the current ones and to adapt them to the needs of HIV infected patients. RESULTS: We propose to adopt the new ACC/AHA guidelines, simple to use and cost effective, to use the ASCVD score that seems to estimate more accurately the cardiovascular risk among these patients. We suggest to start statin therapy in all patients with a calculated 10-year risk of a cardiovascular event of 10% or greater. Rosuvastatin and atorvastatin should be preferred. LDL-C target may be adopted. Aspirin should be always associated with a statin, in secondary prevention, while in primary prevention it should be reserved only to patients with >/= 20% 10-year risk particularly adherent to treatments, and with low risk of bleeding. We suggest to start with a dose of 100 mg/day. Finally, management of antiplatelet agents or novel oral anticoagulants may include selecting antiretrovirals with a

lower potential for drug interactions or choosing agents least likely to interact with antiretrovirals. CONCLUSIONS: As demonstrated in surveys, HIV physicians are generally highly committed regarding CVD and autonomous in prescribing statins and ASA. Consequently, in the light of the previously discussed discrepancies among the different guidelines and of the incomplete indications regarding HIV-positive persons, the present suggestions could overcome the actual differences and limitations among the current ones.

[4] *Ramsaran E, Preusse P, Sundaresan D et al.* **Adherence to Blood Cholesterol Treatment Guidelines Among Physicians Managing Patients With Atherosclerotic Cardiovascular Disease**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31104775
ABSTRACT
The ACC/AHA blood cholesterol treatment guidelines recommend statin therapy for all patients after experiencing an acute cardiovascular event. Previous analyses have shown that physicians have been slow to adopt guidelines, and many patients remain untreated or undertreated with statins after a cardiovascular event. However, reasons for this remain unknown. This analysis used electronic medical records and patient chart data from Reliant Medical Group (Worcester, Massachusetts) to evaluate physician adherence to the 2013 ACC/AHA blood cholesterol guidelines when treating patients with evidence of acute atherosclerotic cardiovascular disease and the reasons for the observed treatment decisions. Less than 50% of acute atherosclerotic cardiovascular disease patients were treated according to the ACC/AHA guidelines. Nearly 42% of patients not treated according to guidelines received a lower statin intensity than recommended. The most common reason cited by 41.8% of physicians for treating with a statin intensity below the recommended intensity was low-density lipoprotein cholesterol stable or at goal, despite ACC/AHA guidelines recommending specific statin intensities rather than specific low-density lipoprotein cholesterol levels. In conclusion, physician and patient education on the importance of maximizing lipid-lowering therapy in this high-risk patient population should be emphasized.

[5] *Maciejko JJ, Jamoua R, Anne P*. **Assessment and Management of Patients with Hyperlipidemia Referred for Initiation of PCSK9 Inhibitor Therapy: A Lipid Clinic Experience**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31119582
ABSTRACT
PURPOSE: Previous studies have reported that monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) in clinical practice have been underutilized due to several barriers, including high cost, stringent insurance authorization, patient cost-sharing and insufficient documentation of a patient's medical history. The purpose of our study was to determine if prescribing PCSK9 inhibitors only to patients meeting the established indications would significantly improve the approval rate and utilization. METHODS: We conducted a review and analysis of the medical records of patients referred by their physician to a hospital-based lipid clinic over a 20-month period specifically for initiation of a PCSK9 inhibitor. RESULTS: There were 180 patients referred to our lipid clinic by their cardiologist or internist specifically for initiation of a PCSK9 inhibitor. Only 76 (42%) of these patients met the approved indications

for this therapy and were provided PCSK9 inhibitor prescriptions. All received insurance approval within 3 weeks. Three did not initiate therapy due to excessive out-of-pocket cost, three discontinued therapy after two injections because of intolerable side effects (rhinorrhea), with the remaining 70 patients starting and continuing therapy, long-term. The remaining 104 patients were not given a PCSK9 inhibitor prescription and were treated with oral lipid-lowering medications. CONCLUSION: Our findings suggest that those physicians who referred patients to our lipid clinic specifically for initiation of a PCSK9 inhibitor were not aware of the established indications. By prescribing a PCSK9 inhibitor to only those patients meeting the established indications, 100% obtained approval. Therefore, to achieve higher insurance approval rates and utilization, it is essential that physicians understand the indications for PCSK9 inhibitor therapy and prescribe them only to patients meeting the established indications.

[6] *Freedman DM, Kuncl RW, Cahoon EK et al.* **Relationship of statins and other cholesterol-lowering medications and risk of amyotrophic lateral sclerosis in the US elderly**. Amyotrophic lateral sclerosis & frontotemporal degeneration 2018; 19:538-546.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31112080
ABSTRACT
OBJECTIVE: Statins are commonly prescribed drugs that have been inconsistently associated with amyotrophic lateral sclerosis (ALS) risk. We examined associations between ALS risk and overall statin use, statin categories based on lipophilicity and other cholesterol-lowering medications, in Medicare beneficiaries. METHODS: In this nation-wide population-based case-control study, 10,450 Medicare participants (ages 66-89 years) diagnosed with ALS, using Medicare Parts A and B claims, between 1 January 2008 and 31 December 2014, were frequency-matched to 104,500 controls on age, sex, and selection year. Odds ratios (ORs) for the association between statins and ALS were estimated using logistic regression models. Covariates included dyslipidemia, other comorbidities, age, sex, race, proxies for smoking and obesity, Medicare use, and indicators of socioeconomic status. Statin use derived from Medicare Part D claims. Non-statin cholesterol-lowering drugs were evaluated as comparison drugs. RESULTS: ALS risk was reduced with statin use (OR = 0.87 (95% confidence interval (CI) = 0.83-0.91)). While risk was unrelated to three cholesterol-lowering medications (nitrates, bile acid sequestrants, and ezetimibe), it was associated with fibrates (OR = 0.88 (95% CI = 0.80-0.97)). Risk for lipophilic statins was slightly lower than for other statins. ALS risk was lower in all statin categories for dyslipidemic individuals, but only lipophilic statins were associated with lower risk in non-dyslipidemic individuals and demonstrated an inverse trend with duration. CONCLUSIONS: Our findings suggest that statins are associated with lower ALS risk and offer new evidence that fibrates may be related to lower risk. However, we were unable to fully adjust for smoking and body mass index.

[7] *Ridruejo E, Romero-Caimi G, Obregon MJ et al.* **Potential molecular targets of statins in the prevention of hepatocarcinogenesis**. Annals of hepatology 2018; 17:490-500.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31103154
ABSTRACT
Introduction and alm. Hepatocellular carcinoma (HCC) represents 90% of liver tumors. Statins, may reduce the incidence of various tumors, including HCC. Antitumoral activities may be

mediated by changes in transforming growth factor-beta (TGF-betaIota) and thyroid hormones (TH) regulation. AIM: The aim of our study is to establish the statins mechanism of action and the potential key molecules involved in an in vivo and in vitro HCC model. MATERIALS AND METHODS: We used two models: in vivo (in rats) using diethylnitrosamine (DEN) and hexachlorobenzene (HCB) to develop HCC. We analyzed cell proliferation parameters (proliferating cell nuclear antigen, PCNA) and cholesterol metabolism (hydroxy-methylglutaryl-CoA reductase, HMGCoAR). In vitro (Hep-G2 cells) we evaluated the effects of different doses of Atorvastatin (AT) and Simvastatin (SM) on HCB induced proliferation and analyzed proliferative parameters, cholesterol metabolism, TGF-betaIota mRNA, c-Src and TH levels. RESULTS: In vivo, we observed that cell proliferation significantly increased as well as cholesterol serum levels in rats treated with HCB. In vitro, we observed the same results on PCNA as in vivo. The statins prevented the increase in HMG-CoAR mRNA levels induced by HCB, reaching levels similar to controls at maximum doses: AT (30 muM), and SM (20 muM). Increases in PCNA, TGF-betaIota, and pc-Src, and decreases in deiodinase I mRNA levels induced by HCB were not observed when cells were pre-treated with AT and SM at maximum doses. CONCLUSION: Statins can prevent the proliferative HCB effects on Hep-G2 cells. TGF-betaIota, c-Src and TH may be the statins molecular targets in hepatocarcinogenesis.

[8] *Momtazi-Borojeni AA, Nik ME, Jaafari MR et al.* **Effects of immunization against PCSK9 in an experimental model of breast cancer**. Archives of medical science : AMS 2019; 15:570-579.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31110521

ABSTRACT

Introduction: Inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) is an efficient strategy for lowering low-density lipoprotein cholesterol (LDL-C). There are, however, scant data on the efficacy and safety of PCSK9 inhibitors in non-cardiovascular diseases, particularly cancer. The present study aimed to evaluate the effect of PCSK9 inhibition using a nanoliposomal antiPCSK9 vaccine on cancer behavior and endpoints in mice bearing breast tumor. Material and methods: To induce antiPCSK9 antibody in vivo, a nanoliposomal antiPCSK9 vaccine absorbed on 0.4% alum adjuvant was used. To induce tumor, BALB/c mice were subcutaneously inoculated with 4T1 breast carcinoma cells. After the tumor mass was palpable (approximately 10 mm(3)), the mice were randomly divided into four groups and subjected to different treatment protocols: (1) PBS (untreated control), (2) vaccine group, (3) combination of vaccine and Doxil, and (4) Doxil (positive control) group. Vaccine was subcutaneously administered to mice four times at 2-week intervals. Two weeks after the last administration, the vaccinated and non-vaccinated mice were subcutaneously inoculated with 4T1 breast carcinoma cells. To evaluate therapeutic efficacy, mouse body weight, tumor size, and survival were monitored every other day for 60 days. Results: The nanoliposomal antiPCSK9 vaccine was found to efficiently induce specific antibodies against PCSK9 in BALB/c mice, thereby decreasing plasma levels of PCSK9 and inhibiting its function. Tumor size analysis showed that time to reach endpoint (TTE) of the vaccine, combination, Doxil, and control groups was 47 +/-10, 57 +/-4, 60 +/-4 and 39 +/-9 days, respectively. Rate of tumor growth in vaccine, combination and Doxil groups was decreased by 21%, 48% and 53%, respectively, compared to the control group. Lifespan was increased by 4.2% in the vaccine group, compared with the control group. Additionally, the survival in the combination and Doxil groups was

significantly higher than the vaccine and control groups. Conclusions: Our results revealed that PCSK9 inhibition may moderately improve breast cancer outcomes while having no harmful effects in tumor-bearing mice.

[9] *Momtazi-Borojeni AA, Nik ME, Jaafari MR et al.* **Potential anti-tumor effect of a nanoliposomal antiPCSK9 vaccine in mice bearing colorectal cancer**. Archives of medical science : AMS 2019; 15:559-569.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31110520
ABSTRACT
Introduction: Inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) is an effective therapeutic tool for lowering low-density lipoprotein cholesterol (LDL-C). There is no available evidence on the efficacy and safety of PCSK9 inhibitors in non-cardiovascular diseases, particularly cancer. The present study aimed to evaluate the effect of PCSK9 inhibition on cancer endpoints in mice bearing colon carcinoma, using a nanoliposomal antiPCSK9 vaccine. Material and methods: The prepared nanoliposomal antiPCSK9 vaccine was subcutaneously inoculated in BALB/c mice four times with a biweekly interval. Two weeks after the last booster, the vaccinated and unvaccinated mice were subcutaneously inoculated with CT26 colon cancer cells into the right flank. After the tumor mass became palpable, the mice were randomly divided into three groups: (1) PBS (untreated control), (2) vaccine group, and (3) pegylated liposomal doxorubicin (PLD; positive control) group. Body weight, tumor size and survival of mice were monitored for 50 days. Results: The nanoliposomal antiPCSK9 vaccine could efficiently provoke specific antibodies against PCSK9 in BALB/c mice and thereby reduced the plasma level and function of PCSK9. Tumor volume was 77% and 87.7% lower ($p < 0.0001$) in the vaccinated mice when compared with Doxil (liposomal doxorubicin) and control mice, respectively. Tumor size analysis showed that time to reach the endpoint of the vaccine group (47 +/-11 days) was slightly but not significantly higher than PLD (46 +/-2.6 days) and the control (43 +/-12 days) groups. The tumor growth rates in the vaccine and PLD groups were reduced by 9.3% and 7.3, respectively, when compared with the control group. The vaccinated mice survived slightly but not significantly longer than PLD and the control mice. The median survival of the vaccine, PLD and control groups were 51, 45, and 41 days, respectively. The vaccinated mice's life was prolonged by 24.4% as compared with the control mice, while it was increased by 9.8% in the PLD group. Conclusions: Our results revealed that PCSK9 inhibition not only exerted no harmful effects but also could moderately inhibit tumor growth, and improve lifespan and survival in mice bearing colon cancer.

[10] *Tabaei S, Tabaee SS*. **DNA methylation abnormalities in atherosclerosis**. Artificial cells, nanomedicine, and biotechnology 2019; 47:2031-2041.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31116040
ABSTRACT
Atherosclerosis is a complex disease with involvement of intermediate-, large-sized arteries. Atherosclerosis is characterized by the accumulation of vascular lipids, immune system activation, inflammation, oxidative stress and oxidized low-density lipoproteins (LDLs), endothelial cell (EC) activation, arterial smooth muscle cell (SMC) proliferation, macrophage activation and foam cell formation that cause endothelial dysfunction. DNA methylation is one

of important epigenetic mechanisms which changes gene expression. It has been evident that this mechanism plays an important role in the initiation and propagation of atherosclerosis. Furthermore, DNA methylation is a crucial and distinct mechanism that modulates genes governing cell proliferation, thereby connecting environmental insults with gene expression. This study represents many atherosclerosis-related genes which are regulated through DNA methylation mechanism. Although the role of epigenetics in atherosclerosis is at their infancy. Nevertheless, various studies demonstrated that DNA methylation involvement in this disease is undeniable. DNA methyltransferases are the main player of the smooth muscle cell proliferation, endothelial cell integrity, as well as arteriosclerosis formation. In this review, we focus on recent achievements in the functional and description interpretation of the DNA methylation pattern of cells and tissues implicated in atherosclerosis. Besides, we discuss the association of DNA methylation with oxidative stress, hyperhomocysteinemia (HHcy), ageing, and inflammation in the development and pathogenesis of atherosclerosis.

[11] *Potunuru UR, Priya KV, Varsha M et al.* **Amarogentin, a secoiridoid glycoside, activates AMP- activated protein kinase (AMPK) to exert beneficial vasculo-metabolic effects**. Biochimica et biophysica acta. General subjects 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31125678
ABSTRACT
INTRODUCTION: AMP-activated protein kinase (AMPK) is a drug target for treatment of metabolic and cardiovascular complications. Extracts of Gentianaceace plants exhibit anti-diabetic and anti-atherosclerotic effects, however, whether their phyto-constitutents activate AMPK remains to be determined. METHODS: Molecular docking of Gentiana lutea constituents was performed with crystal structure of human alpha2beta1gamma1 trimeric AMPK (PDB ID: 4CFE). Binding of Amarogentin (AG) to alpha2 subunit was confirmed through isothermal titration calorimetry (ITC) and in vitro kinase assays were performed. L6 myotube, HUH7 and endothelial cell cultures were employed to validate in silico and in vitro observations. Lipid lowering and anti-atherosclerotic effects were confirmed in streptozotocin induced diabetic mice via biochemical measurements and through heamatoxylin and eosin, Masson's trichrome and Oil Red O staining. RESULTS: AG interacts with the alpha2 subunit of AMPK and activates the trimeric kinase with an EC50 value of 277 pM. In cell culture experiments, AG induced phosphorylation of AMPK as well as its downstream targets, acetyl-coA-carboxylase (ACC) and endothelial nitric oxide synthase (eNOS). Additionally, it enhanced glucose uptake in myotubes and blocked TNF-alpha induced endothelial inflammation. Oral supplementation of AG significantly attenuated diabetes-mediated neointimal thickening, and collagen and lipid deposition in the aorta. It also improved circulating levels of lipids and liver function in diabetic mice. CONCLUSION: In conclusion, AG exerts beneficial vasculo-metabolic effects by activating AMPK. GENERAL SIGNIFICANCE: Amarogentin, a naturally occurring secoiridoid glycoside, is a promising lead for design and synthesis of novel drugs for treatment and management of dyslipidemia and cardiovascular diseases.

[12] *Weigert A, von Knethen A, Thomas D et al.* **Sphingosine kinase 2 is a negative regulator of inflammatory macrophage activation**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31128248

ABSTRACT

Sphingosine kinases (SPHK) generate the sphingolipid sphingosine-1-phosphate, which, among other functions, is a potent regulator of inflammation. While SPHK1 produces S1P to promote inflammatory signaling, the role of SPHK2 is unclear due to divergent findings in studies utilizing gene depletion versus inhibition of catalytic activity. We sought to clarify how SPHK2 affects inflammatory signaling in human macrophages, which are main regulators of inflammation. SPHK2 expression and activity were rapidly decreased within 6h upon stimulating primary human macrophages with lipopolysaccharide (LPS), but was upregulated after 24h. At 24h following LPS stimulation, targeting SPHK2 with the inhibitor ABC294640, a specific siRNA or by using Sphk2(-/-) mouse peritoneal macrophages increased inflammatory cytokine production. Downregulation of SPHK2 in primary human macrophages within 6h of LPS treatment was blocked by inhibiting autophagy. SPHK2 overexpression or inhibiting autophagy 6h after human macrophage activation with LPS suppressed inflammatory cytokine release. Mechanistically, SPHK2 suppressed LPS-triggered NF-kappaB activation independent of its catalytic activity and prevented increased mitochondrial ROS formation downstream of LPS. In conclusion, SPHK2 is an anti-inflammatory protein in human macrophages that is inversely coupled to inflammatory cytokine production. This needs consideration when targeting SPHK2 with specific inhibitors.

[13] *Ong M, Jerreat L, Hameed A*. **Familial hypertriglyceridaemia and type 2 diabetes in pregnancy: prevention of acute pancreatitis with diet control and omega-3 fatty acids**. BMJ case reports 2019; 12.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31110063

ABSTRACT

Acute pancreatitis in pregnancy is rare and can be caused by hypertriglyceridaemia. The management of hypertriglyceridaemia in pregnancy is complex and challenging as many lipid-lowering medications have been found to be unsafe in pregnancy. Patients who present with hypertriglyceridaemia commonly have multiple risk factors such as, diabetes, alcohol excess and hypothyroidism which pose a greater challenge to the management of these patients. We present a case of a 31-year-old woman presenting with familial hypertriglyceridaemia and type 2 diabetes mellitus in her third pregnancy. She had an uneventful pregnancy with the use of omega-3 fatty acids nutritional support, low-fat diet and tight glucose control with insulin and metformin.

[14] *Karlsson SA, Eliasson B, Franzen S et al.* **Risk of cardiovascular event and mortality in relation to refill and guideline adherence to lipid-lowering medications among patients with type 2 diabetes mellitus in Sweden**. BMJ open diabetes research & care 2019; 7:e000639.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31114701

ABSTRACT

Objective: To analyze the risk of cardiovascular (CV) events and mortality in relation to adherence to lipid-lowering medications by healthcare centers and patients with type 2 diabetes mellitus (T2DM). Research design and methods: We included 121 914 patients (12% secondary prevention) with T2DM reported by 1363 healthcare centers. Patients initiated lipid-lowering medications between July 2006 and December 2012 and were followed from

cessation of the first filled supply until multidose dispensed medications, migration, CV events, death or December 2016. The study period was divided into 4-month intervals through 2014, followed by annual intervals through 2016. Adherence measures were assessed for each interval. Patients' (refill) adherence was measured using the medication possession ratio (MPR). Healthcare centers' (guideline) adherence represented the prescription prevalence of lipid-lowering medications according to guidelines. The risk of CV events and mortality was analyzed for each interval using Cox proportional hazard regression and Kaplan-Meier. Results: Compared with high-adherent patients (MPR >80%), low-adherent primary prevention patients (MPR </=80%) showed higher risk of all outcomes: 44%-51 % for CV events, doubled for all-cause mortality and 79%-90% for CV mortality. Corresponding risks for low-adherent secondary prevention patients were 17%-19% for CV events, 88%-97% for all-cause and 66%-79% for CV mortality. Primary prevention patients treated by low-adherent healthcare centers (guideline adherence <48%) had a higher risk of CV events and CV mortality. Otherwise, no difference in the risk of CV events or mortality was observed by guideline adherence level. Conclusions: Our results demonstrate the importance of high refill adherence and thus the value of individualized care among patients with T2DM.

[15] *Nishikawa S, Menju T, Takahashi K et al.* **Statins may have double-edged effects in patients with lung adenocarcinoma after lung resection**. Cancer management and research 2019; 11:3419-3432.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31114376
ABSTRACT
Purpose: The epithelial to mesenchymal transition (EMT) is pivotal for driving metastasis and recurrence in lung cancer. Some in vitro reports have shown that statins suppress EMT by inactivating mutant p53 functions. Several clinical trials of conventional treatments with statins have been performed, but the effect of these drugs on prognosis is still uncertain. The purpose of this study is to examine the impact of statins on EMT and the prognosis of patients with lung adenocarcinoma. Materials and methods: Morphological changes were evaluated and EMT markers (E-cadherin, vimentin) were analyzed by Western blotting in p53-overexpressing H1650 and mutant p53-harboring H1975 lung adenocarcinoma cells, with and without simvastatin administration. The invasive ability of these cells was analyzed in a Matrigel chemoinvasion assay. A total of 250 lung adenocarcinoma specimens were also collected from patients who underwent surgery in our institute. EMT markers in these tumor specimens were evaluated by immunostaining and p53 mutation status was determined by direct sequencing. Associations among EMT status, p53 mutation status, and statin use were evaluated, and prognosis was analyzed using a marginal structural model. Results: Mutant p53 induced EMT and increased the invasive ability of H1650 cells. Simvastatin restored the epithelial phenotype and decreased the invasive ability of both H1650 and H1975 cells. Statin administration was associated with inactivation of EMT only in patients with mutant p53, which was consistent with the in vitro results. Moreover, in patients with mutant p53, statin users had significantly better survival than non-statin users. In contrast, statins significantly worsened the prognosis of patients with wild type p53 (HR 2.10, 95% CI 1.14-3.85). Conclusion: Statins suppress EMT and change the prognosis of patients with lung adenocarcinoma in a p53 mutation-dependent manner.

[16] *Huang P, Wang L, Li Q et al.* **Atorvastatin Enhances the Therapeutic Efficacy of Mesenchymal Stem Cells Derived Exosomes in Acute Myocardial Infarction via Up-regulating Long Non-coding RNA H19**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31119268
ABSTRACT
AIMS: Naturally secreted nanovesicles, known as exosomes, play important roles in stem cell-mediated cardioprotection. We have previously demonstrated that atorvastatin (ATV) pretreatment improved the cardioprotective effects of mesenchymal stem cells (MSCs) in a rat model of acute myocardial infarction (AMI). The aim of this study was to investigate if exosomes derived from ATV-pretreated MSCs exhibit more potent cardioprotective function in a rat model of AMI and if so to explore the underlying mechanisms. METHODS AND RESULTS: Exosomes were isolated from control MSCs (MSC-Exo) and ATV-pretreated MSCs (MSCATV-Exo), and were then delivered to endothelial cells and cardiomyocytes in vitro under hypoxia and serum deprivation (H/SD) condition or in vivo in an acutely infarcted Sprague-Dawley rat heart. Regulatory genes and pathways activated by ATV pretreatment were explored using genomics approaches and functional studies. In vitro, MSCATV-Exo accelerated migration, tube-like structure formation and increased survival of endothelial cells but not cardiomyocytes, whereas the exosomes derived from MSCATV-Exo treated endothelial cells prevented cardiomyocytes from H/SD-induced apoptosis. In a rat AMI model, MSCATV-Exo resulted in improved recovery in cardiac function, further reduction in infarct size and reduced cardiomyocyte apoptosis compared to MSC-Exo. In addition, MSCATV-Exo promoted angiogenesis and inhibited the elevation of IL-6 and TNF-alpha in the peri-infarct region. Mechanistically, we identified lncRNA H19 as a mediator of the role of MSCATV-Exo in regulating expression of miR-675 and activation of proangiogenic factor VEGF and ICAM-1. Consistently, the cardioprotective effects of MSCATV-Exo was abrogated when lncRNA H19 was depleted in the ATV-pretreated MSCs and was mimicked by overexpression of lncRNA H19. CONCLUSIONS: Exosomes obtained from ATV-pretreated MSCs have significantly enhanced therapeutic efficacy for treatment of AMI possibly through promoting endothelial cell function. LncRNA H19 mediates, at least partially, the cardioprotective roles of MSCATV-Exo in promoting angiogenesis.

[17] **Correction to: Variation in Serum PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9), Cardiovascular Disease Risk, and an Investigation of Potential Unanticipated Effects of PCSK9 Inhibition: A Genome-Wide Association Study and Mendelian Randomization Study in the HUNT, Norway**. Circulation. Genomic and precision medicine 2019; 12:e000055.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31112423
ABSTRACT

[18] *Sun YV, Damrauer SM, Hui Q et al.* **Effects of Genetic Variants Associated with Familial Hypercholesterolemia on Low-Density Lipoprotein-Cholesterol Levels and Cardiovascular Outcomes in the Million Veteran Program**. Circulation. Genomic and precision medicine 2018; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31106297

ABSTRACT
Background: Familial hypercholesterolemia (FH) is characterized by inherited high levels of low-density lipoprotein cholesterol (LDL-C) and premature coronary heart disease (CHD). Over a thousand low-frequency variants in LDLR, APOB and PCSK9 have been implicated in FH but few have been examined at the population level. We aim to estimate the phenotypic effects of a subset of FH variants on LDL-C and clinical outcomes among 331,107 multi-ethnic participants. Methods: We examined the individual and collective association between putatively pathogenic FH variants included on the MVP biobank array and the maximum LDL-C level over an interval of 15 years (maxLDL). We assessed the collective effect on clinical outcomes by leveraging data from 61.7 million clinical encounters. Results: We found 8 out of 16 putatively pathogenic FH variants with >/=30 observed carriers to be significantly associated with elevated maxLDL (9.4-80.2 mg/dL). Phenotypic effects were similar for European and African Americans despite substantial differences in carrier frequencies. Based on observed effects on maxLDL, we identified a total of 748 carriers (1:443) who had elevated maxLDL (36.5+/-1.4 mg/dL, p=1.2x10(-152)), and higher prevalence of clinical diagnoses related to hypercholesterolemia and CHD in a phenome-wide scan. Adjusted for maxLDL, FH variants collectively associated with higher prevalence of CHD (odds ratio, 1.59 [95% CI 1.36-1.86], p=1.1x10(-8)) but not peripheral artery disease. Conclusions: The distribution and phenotypic effects of putatively pathogenic FH variants were heterogeneous within and across variants. More robust evidence of genotype-phenotype associations of FH variants in multi-ethnic populations is needed to accurately infer at-risk individuals from genetic screening.

[19] *Ozaki Y, Garcia-Garcia HM, Beyene SS et al.* **Effect of Statin Therapy on Fibrous Cap Thickness in Coronary Plaque on Optical Coherence Tomography- Review and Meta-Analysis**. Circulation journal : official journal of the Japanese Circulation Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31118354

ABSTRACT
BACKGROUND: Statin therapy has been shown to result in coronary plaque regression, but the relationship between statin use and stabilization of coronary plaque has not been elucidated. We conducted a systematic review and meta-analysis to evaluate the effect of statin therapy on fibrous cap thickness (FCT) on optical coherence tomography (OCT).Methods and Results:Nine OCT studies (6 randomized controlled trials and 3 observational studies) were enrolled with a total of 341 patients (390 lesions). Arms of the studies were grouped according to statin type and/or dose. Random effects meta-analysis was used to estimate a pooled mean change in FCT from baseline to follow-up. The overall effect mean FCT change was 67.7 microm (95% CI: 51.4-84.1, I(2)=95.0%, P<0.001). All statin groups had an increase in FCT, but the magnitude of the increase differed according to the statin. Two homogeneous subgroups with I(2)=0 were identified: mean FCT change was 27.8 microm (for subgroup atorvastatin 5 mg and rosuvastatin), and 61.9 microm (for subgroup atorvastatin 20 mg, fluvastatin 30 mg, and pitavastatin 4 mg). On meta-regression modeling, statin therapy alone explained most of the change in FCT. CONCLUSIONS: Statin therapy induced a significant increase in FCT as assessed on OCT, independent of coronary risk factors and other medications.

[20] *Steg PG, Szarek M, Bhatt DL et al.* **Effect of Alirocumab on Mortality After Acute Coronary Syndromes: An Analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial**. Circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31117810

ABSTRACT
BACKGROUND: Trials of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors demonstrated reductions in major adverse cardiovascular events, but not death. We assessed the effects of alirocumab on death after index acute coronary syndrome (ACS). METHODS: ODYSSEY OUTCOMES was a double-blind, randomized comparison of alirocumab or placebo in 18 924 patients who had an ACS 1-12 months previously and elevated atherogenic lipoproteins despite intensive statin therapy. Alirocumab dose was blindly titrated to target achieved low-density lipoprotein cholesterol (LDL-C) between 25 and 50 mg/dL. We examined the effects of treatment on all-cause death and its components, cardiovascular and noncardiovascular death, with log-rank testing. Joint semiparametric models tested associations between nonfatal cardiovascular events and cardiovascular or noncardiovascular death. RESULTS: Median follow-up was 2.8 years. Death occurred in 334 (3.5%) and 392 (4.1%) patients, respectively, in the alirocumab and placebo groups (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.73 to 0.98; P=0.03, nominal P value). This resulted from nonsignificantly fewer cardiovascular (240 [2.5%] vs 271 [2.9%]; HR, 0.88; 95% CI, 0.74 to 1.05; P=0.15) and noncardiovascular (94 [1.0%] vs 121 [1.3%]; HR, 0.77; 95% CI, 0.59 to 1.01; P=0.06) deaths with alirocumab. In a prespecified analysis of 8242 patients eligible for >/=3 years' follow-up, alirocumab reduced death (HR, 0.78; 95% CI, 0.65 to 0.94; P=0.01). Patients with nonfatal cardiovascular events were at increased risk for cardiovascular and noncardiovascular deaths (P<0.0001 for the associations). Alirocumab reduced total nonfatal cardiovascular events (P<0.001) and thereby may have attenuated the number of noncardiovascular deaths. A post-hoc analysis found that, compared to patients with lower LDL-C, patients with baseline LDL-C >/=100 mg/dL (2.59 mmol/L) had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR, 0.71; 95% CI, 0.56 to 0.90; Pinteraction=0.007). In the alirocumab group, all-cause death declined with achieved LDL-C at 4 months of treatment, to a level of approximately 30 mg/dL (adjusted P=0.017 for linear trend). CONCLUSIONS: Alirocumab added to intensive statin therapy has the potential to reduce death after ACS, particularly if treatment is maintained for >/=3 years, if baseline LDL-C is >/=100 mg/dL, or if achieved LDL-C is low. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique Identifier: NCT01663402.

[21] *Sobhan M, Gholampoor G, Firozian F et al.* **Comparison of efficacy and safety of atorvastatin 5% lotion and betamethasone 0.1% lotion in the treatment of scalp seborrheic dermatitis**. Clinical, cosmetic and investigational dermatology 2019; 12:267-275.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31118730

ABSTRACT
Purpose: Seborrheic dermatitis (SD) is a chronic inflammatory skin disorder that mainly affects areas rich in sebaceous glands, such as the scalp. Although the exact cause of SD is not clearly understood, it seems that skin colonization with Malassezia fungus and the inflammatory responses of the immune system to this fungus play an important role in the pathology of SD. Recently a growing body of evidence has shown anti-inflammatory and anti-fungal effects of

statins. Thus, this study aimed to evaluate the efficacy of topical atorvastatin in the treatment of scalp SD. Patients and methods: In this double-blind, clinical trial, 86 patients with mild-to-moderate scalp SD were divided into either atorvastatin (n=45) or betamethasone groups (n=41) by block randomization method. In addition to the ketoconazole 2% shampoo (3 times per week), the atorvastatin group received atorvastatin 5% lotion and the betamethasone group received betamethasone 0.1% lotion daily for 4 weeks. The SD severity of each patient was determined by Symptom Scale of Seborrheic Dermatitis (SSSD) at baseline and 4 weeks after treatment. Also, the patient's satisfaction of the treatment and adverse effects were investigated through individual reporting. Results: After 4 weeks of treatment, the score of SD severity decreased significantly in both groups, while changes of SSSD score from baseline to the fourth week of treatment were comparable in the two groups (P-value=0.476). Regarding patient's satisfaction of the treatment, results demonstrated the non-inferiority of atorvastatin as compared to betamethasone. Topical atorvastatin was also well-tolerated in almost all patients. Conclusion: Although preliminary, the results of the present study showed that topical atorvastatin has a comparable effect to topical betamethasone and can be considered as an alternative therapeutic modality in the treatment of scalp SD. However, these results need to be confirmed in future studies while taking into consideration the improvement of topical statin formulations.

[22] *Leonard CE, Zhou M, Brensinger CM et al.* **Clopidogrel Drug Interactions and Serious Bleeding: Generating Real World Evidence via Automated High-Throughput Pharmacoepidemiologic Screening**. Clinical pharmacology and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31106397
ABSTRACT
Few population-based studies have examined bleeding associated with clopidogrel drug-drug interactions (DDIs). We sought to identify precipitant drugs taken concomitantly with clopidogrel (an object drug) that increased serious bleeding rates. We screened 2000-2015 Optum commercial health insurance claims to identify DDI signals. We performed self-controlled case series studies for clopidogrel + precipitant pairs, examining associations with gastrointestinal bleeding or intracranial hemorrhage. To distinguish native bleeding effects of a precipitant, we reexamined associations using pravastatin as a negative control object drug. Among 431 analyses, 28 clopidogrel + precipitant pairs were statistically significantly positively associated with serious bleeding. Ratios of rate ratios ranged from 1.13-3.94. Among these pairs, 13 were expected given precipitant drugs alone increased and/or were harbingers of serious bleeding. The remaining 15 pairs constituted new DDI signals, none of which are currently listed in two major DDI knowledge bases.

[23] *Langsted A, Nordestgaard BG*. **Antisense Oligonucleotides Targeting Lipoprotein(a)**. Current atherosclerosis reports 2019; 21:30.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31111240
ABSTRACT
PURPOSE OF REVIEW: High lipoprotein(a) levels are observationally and causally, from human genetics, associated with increased risk of cardiovascular disease including myocardial

infarction and aortic valve stenosis. The European Atherosclerosis Society recommends screening for elevated lipoprotein(a) levels in high-risk patients. Different therapies have been suggested and some are used to treat elevated lipoprotein(a) levels such as niacin, PCSK9 inhibitors, and CETP inhibitors; however, to date, no randomized controlled trial has demonstrated that lowering of lipoprotein(a) leads to lower risk of cardiovascular disease. RECENT FINDINGS: Synthetic oligonucleotides can be used to inactivate genes involved in disease processes. To lower lipoprotein(a), two antisense oligonucleotides have been developed, one targeting apolipoprotein B and one targeting apolipoprotein(a). Mipomersen is an antisense oligonucleotide targeting apolipoprotein B and thereby reducing levels of all apolipoprotein B containing lipoproteins in the circulation. Mipomersen has been shown to lower lipoprotein(a) by 20-50% in phase 3 studies. AKCEA-APO(a)-LRx is the most recent antisense oligonucleotide targeting apolipoprotein(a) and thereby uniquely targeting lipoprotein(a). It has been tested in a phase 2 study and has shown to lower lipoprotein(a) levels by 50-80%. The treatment of elevated lipoprotein(a) levels with the newest antisense oligonucleotides seems promising; however, no improvement in cardiovascular disease risk has yet been shown. However, a phase 3 study of AKCEA-APO(a)-LRx is being planned with cardiovascular disease as outcome, and results are awaited with great anticipation.

[24] *Mihaila RG*. **Pragmatic Analysis of Dyslipidemia Involvement in Coronary Artery Disease: A Narrative Review**. Current cardiology reviews 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31113345
ABSTRACT
BACKGROUND: Dyslipidemia is the main factor involved in the occurrence and progression of coronary artery disease. OBJECTIVE: The research strategy is aimed at analyzing new data on the pathophysiology of dyslipidemia involvement in coronary artery disease, the modalities of atherogenic risk estimation and therapeutic advances. METHOD: Scientific articles published in PubMed from January 2017 to February 2018 were searched using the terms "dyslipidemia" and "ischemic heart disease". RESULTS: PCSK9 contributes to the increase in serum levels of low-density lipoprotein-cholesterol and lipoprotein (a). The inflammation is involved in the progression of hyperlipidemia and atherosclerosis. Hypercholesterolemia changes the global cardiac gene expression profile and is thus involved in the increase of oxidative stress, mitochondrial dysfunction, and apoptosis initiated by inflammation. Coronary artery calcifications may estimate the risk of coronary events. The cardio-ankle vascular index evaluates the arterial stiffness and correlates with subclinical coronary atherosclerosis. The carotid plaque score is superior to carotid intima-media thickness for risk stratification in patients with familial hypercholesterolemia and both can independently predict coronary artery disease. The lipoprotein (a) and familial hypercholesterolemia have a synergistic role in predicting the risk of early onset and severity of coronary atherosclerosis. A decrease in atherosclerotic coronary plaque progression can be achieved in patients with plasma LDL-cholesterol levels below 70 mg/dL. A highly durable RNA interference therapeutic inhibitor of PCSK9 synthesis could be a future solution. CONCLUSION: The prophylaxis and treatment of coronary artery disease in a dyslipidemic patient should be based on a careful assessment of cardio-vascular risk factors and individual metabolic particularities, so it may be personalized.

Literature update week 21 (2019)

[25] *Rana R, Sharma R, Kumar A*. **Repurposing of Fluvastatin against Candida albicans CYP450 lanosterol 14 alpha-demethylase, a target enzyme for antifungal therapy: An In silico and In vitro study**. Current molecular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31109273
ABSTRACT
BACKGROUND AND OBJECTIVES: The incidence of fungal infections has increased significantly specifically the cases of candida albican infection is increasing day by day and their resistance to clinically approved drugs are major concerns for a human. Various classes of antifungal drugs are available in the market for the treatment of these infections but unfortunately, none of them is able to treat the infection. Thus, in the present investigation, we have repurposed the well-known drug (Fluvastatin) in the treatment of Candida albican infections by using in silico, in vitro and ex vivo techniques. METHODS AND RESULTS: Firstly, we have developed and validated a simple model of CYP45014alpha-lanosterol demethylase of Candida albican by using crystal structure of Mycobacterium tuberculosis (1EA1). Further, fluvastatin was docked with a validated model of CYP45014alpha-lanosterol demethylase and revealed good binding affinity as that of fluconazole. In vitro results (Percentage growth retardation, Fungal growth kinetics, Biofilm test and Post antibiotic test) have shown the good antifungal activity of fluvastatin. Finally, the results of MTT assay have shown non-cytotoxic effect of fluvastatin in murine splenocytes and thymocytes. CONCLUSION: However, further, in vivo studies are required to confirm the complete role of fluvastatin as an antifungal agent.

[26] *Farokhnia M, Browning BD, Leggio L*. **Prospects for pharmacotherapies to treat alcohol use disorder: an update on recent human studies**. Current opinion in psychiatry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31107292
ABSTRACT
PURPOSE OF REVIEW: The aim of this study was to provide an update on medication development efforts for alcohol use disorder (AUD) by reviewing recently published (past 2 years) human studies that evaluated medications' effects on alcohol-related outcomes. RECENT FINDINGS: Forty-five publications were found suitable for this review. A variety of compounds have been tested in the past 2 years as potential pharmacological options for AUD, including medications that act on multiple targets (topiramate, aripiprazole, quetiapine), calcium channels (gabapentin), gamma-Aminobutyric acid receptors (baclofen, diazepam), glutamate receptors (ifenprodil, memantine, glycine), nicotinic acetylcholine receptors (varenicline, mecamylamine), alpha1 adrenergic receptors (prazosin, doxazosin), neuroendocrine pathways (oxytocin, a vasopressin receptor 1b antagonist, a ghrelin receptor inverse agonist) and others (samidorphan, ibudilast, N-acetylcysteine, citoline). Important findings and limitations regarding the effects of these medications on alcohol-related outcomes are discussed. SUMMARY: There is a critical need to increase the armamentarium of medications for AUD. Human laboratory studies may help screen and prioritize promising targets and compounds before running large clinical trials. Given the complexity of AUD and the heterogeneity of afflicted patients, future studies should also investigate potential moderators and predictors of response to each pharmacological intervention.

[27] *Oh M, Shin JG, Ahn S et al.* **Pharmacokinetic comparison of a fixed-dose combination versus concomitant administration of amlodipine, olmesartan, and rosuvastatin in healthy adult subjects**. Drug design, development and therapy 2019; 13:991-997.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31114155

ABSTRACT
Objective: The aim of this study was to compare the pharmacokinetic (PK) and safety profiles of a fixed dose combination (FDC) formulation and co-administration of amlodipine, olmesartan, and rosuvastatin. Materials and methods: This study was an open-label, randomized, cross-over design conducted in healthy male volunteers. All subjects received either a single FDC tablet containing amlodipine 10 mg/olmesartan 40 mg/rosuvastatin 20 mg, or were co-administered an FDC tablet containing amlodipine 10 mg/olmesartan 40 mg and a tablet containing rosuvastatin 20 mg, for each period, with 14-day washout periods. Plasma concentrations of amlodipine, olmesartan, and rosuvastatin were measured by liquid chromatography tandem mass spectrometry. Safety was evaluated by measuring vital signs, clinical laboratory parameters, physical examinations, and medical interviews. Results: Sixty-four subjects were enrolled, and 54 completed the study. The geometric mean ratios and 90% CI for the maximum plasma concentration (Cmax) and area under the curve from time zero to the last sampling time (AUCt) were 1.0716 (1.0369,1.1074) and 1.0497 (1.0243,1.0757) for amlodipine, 1.0396 (0.9818,1.1009) and 1.0138 (0.9716,1.0578) for olmesartan, and 1.0257 (0.9433,1.1152) and 1.0043 (0.9453,1.0669) for rosuvastatin. Fourteen cases of adverse events occurred in 12 subjects. There was no statistically significant clinical difference between the formulation groups. Conclusion: The 90% CI of the primary PK parameters were within the acceptance bioequivalence criteria, which is ln (0.8) and ln (1.25). These results indicate that the FDC formulation and co-administration of amlodipine, olmesartan and rosuvastatin are pharmacokinetically bioequivalent and have similar safety profiles.

[28] *Johnson KW, Glicksberg BS, Shameer K et al.* **A transcriptomic model to predict increase in fibrous cap thickness in response to high-dose statin treatment: Validation by serial intracoronary OCT imaging**. EBioMedicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31126891

ABSTRACT
BACKGROUND: Fibrous cap thickness (FCT), best measured by intravascular optical coherence tomography (OCT), is the most important determinant of plaque rupture in the coronary arteries. Statin treatment increases FCT and thus reduces the likelihood of acute coronary events. However, substantial statin-related FCT increase occurs in only a subset of patients. Currently, there are no methods to predict which patients will benefit. We use transcriptomic data from a clinical trial of rosuvastatin to predict if a patient's FCT will increase in response to statin therapy. METHODS: FCT was measured using OCT in 69 patients at (1) baseline and (2) after 8-10weeks of 40 mg rosuvastatin. Peripheral blood mononuclear cells were assayed via microarray. We constructed machine learning models with baseline gene expression data to predict change in FCT. Finally, we ascertained the biological functions of the most predictive transcriptomic markers. FINDINGS: Machine learning models were able to predict FCT responders using baseline gene expression with high fidelity (Classification AUC=0.969 and 0.972). The first model (elastic net) using 73 genes had an accuracy of 92.8%, sensitivity of

94.1%, and specificity of 91.4%. The second model (KTSP) using 18 genes has an accuracy of 95.7%, sensitivity of 94.3%, and specificity of 97.1%. We found 58 enriched gene ontology terms, including many involved with immune cell function and cholesterol biometabolism. INTERPRETATION: In this pilot study, transcriptomic models could predict if FCT increased following 8-10 weeks of rosuvastatin. These findings may have significance for therapy selection and could supplement invasive imaging modalities.

[29] *Tsimikas S, Gordts P, Nora C et al.* **Statin therapy increases lipoprotein(a) levels**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31111151
ABSTRACT
AIMS: Lipoprotein(a) [Lp(a)] is elevated in 20-30% of people. This study aimed to assess the effect of statins on Lp(a) levels. METHODS AND RESULTS: This subject-level meta-analysis includes 5256 patients (1371 on placebo and 3885 on statin) from six randomized trials, three statin-vs.-placebo trials, and three statin-vs.-statin trials, with pre- and on-treatment (4-104 weeks) Lp(a) levels. Statins included atorvastatin 10 mg/day and 80 mg/day, pravastatin 40 mg/day, rosuvastatin 40 mg/day, and pitavastatin 2 mg/day. Lipoprotein(a) levels were measured with the same validated assay. The primary analysis of Lp(a) is based on the log-transformed data. In the statin-vs.-placebo pooled analysis, the ratio of geometric means [95% confidence interval (CI)] for statin to placebo is 1.11 (1.07-1.14) ($P < 0.0001$), with ratio >1 indicating a higher increase in Lp(a) from baseline in statin vs. placebo. The mean percent change from baseline ranged from 8.5% to 19.6% in the statin groups and -0.4% to -2.3% in the placebo groups. In the statin-vs.-statin pooled analysis, the ratio of geometric means (95% CI) for atorvastatin to pravastatin is 1.09 (1.05-1.14) ($P < 0.0001$). The mean percent change from baseline ranged from 11.6% to 20.4% in the pravastatin group and 18.7% to 24.2% in the atorvastatin group. Incubation of HepG2 hepatocytes with atorvastatin showed an increase in expression of LPA mRNA and apolipoprotein(a) protein. CONCLUSION: This meta-analysis reveals that statins significantly increase plasma Lp(a) levels. Elevations of Lp(a) post-statin therapy should be studied for effects on residual cardiovascular risk.

[30] *White HD, Steg PG, Szarek M et al.* **Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31121022
ABSTRACT
AIMS: The third Universal Definition of Myocardial Infarction (MI) Task Force classified MIs into five types: Type 1, spontaneous; Type 2, related to oxygen supply/demand imbalance; Type 3, fatal without ascertainment of cardiac biomarkers; Type 4, related to percutaneous coronary intervention; and Type 5, related to coronary artery bypass surgery. Low-density lipoprotein cholesterol (LDL-C) reduction with statins and proprotein convertase subtilisin-kexin Type 9 (PCSK9) inhibitors reduces risk of MI, but less is known about effects on types of MI. ODYSSEY OUTCOMES compared the PCSK9 inhibitor alirocumab with placebo in 18 924 patients with recent acute coronary syndrome (ACS) and elevated LDL-C (>/=1.8 mmol/L) despite intensive statin therapy. In a pre-specified analysis, we assessed the effects of alirocumab on types of MI. METHODS AND RESULTS: Median follow-up was 2.8 years. Myocardial infarction types were

prospectively adjudicated and classified. Of 1860 total MIs, 1223 (65.8%) were adjudicated as Type 1, 386 (20.8%) as Type 2, and 244 (13.1%) as Type 4. Few events were Type 3 (n = 2) or Type 5 (n = 5). Alirocumab reduced first MIs [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.77-0.95; P = 0.003], with reductions in both Type 1 (HR 0.87, 95% CI 0.77-0.99; P = 0.032) and Type 2 (0.77, 0.61-0.97; P = 0.025), but not Type 4 MI. CONCLUSION: After ACS, alirocumab added to intensive statin therapy favourably impacted on Type 1 and 2 MIs. The data indicate for the first time that a lipid-lowering therapy can attenuate the risk of Type 2 MI. Low-density lipoprotein cholesterol reduction below levels achievable with statins is an effective preventive strategy for both MI types.

[31] *Falomir-Lockhart LJ, Cavazzutti GF, Gimenez E, Toscani AM*. **Fatty Acid Signaling Mechanisms in Neural Cells: Fatty Acid Receptors**. Frontiers in cellular neuroscience 2019; 13:162.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31105530
ABSTRACT
Fatty acids (FAs) are typically associated with structural and metabolic roles, as they can be stored as triglycerides, degraded by beta-oxidation or used in phospholipids' synthesis, the main components of biological membranes. It has been shown that these lipids exhibit also regulatory functions in different cell types. FAs can serve as secondary messengers, as well as modulators of enzymatic activities and substrates for cytokines synthesis. More recently, it has been documented a direct activity of free FAs as ligands of membrane, cytosolic, and nuclear receptors, and cumulative evidence has emerged, demonstrating its participation in a wide range of physiological and pathological conditions. It has been long known that the central nervous system is enriched with poly-unsaturated FAs, such as arachidonic (C20:4omega-6) or docosohexaenoic (C22:6omega-3) acids. These lipids participate in the regulation of membrane fluidity, axonal growth, development, memory, and inflammatory response. Furthermore, a whole family of low molecular weight compounds derived from FAs has also gained special attention as the natural ligands for cannabinoid receptors or key cytokines involved in inflammation, largely expanding the role of FAs as precursors of signaling molecules. Nutritional deficiencies, and alterations in lipid metabolism and lipid signaling have been associated with developmental and cognitive problems, as well as with neurodegenerative diseases. The molecular mechanism behind these effects still remains elusive. But in the last two decades, different families of proteins have been characterized as receptors mediating FAs signaling. This review focuses on different receptors sensing and transducing free FAs signals in neural cells: (1) membrane receptors of the family of G Protein Coupled Receptors known as Free Fatty Acid Receptors (FFARs); (2) cytosolic transport Fatty Acid-Binding Proteins (FABPs); and (3) transcription factors Peroxisome Proliferator-Activated Receptors (PPARs). We discuss how these proteins modulate and mediate direct regulatory functions of free FAs in neural cells. Finally, we briefly discuss the advantages of evaluating them as potential targets for drug design in order to manipulate lipid signaling. A thorough characterization of lipid receptors of the nervous system could provide a framework for a better understanding of their roles in neurophysiology and, potentially, help for the development of novel drugs against aging and neurodegenerative processes.

[32] *Bartoloni E, Alunno A, Cafaro G et al.* **Subclinical Atherosclerosis in Primary Sjogren's Syndrome: Does Inflammation Matter?** Frontiers in immunology 2019; 10:817.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31110500

ABSTRACT

Sjogren's syndrome (SS) is a systemic autoimmune disease mainly characterized by inflammatory involvement of exocrine gland. Atherosclerosis is a complex process leading to plaque formation in arterial wall with subsequent cardiovascular (CV) events. Recently, numerous studies demonstrated that SS patients bear an increased CV risk. Since activation of immune system is a key element in atherosclerosis, it is interesting to analyze whether and how the autoimmune and inflammatory events characterizing SS pathogenesis directly or indirectly contribute to atherosclerosis risk in these patients. An increase in circulating endothelial microparticles and integrins, which may be a consequence of endothelial damage and impaired repair mechanisms, has been demonstrated in SS. Increased endothelial expression of adhesion molecules with subsequent infiltration of inflammatory cells into arterial wall is also a critical event in atherosclerosis. The early inflammatory events taking place in the atherosclerotic plaque cause an increase in alarmins, such as S100A8/A9, which seems to be associated with SS disease activity and, in turn, induce up-regulation of interleukin (IL)-1beta and other pro-atherogenic cytokines. Interestingly, increased IL-1beta levels were also detected in tertiary lymphoid structures developing in vessel adventitia adjacent to the atherosclerotic plaque, suggesting a direct role of IL-1beta in this process. Similar to these structures, germinal center-like structures arising in SS exocrine glands are also tertiary lymphoid systems where T-helper (Th) cell subsets govern the adaptive immune response. Th1 cells are the most prevalent subtype and have been shown to be strongly involved in both SS pathogenesis and atherosclerosis. Th17 cells are attracting great interest and few studies showed its importance in SS development. Albeit in low amounts, a Th17 signature was also detected in atherosclerotic plaques and some animal models demonstrated a significant pro-atherogenic role and positive effects of IL-17A blockade. Despite the fact that T cells have a pivotal role in the inflammatory process that ultimately leads to atherosclerosis, B cells have also been detected in atherosclerotic plaques, although their exact role is still mostly unknown with studies showing contrasting results. In this scenario, the role of inflammation in atherosclerosis pathogenesis in patients with SS needs to be further explored.

[33] *Makela KA, Leppaluoto J, Jokelainen J et al.* **Effect of Physical Activity on Plasma PCSK9 in Subjects With High Risk for Type 2 Diabetes**. Front Physiol 2019; 10:456.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31114503

ABSTRACT

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a liver serine protease regulating LDL cholesterol metabolism. PCSK9 binds to LDL receptors and guides them to lysosomes for degradation, thus increasing the amount of circulating LDL cholesterol. The aim of the study was to investigate associations between physical activity and plasma PCSK9 in subjects with high risk for type 2 diabetes (T2D). Methods: Sixty-eight subjects from both genders with a high risk for T2D were included to a randomized controlled trial with a 3-month physical activity intervention. Physical activity intensities and frequencies were monitored throughout the intervention using a hip worn portable accelerometer. The plasma was

collected before and after intervention for analysis of PCSK9 and cardiovascular biomarkers. Results: Plasma PCSK9 did not relate to physical activity although number of steps were 46% higher in the intervention group than in the control group ($p < 0.029$). Total cholesterol was positively correlated with plasma PCSK9 ($R = 0.320$, $p = 0.008$), while maximal oxygen uptake was negatively associated ($R = -0.252$, $p = 0.044$). After the physical activity intervention PCSK9 levels were even stronger inversely associated with maximal oxygen uptake ($R = -0.410$, $p = 0.0008$) and positively correlated with HDL cholesterol ($R = 0.264$, $p = 0.030$). Interestingly, plasma PCSK9 levels were higher in the beginning than at the end of the study. Conclusion: The low physical activity that our subjects with high risk for T2D could perform did not influence plasma PCSK9 levels. Intervention with higher physical activities might be more effective in influencing PCSK9 levels.

[34] *Scherer DJ, Nelson AJ, O'Brien R et al.* **Status of PCSK9 Monoclonal Antibodies in Australia**. Heart, lung & circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31104887
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAb) have progressed from showing marked low density lipoprotein cholesterol lowering in early phase trials through to reducing cardiovascular events in large clinical outcome trials. Recently in Australia, the indication for evolocumab has been expanded to include both heterozygous and homozygous familial hypercholesterolaemia under the Pharmaceutical Benefits Scheme (PBS). With prices remaining high currently their use in non-familial hypercholesterolaemia in Australia remains by private prescription only at this stage. This manuscript summarises the major outcomes trials of the PCSK9 mAbs and the secondary analyses that have assessed their benefits in high risk patient groups, and describes the consensus of authors on which patients would most likely benefit from PCSK9 mAb therapy.

[35] *Rodriguez-Jimenez C, Pernia O, Mostaza J et al.* **Functional analysis of new variants at the Low Density Lipoprotein Receptor associated with familial hypercholesterolemia**. Human mutation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31106925
ABSTRACT
Familial hypercholesterolemia is an autosomal dominant disease of lipid metabolism caused by defects in the genes LDLR, APOB, PCSK9. The prevalence of heterozygous familial hypercholesterolemia (HeFH) is estimated between 1/200 and 1/250. Early detection of patients with FH allows initiation of treatment, thus reducing the risk of coronary heart disease. In this study we performed in vitro characterization of new LDLR variants found in our patients. Genetic analysis was performed by Next Generation Sequencing (NGS) using a customized panel of 198 genes in DNA samples of 516 subjects with a clinical diagnosis of probable or definitive FH. All new LDLR variants found in our patients were functionally validated in CHO-ldlA7 cells. LDLR activity was measured by flow cytometry and LDLR expression was detected by immunofluorescence. Seven new variants at LDLR were tested: c.518 G>C;p.(Cys173Ser), c.[684G>T;694G>T];p.[Glu228Asp;Ala232Ser], c.926C>A;p.(Pro309His), c.1261A>G;p.(Ser421Gly), c.1594T>A;p.(Tyr532Asn), and c.2138delC;p.(Thr713Lysfs*17). We

classified all variants as pathogenic except p.(Ser421Gly) and p.(Ala232Ser). The functional in vitro characterization of rare variants at the LDLR is a useful tool to classify the new variants. This approach allows us to confirm the genetic diagnosis of FH, avoiding the classification as "uncertain significant variants", and therefore, carry out cascade family screening.

[36] *Flores-Castillo C, Luna-Luna M, Carreon-Torres E et al.* **Atorvastatin and Fenofibrate Increase the Content of Unsaturated Acyl Chains in HDL and Modify In Vivo Kinetics of HDL-Cholesteryl Esters in New Zealand White Rabbits**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31121898
ABSTRACT
Previous studies demonstrated modifications of high-density lipoproteins (HDL) structure and apolipoprotein (apo) A-I catabolism induced by the atorvastatin and fenofibrate combination. However, it remains unknown whether such structural and metabolic changes of HDL were related to an improvement of the HDL-cholesteryl esters (HDL-CE) metabolism. Therefore, we determined the structure of HDL and performed kinetic studies of HDL-CE radiolabeled with tritium in rabbits treated with atorvastatin, fenofibrate, and a combination of both drugs. The atorvastatin and fenofibrate combination increased the HDL size and the cholesterol and phospholipid plasma concentrations of the largest HDL subclasses. Moreover, the relative amount of unsaturated fatty acids contained in HDL increased, in detriment of saturated fatty acids as determined by gas chromatography-mass spectrometry. The transfers of cholesteryl esters (CE) from HDL to very low-density lipoproteins/low-density lipoproteins (VLDL/LDL) and vice versa were enhanced with atorvastatin, alone or in combination. Moreover, the direct elimination of CE from plasma via VLDL/LDL decreased with fenofibrate, whereas the direct elimination of CE via HDL augmented with the combination treatment. Taken together, the rise of unsaturated fatty acid content and the size increase of HDL, suggest that atorvastatin and fenofibrate induce more fluid HDL particles, which in turn favor an enhanced CE exchange between HDL and VLDL/LDL. Our results contribute to a better understanding of the relationship between the structure and function of HDL during the use of anti-dyslipidemic drugs.

[37] *Vlad C, Burlacu A, Florea L et al.* **A comprehensive review on apolipoproteins as nontraditional cardiovascular risk factors in end-stage renal disease: current evidence and perspectives**. International urology and nephrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31119518
ABSTRACT
PURPOSE: Nontraditional cardiovascular risk factors such as lipoprotein(a) (Lp(a)), the genetic polymorphisms of apolipoprotein(a), apolipoprotein E (ApoE), and apolipoprotein B (ApoB) increase the prevalence of atherosclerosis in end-stage renal disease (ESRD) through quantitative and qualitative alterations. Given the high burden of cardiovascular fatal events in ESRD, this review aims to gather studies depicting apolipoproteins' changes in ESRD, to describe current evidence and to explore potential lipid-lowering therapies. METHODS: We searched the electronic database of PubMed, SCOPUS, EBSCO, and Cochrane CENTRAL for studies evaluating

apolipoproteins in ESRD. Randomized controlled trials, observational studies (including case-control, prospective, or retrospective cohort), and reviews/meta-analysis were included if reference was made to apolipoproteins and cardiovascular consequences in ESRD. RESULTS: 21 studies met the inclusion criteria. We found a significant correlation between Lp(a) plasma concentrations and atherosclerosis. Lp(a) levels were independent risk factors for atherothrombosis and cardiovascular mortality. LMW apo(a) phenotype proved to be the best predictor for coronary events in ESRD. Single nucleotide polymorphisms in ApoE gene affected the expression and function of the protein, increasing the risk of cardiovascular events. ApoB had a significant correlation with the value of carotid intima-media thickness and vascular stiffness. CONCLUSIONS: The picture of "lipid milieu" in ESRD has not been clearly described. Novel studies show that specific apolipoproteins suffer modifications in uremic patients, being correlated with cardiovascular events. Probably in the next years, the treatment of dyslipidemia in ESRD will not merely target LDL or total cholesterol, but specific isoforms of apolipoproteins which seem to become the central part of the problem.

[38] *Daida H, Dohi T, Fukushima Y et al.* **The Goal of Achieving Atherosclerotic Plaque Regression with Lipid-Lowering Therapy: Insights from IVUS Trials**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31118346
ABSTRACT
Enormous effort has been put into the prevention of atherosclerosis through risk modification, especially with lipid-lowering therapies. Regression, that is, the reversal of the atherosclerosis process, has long been a goal of atherosclerosis research among basic and clinical investigators. Intravascular ultrasound (IVUS) was developed in the 1990s as an intracoronary imaging technique to observe the details of the vessel walls and to measure the vessel lumen and plaque area with high reproducibility. Compared with the coronary angiogram, IVUS provides far more detailed information on the vessel wall. In this article, we review lipid-lowering trials that have used IVUS and discuss the current understanding of the effectiveness of aggressive lipid-lowering therapy, which inhibits atherosclerotic progression and induces regression and plaque stabilization.

[39] *Ashraf AP, Kohn B, Wilson DP*. **Improving Long-term Outcomes of Youth with Lipid Abnormalities- Expanding the Role of Pediatric Endocrinologists**. The Journal of clinical endocrinology and metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31120509
ABSTRACT
BACKGROUND: There is disturbingly high prevalence of dyslipidemia in youth. Although, pediatric endocrinologists are aware of the significant cardiovascular (CV) risk associated with monogenic disorders of lipid and lipoprotein metabolism, relatively few recognize the CV disease (CVD)-related morbidity and premature mortality incurred by common endocrine disorders associated with dyslipidemia, such as diabetes mellitus, growth hormone deficiency, congenital adrenal hyperplasia, and hypopituitarism. AIM: In this article we discuss the expanding role of pediatric endocrinologists in cardiovascular health and risk prevention. METHODS: We reviewed available literature and summarized discussions with opinion leaders

in pediatric endocrinology to 1) provide an overview of this timely topic; 2) identify opportunities for targeted education; and 3) discuss ways of expanding clinical services to improve outcomes. RESULTS: In addition to well-known genetic disorders of lipid and lipoprotein metabolism, youth with common endocrine disorders, including type 1 and type 2 diabetes, would benefit from cholesterol screening and, in some, early intervention including use of lipid-lowering medications. Despite the growing need, the location and extent of services available to youth with dyslipidemia and the availability of providers with experience in treatment of dyslipidemia are largely unknown, but likely inadequate to provide accessible, timely, and cost-effective intervention. CONCLUSION: With a new awareness of opportunities to prevent premature CVD in youth including those with common endocrine disorders, and CVD-related events during adulthood, there is an urgent need for additional clinical services and targeted education of current as well as future pediatric endocrinologists.

[40] *Jacobson TA, Cheeley MK, Jones PH et al.* **The STatin Adverse Treatment Experience Survey: Experience of patients reporting side effects of statin therapy**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31113745
ABSTRACT
BACKGROUND: It is important to understand patients' experiences of statin-associated adverse effects to potentially identify those at risk for stopping treatment. OBJECTIVE: The goal of the STatin Adverse Treatment Experience survey was to describe patients' experiences after reporting >/=1 recent statin-associated adverse event and identify opportunities to improve adherence and outcomes. METHODS: The survey was developed in 3 stages: qualitative item development, pilot evaluation of initial item performance, and quantitative evaluation using a large commercial sample. Respondents with self-reported high cholesterol who had taken a statin in the past 2 years and experienced >/=1 statin-associated symptom in the past 6 months were included (N = 1500). RESULTS: Mean age was 58 years, 40.3% were men, and 43.2% had tried >/=2 statins. Many had clinical comorbidities associated with increased risk for cardiovascular disease (atherosclerotic cardiovascular disease, 22.5%; diabetes, 25.8%; hypertension, 56.0%). The most important patient-reported reasons for continuing current statin therapy (n = 1168; 77.9%) were avoiding a heart attack or stroke, lowering cholesterol, and doctor recommendation. Being bothered by and not being able to tolerate side effects were the main reasons respondents discontinued statins (n = 332; 22.1%). Respondents who discontinued statins reported significantly higher mean Symptom Severity (10.6 vs 8.7, P < .001) and Impact Severity scores (11.8 vs 9.8, P < .001) compared with those who continued. CONCLUSION: The STatin Adverse Treatment Experience survey highlights the importance of patients' adverse experiences with statins and how symptom and impact scores affect decisions to continue or discontinue therapy. These data provide a foundation to increase providers' awareness of statin tolerability from the patient's perspective and encourage benefit-risk discussions.

[41] *Krittayaphong R, Phrommintikul A, Boonyaratvej S et al.* **The rate of patients at high risk for cardiovascular disease with an optimal low-density cholesterol level: a multicenter study from Thailand**. Journal of geriatric cardiology : JGC 2019; 16:344-353.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31105755

ABSTRACT

Background: Hypercholesterolemia is a major risk factor for cardiovascular events in patients with established atherosclerotic disease (EAD) and in those with multiple risk factors (MRFs). This study aimed to investigate the rate of optimal low-density lipoprotein (LDL) cholesterol level in a multicenter registry of patients at high risk for cardiovascular events. Methods: A multicenter registry of EAD and MRF patients was conducted. Demographic data, medical history, cardiovascular risk factors, anthropometric data, laboratory data, and medications were recorded and analyzed. We classified patients according to target LDL levels based on recommendation by the European Society of Cardiology (ESC) 2011 into Group 1 which is EAD and diabetes or chronic kidney disease (CKD)-target LDL below 70 mg/dL, and Group 2 which is MRF without diabetes or CKD-target LDL below 100 mg/dL. The rate of optimal LDL level in patients with Group 1 and Group 2 was analyzed and stratified according to the treatment pattern of lipid-lowering medications. Results: A total of 3100 patients were included. Of those, 51.7% were male. Average age was 65.8 +/- 9.7 years. Average LDL level was 96.3 +/- 32.6 mg/dL. A vast majority (92.7%) received statin and 9.3% received ezetimibe. Optimal LDL level was achieved in 20.3% of patients in Group 1 (LDL < 70 mg/dL), and in 46.6% in Group 2 (LDL < 100 mg/dL). The overall rate of optimal LDL control was 23% since 89.6% of study population belongs to Group 1. The rate of optimal LDL was not different between high and low potency statin. Factors that were associated with optimal LDL control were older age, the presence of coronary artery disease or peripheral artery disease. Conclusions: The rates of optimal LDL level were unacceptably low in this study population. As such, a strategy to improve LDL control in high-risk population should be implemented.

[42] *Pereira-Dutra FS, Teixeira L, de Souza Costa MF, Bozza PT*. **Fat, fight, and beyond: The multiple roles of lipid droplets in infections and inflammation**. Journal of leukocyte biology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31121077

ABSTRACT

Increased accumulation of cytoplasmic lipid droplets (LDs) in host nonadipose cells is commonly observed in response to numerous infectious diseases, including bacterial, parasite, and fungal infections. LDs are lipid-enriched, dynamic organelles composed of a core of neutral lipids surrounded by a monolayer of phospholipids associated with a diverse array of proteins that are cell and stimulus regulated. Far beyond being simply a deposit of neutral lipids, LDs have come to be seen as an essential platform for various cellular processes, including metabolic regulation, cell signaling, and the immune response. LD participation in the immune response occurs as sites for compartmentalization of several immunometabolic signaling pathways, production of inflammatory lipid mediators, and regulation of antigen presentation. Infection-driven LD biogenesis is a complexly regulated process that involves innate immune receptors, transcriptional and posttranscriptional regulation, increased lipid uptake, and new lipid synthesis. Accumulating evidence demonstrates that intracellular pathogens are able to exploit LDs as an energy source, a replication site, and/or a mechanism of immune response evasion. Nevertheless, LDs can also act in favor of the host as part of the immune and inflammatory

response to pathogens. Here, we review recent findings that explored the new roles of LDs in the context of host-pathogen interactions.

[43] *Song TJ, Oh SH, Kim J*. **The impact of statin therapy after surgical or endovascular treatment of cerebral aneurysms**. Journal of neurosurgery 2019:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31125972
ABSTRACT
OBJECTIVECerebral aneurysms represent the most common cause of spontaneous subarachnoid hemorrhage. Statins are lipid-lowering agents that may expert multiple pleiotropic vascular protective effects. The authors hypothesized that statin therapy after coil embolization or surgical clipping of cerebral aneurysms might improve clinical outcomes.METHODSThis was a retrospective cohort study using the National Health Insurance Service-National Sample Cohort Database in Korea. Patients who underwent coil embolization or surgical clipping for cerebral aneurysm between 2002 and 2013 were included. Based on prescription claims, the authors calculated the proportion of days covered (PDC) by statins during follow-up as a marker of statin therapy. The primary outcome was a composite of the development of stroke, myocardial infarction, and all-cause death. Multivariate time-dependent Cox regression analyses were performed.RESULTSA total of 1381 patients who underwent coil embolization (n = 542) or surgical clipping (n = 839) of cerebral aneurysms were included in this study. During the mean (+/- SD) follow-up period of 3.83 +/- 3.35 years, 335 (24.3%) patients experienced the primary outcome. Adjustments were performed for sex, age (as a continuous variable), treatment modality, aneurysm rupture status (ruptured or unruptured aneurysm), hypertension, diabetes mellitus, household income level, and prior history of ischemic stroke or intracerebral hemorrhage as time-independent variables and statin therapy during follow-up as a time-dependent variable. Consistent statin therapy (PDC > 80%) was significantly associated with a lower risk of the primary outcome (adjusted hazard ratio 0.34, 95% CI 0.14-0.85).CONCLUSIONSConsistent statin therapy was significantly associated with better prognosis after coil embolization or surgical clipping of cerebral aneurysms.

[44] *Murphy SA, Pedersen TR, Gaciong ZA et al.* **Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients With Cardiovascular Disease: A Prespecified Analysis From the FOURIER Trial**. JAMA cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31116355
ABSTRACT
Importance: The PCSK9 inhibitor evolocumab reduced low-density lipoprotein cholesterol and first cardiovascular events in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, but patients remain at high risk of recurrent cardiovascular events. Objective: To evaluate the effect of evolocumab on total cardiovascular events, given the importance of total number of cardiovascular events to patients, clinicians, and health economists. Design, Setting, and Participants: Secondary analysis of a randomized, double-blind clinical trial. The FOURIER trial compared evolocumab or matching placebo and followed up patients for a median of 2.2 years. The study included 27564 patients with stable atherosclerotic disease receiving statin therapy. Data were analyzed

between May 2017 and February 2019. Main Outcomes and Measures: The primary end point (PEP) was time to first cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; the key secondary end point was time to first cardiovascular death, myocardial infarction, or stroke. In a prespecified analysis, total cardiovascular events were evaluated between treatment arms. Results: The mean age of patients was 63 years, 69% of patients were taking high-intensity statin therapy, and the median LDL-C at baseline was 92 mg/dL (to convert to millimoles per liter, multiply by 0.0259). There were 2907 first PEP events and 4906 total PEP events during the trial. Evolocumab reduced total PEP events by 18% (incidence rate ratio [RR], 0.82; 95% CI, 0.75-0.90; P < .001) including both first events (hazard ratio, 0.85; 95% CI, 0.79-0.92; P < .001) and subsequent events (RR, 0.74; 95% CI, 0.65-0.85). There were 2192 total primary events in the evolocumab group and 2714 total events in the placebo group. For every 1000 patients treated for 3 years, evolocumab prevented 22 first PEP events and 52 total PEP events. Reductions in total events were driven by fewer total myocardial infarctions (RR, 0.74; 95% CI, 0.65-0.84; P < .001), strokes (RR, 0.77; 95% CI, 0.64-0.93; P = .007), and coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; P < .001). Conclusions and Relevance: The addition of the PCSK9 inhibitor evolocumab to statin therapy improved clinical outcomes, with significant reductions in total PEP events, driven by decreases in myocardial infarction, stroke, and coronary revascularization. More than double the number of events were prevented with evolocumab vs placebo as compared with the analysis of only first events. These data provide further support for the benefit of continuing aggressive lipid-lowering therapy to prevent recurrent cardiovascular events. Trial Registration: ClinicalTrials.gov identifier: NCT01764633.

[45] *Peppone LJ, Inglis JE, Mustian KM et al.* **Multicenter Randomized Controlled Trial of Omega-3 Fatty Acids Versus Omega-6 Fatty Acids for the Control of Cancer-Related Fatigue Among Breast Cancer Survivors**. JNCI cancer spectrum 2019; 3:pkz005.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31119206

ABSTRACT

Background: Cancer-related fatigue (CRF) is a common side effect of adjuvant therapy and becomes a chronic problem for approximately one-third of survivors. Omega-3 polyunsaturated fatty acids (O3-PUFA) demonstrated preliminary antifatigue effects in previous research, but have not been investigated in fatigued cancer survivors. Methods: Breast cancer survivors 4-36 months posttreatment with a CRF score of 4 or more of 10 using the symptom inventory (SI) were randomly assigned to O3-PUFA (fish oil, 6 g/d), omega-6 PUFA (O6-PUFA; soybean oil, 6 g/d), or a low-dose combination of O3-/O6-PUFA (3 g/d O3-PUFA and O6-PUFA) for 6 weeks. CRF was assessed by the SI (screening question), the Brief Fatigue Inventory, and the Multidimensional Fatigue Symptom Index. Protein and mRNA levels of inflammatory and antioxidant biomarkers, along with fatty acid and lipid levels, were assessed at baseline and week 6. Statistical tests were two-sided. Results: A total of 108 breast cancer survivors consented; 97 subjects were randomly assigned and 81 completed the trial. The SI CRF score decreased by 2.51 points at week 6 with O6-PUFA and by 0.93 points with O3-PUFA, with statistically significant between-group difference (effect size = -0.86, P < .01). Similar changes were observed for the Brief Fatigue Inventory and Multidimensional Fatigue Symptom Index but were not statistically significant. Stratified analyses showed the largest benefit was

observed in those with severe baseline CRF (>/=7). Compared with O3-PUFA, O6-PUFA supplementation statistically significantly decreased proinflammatory markers in the TNF-alpha signaling pathway. Conclusion: Contrary to our original hypothesis, O6-PUFA statistically significantly reduced CRF compared with O3-PUFA. Further research is needed to confirm these findings and to elucidate mechanisms of action.

[46] *Jiang C, Qi Z, Tang Y et al.* **Rational Design of Lovastatin-Loaded Spherical Reconstituted High Density Lipoprotein for Efficient and Safe Anti-Atherosclerotic Therapy**. Molecular pharmaceutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31117743
ABSTRACT
Reconstituted high density lipoprotein (rHDL) is a biomimetic nanoparticle with plaque targeting and anti-atherosclerotic efficacy. In this work, we report on a strategy to rational design of lovastatin (LOV)-loaded spherical rHDL (LOV-s-rHDL) for efficient and safe anti-atherosclerotic therapy. Briefly, three LOV-s-rHDLs were formulated with LOV/s-rHDL at ratios of 8:1, 10:1, and 15:1 upon their respective median-effect values (Dm). The combined inhibitory effect between LOV and s-rHDL of different LOV-s-rHDL formulations on DiI-labeled oxLDL internalization was systemically investigated in RAW 264.7 cells based on the median-effect principle. Median-effect analysis demonstrated that the optimized LOV-s-rHDL was formulated with a ratio of 10:1 (Dm LOV: Dm s-rHDL), in which LOV and s-rHDL carrier showed the best synergistic effect, presumably ascribed to their inhibitory effect on CD36 and SR-A expression according to the Western blot analysis. In vivo pharmacodynamics studies showed that the optimized LOV-s-rHDL displayed the most pronounced anti-atherosclerotic effect on decreasing plaque area and reducing the MMP level following an 8-week dosing regimen. In vivo atherosclerotic plaque targeting analysis revealed that s-rHDL had potent plaque targeting efficacy, probably owing to the interaction between apoA-I and scavenger receptor B-I. Furthermore, we observed that the optimized LOV-s-rHDL exhibited a favorable safety profile as evidenced by the results of a hemolysis assay, cell cytotoxicity study, and in vivo safety test. Collectively, the rational design of the biomimetic LOV-s-rHDL based on the median-effect analysis provides an efficient strategy to achieve a synergistic and safe anti-atherosclerotic therapy.

[47] *Malagnino V, Duthaler U, Seibert I et al.* **OATP1B3-1B7 (LST-3TM12) is a drug transporter that affects endoplasmic reticulum access and the metabolism of ezetimibe**. Molecular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31127008
ABSTRACT
Drug transporters play a crucial role in pharmacokinetics. One subfamily of transporters with proven clinical relevance are the OATP1B transporters. Recently, we have identified a new member of the OATP1B family named OATP1B3-1B7 (LST-3TM12). This functional transporter is encoded by SLCO1B3 and SLCO1B7. OATP1B3-1B7 is expressed in hepatocytes and is located in the membrane of the smooth endoplasmic reticulum (SER). One aim of this study was to test whether OATP1B3-1B7 interacts with commercial drugs. First, we screened a selection of OATP1B substrates for inhibition of OATP1B3-1B7 mediated transport of

dehydroepiandrosterone sulfate and identified several inhibitors. One such inhibitor was ezetimibe, which not only inhibited OATP1B3-1B7, but is also a substrate, as its cellular content was significantly increased in cells heterologously expressing the transporter. In humans, ezetimibe is extensively metabolized by hepatic and intestinal 5'-diphospho-glucuronosyltransferases (UGTs), the catalytic site of which is located within the SER lumen. After verification of OATP1B3-1B7 expression in the small intestine, we determined in microsomes whether SER access can be modulated by inhibitors of OATP1B3-1B7. We were able to show that these compounds significantly reduced accumulation in small intestinal and hepatic microsomes, which influenced the rate of ezetimibe beta-D-glucuronide formation as determined in microsomes treated with bromsulphtalein. Notably, this molecule not only inhibits the herein reported transporter, but also other transport systems. In conclusion, we report that multiple drugs interact with OATP1B3-1B7 and for ezetimibe, we were able to show that SER access and metabolism is significantly reduced by bromosulphthalein, which is an inhibitor of OATP1B3-1B7. SIGNIFICANCE STATEMENT: OATP1B3-1B3 (LST-3TM12) is a transporter, which has not been fully characterized yet. By this study, we provide valuable insight in the interaction potential of this transporter with several marketed drugs. One drug that showed interaction with OATP1B3-1B7 was ezetimibe. This drug is highly metabolized by 5'-diphospho-glucuronosyltransferases (UGTs), the catalytic site of which is located within the smooth endoplasmic reticulum (SER) lumen. By doing microsomal assays with ezetimibe and the transport inhibitor bromsulphtalein we have investigated the interdependence of SER access and the glucuronidtaion rate of ezetimibe. These findings lead us to the hypothesis that access or exit of drugs to the SER is orchestrated by SER transporters such as OATP1B3-1B7.

[48] *Papanikolaou Y, Fulgoni VL, 3rd*. **Egg Consumption in U.S. Children is Associated with Greater Daily Nutrient Intakes, including Protein, Lutein + Zeaxanthin, Choline, alpha-Linolenic Acid, and Docosahexanoic Acid**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31121847

ABSTRACT

Dietary pattern recommendations include consuming a variety of nutrient-dense foods in children and adolescents to promote optimal growth and development. The current study investigated associations with egg consumption and nutrient intakes, diet quality, and growth outcomes relative to non-egg consumers. The analysis used data from the U.S. National Health and Nutrition Examination Survey (NHANES) 2001-2012 in children and adolescents aged 2-18 years (N = 3,299, egg consumers; N = 17,030, egg non-consumers). Daily energy and nutrient intakes were adjusted for the complex sample design of NHANES using appropriate weights. Consuming eggs was associated with increased daily energy intake relative to non-egg consumption. Children and adolescents consuming eggs had elevated daily intake of protein, polyunsaturated, monounsaturated and total fat, alpha-linolenic acid, docosahexaenoic acid (DHA), choline, lutein + zeaxanthin, vitamin D, potassium, phosphorus, and selenium. Egg consumers had greater consumption, sodium, saturated fat, with reduced total and added sugar versus egg non-consumers. The analysis also showed that egg consumption was linked with lower intake of dietary folate, iron, and niacin. No associations were determined when examining diet quality and growth-related measures. A sub-analysis considering socioeconomic status showed that egg consumption was positively related with daily lutein + zeaxanthin and

DHA intake. The current analysis demonstrated several nutrient-related benefits to support the continued inclusion of eggs in the dietary patterns of children and adolescents.

[49] *Li C, Hu Z, Zhang W et al.* **Regulation of Cholesterol Homeostasis by a Novel Long Non-coding RNA LASER**. Scientific reports 2019; 9:7693.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31118464
ABSTRACT
Genome-wide association studies (GWAS) have identified many genetic variants in genes related to lipid metabolism. However, how these variations affect lipid levels remains elusive. Long non-coding RNAs (lncRNAs) have been implicated in a variety of biological processes. We hypothesize lncRNAs are likely to be located within disease or trait-associated DNA regions to regulate lipid metabolism. The aim of this study was to investigate whether and how lncRNAs in lipid- associated DNA regions regulate cholesterol homeostasis in hepatocytes. In this study, we identified a novel long non-coding RNA in Lipid Associated Single nucleotide polymorphism gEne Region (LASER) by bioinformatic analysis. We report that LASER is highly expressed in both hepatocytes and peripheral mononuclear cells (PBMCs). Clinical studies showed that LASER expression is positively related with that of cholesterol containing apolipoprotein levels. In particular, we found that LASER is positively correlated with plasma PCSK9 levels in statin free patients. siRNAs mediated knock down of LASER dramatically reduces intracellular cholesterol levels and affects the expression of genes involved in cholesterol metabolism. Transcriptome analyses show that knockdown of LASER affects the expression of genes involved in metabolism pathways. We found that HNF-1alpha and PCSK9 were reduced after LASER knock-down. Interestingly, the reduction of PCSK9 can be blocked by the treatment of berberine, a natural cholesterol-lowering compound which functions as a HNF-1alpha antagonist. Mechanistically, we found that LASER binds to LSD1 (lysine-specific demethylase 1), a member of CoREST/REST complex, in nucleus. LASER knock-down enhance LSD1 targeting to genomic loci, resulting in decreased histone H3 lysine 4 mono-methylation at the promoter regions of HNF-1alpha gene. Conversely, LSD1 knock-down abolished the effect of LASER on HNF-1alpha and PCSK9 expressions. Finally, we found that statin treatment increased LASER expression, accompanied with increased PCSK9 expression, suggesting a feedback regulation of cholesterol on LASER expression. This observation may partly explain the statin escape during anti-cholesterol treatment. These findings identified a novel lncRNA in cholesterol homeostasis. Therapeutic targeting LASER might be an effective approach to augment the effect of statins on cholesterol levels in clinics.

[50] *Wu J, Wang Y, Li H et al.* **Serum apolipoprotein B-to-apolipoprotein A1 ratio is independently associated with disease severity in patients with acute pancreatitis**. Scientific reports 2019; 9:7764.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31123322
ABSTRACT
Early identification of severe acute pancreatitis (SAP) is critical for clinical decision-making. The apolipoprotein B-to-apolipoprotein A1 ratio (ApoB/A1 ratio) reflects the balance between pro-inflammation and anti-inflammation in vivo. This study investigated the association between serum ApoB/A1 ratio at admission and acute pancreatitis (AP) severity. A total of 375 patients

with first attack of AP were retrospectively recruited from January 2014 to December 2017. The severity of AP was assessed at admission based on the 2012 revised Atlanta Classification. Serum lipids levels were tested on the first 24 h of hospitalization, of which the correlations with clinical features or scoring systems were also measured. The ApoB/A1 ratio markedly increased across disease severity of AP. The ApoB/A1 ratio, expressed as both quartile and continuous variables, was significantly associated with a high risk of SAP, even after adjustment for other conventional SAP risk factors. The ApoB/A1 ratio positively correlated with the revised 2012 Atlanta Classification, Ranson score, Bedside Index for Severity in AP score, Modified Computed Tomography Severity Index score, and Acute Physiology and Chronic Health Evaluation II score for AP severity. The optimal cut-off value of ApoB/A1 ratio for detecting SAP was 0.88, with a sensitivity of 83.08% and a specificity of 69.03%. Serum ApoB/A1 ratio at admission is closely correlated with disease severity in patients with AP and can serve as a reliable indicator for SAP in clinical setting.