Literature update week 15 (2018)

[1] *Yu CY, Liu GY, Liu XH et al.* **Proteomics analysis reveals a potential new target protein for the lipid-lowering effect of Berberine8998**. Acta pharmacologica Sinica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29645002
ABSTRACT
Berberine8998 is a newly synthesized berberine derivative with better lipid-lowering activity and improved absorption. The objective of this study was to investigate the effects of berberine8998 on serum cholesterol and lipid levels in vivo and to examine the mechanisms involved. Hamsters on high-fat diet (HFD) were administered berberine or berberine8998 (50 mg.kg(-1).d(-1), ig) for 3 weeks. Berberine8998 administration significantly lowered the total cholesterol, triglycerides and LDL-C levels in HFD hamsters. Bioinformatics revealed that berberine and berberine8998 shared similar metabolic pathways and fatty acid metabolism was the predominant pathway. Western blot validation results showed that peroxisomal acyl-coenzyme A oxidase 1 (ACOX1) and long-chain fatty acid-CoA ligase 1 (ACSL1), two proteins involved in fatty acid metabolism, were expressed differently in the berberine8998 group than in the untreated group and the berberine treatment group. Biochemistry results showed that berberine8998 significantly lowered the non-esterified fatty acid (NEFA) levels, which may lead to a reduction in TG levels in the berberine8998 treatment group and the differences observed in proteomics analyses. Pharmacokinetic analysis conducted in rats. After administration of berberine or berberine8998 (50 mg/kg, ig), berberine8998 exhibited a remarkably improved absorption with increasing bioavailability by 6.7 times compared with berberine. These findings suggest that berberine8998 lowers cholesterol and lipid levels via different mechanisms than berberine, and its improved absorption makes it a promising therapeutic candidate for the treatment of hypercholesterolemia and obesity.

[2] *Berwanger O, de Barros ESPGM, Dall Orto FTC et al.* **Rationale and design of the Statins Evaluation in Coronary procedUres and REvascularization: The SECURE-PCI Trial**. American heart journal 2018; 198:129-134.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29653634
ABSTRACT
BACKGROUND: Previous evidence suggests that acute treatment with statins reduce atherosclerotic complications, including periprocedural myocardial infarction, but currently, there are no large, adequately powered studies to define the effects of early, high-dose statins in patients with acute coronary syndrome (ACS) and planned invasive management. OBJECTIVES: The main goal of Statins Evaluation in Coronary procedUres and REvascularization (SECURE-PCI) Trial is to determine whether the early use of a loading dose of 80 mg of atorvastatin before an intended percutaneous coronary intervention followed by an additional dose of 80 mg 24 hours after the procedure will be able to reduce the rates of major cardiovascular events at 30 days in patients with an ACS. DESIGN: The SECURE-PCI study is a pragmatic, multicenter, double-blind, placebo-controlled randomized trial planned to enroll around 4,200 patients in 58 different sites in Brazil. The primary outcome is the rate of major cardiovascular events at 30 days defined as a composite of all-cause mortality, nonfatal acute myocardial infarction, nonfatal stroke, and coronary revascularization. SUMMARY: The SECURE PCI is a large randomized trial testing a strategy of early, high-dose statin in patients with ACS and will provide important information about the acute treatment of this patient population.

Literature update week 15 (2018)

[3] *Carr JA*. **Role of Fish Oil in Post-Cardiotomy Bleeding: A Summary of the Basic Science and Clinical Trials**. The Annals of thoracic surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627068
ABSTRACT
BACKGROUND: Omega-3 fatty acids are widely used. This article reviews the coagulopathic effects of fish oil. METHODS: A review was performed of all English articles that addressed the topic from 1980 to 2017. RESULTS: Fish oil induces an in vitro coagulopathy in humans due to inhibitory effects in platelet-to-platelet adhesion and platelet-stimulated thrombin generation. The effect from fish oil alone is weak, but it is enhanced and may become clinically noticeable in patients taking antiplatelet therapy, and, to a lesser extent, in patients on factor Xa inhibitors and warfarin. In the absence of other anticoagulants, fish oil alone is not capable of producing a clinically significant coagulopathy that would induce or contribute to surgical bleeding. CONCLUSIONS: Patients who are taking fish oil without other anticoagulants do not have an increased risk of bleeding surgical complications. Because of the highly variable amounts of actual eicosapentaenoic acid and docosahexaenoic acid in commercially available supplements, thromboelastography with platelet mapping would allow a surgeon to know if a coagulopathic effect is present in a patient taking fish oil, especially if the patient was also taking other anticoagulants.

[4] *Platania A, Castiglione D, Sinatra D et al.* **Fluid Intake and Beverage Consumption Description and Their Association with Dietary Vitamins and Antioxidant Compounds in Italian Adults from the Mediterranean Healthy Eating, Aging and Lifestyles (MEAL) Study**. Antioxidants (Basel, Switzerland) 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29642527
ABSTRACT
The aim of the present study was to investigate the total water intake (TWI) from drinks and foods and to evaluate the correlation between the different types of drinks on energy and antioxidant intake. The cohort comprised 1602 individuals from the city of Catania in Southern Italy. A food frequency questionnaire was administered to assess dietary and water intake. The mean total water intake was 2.7 L; more than about two thirds of the sample met the European recommendations for water intake. Water and espresso coffee were the most consumed drinks. Alcohol beverages contributed about 3.0% of total energy intake, and sugar sweetened beverages contributed about 1.4%. All antioxidant vitamins were significantly correlated with TWI. However, a higher correlation was found for water from food rather than water from beverages, suggesting that major food contributors to antioxidant vitamin intake might be fruits and vegetables, rather than beverages other than water. A mild correlation was found between fruit juices and vitamin C; coffee, tea and alcohol, and niacin and polyphenols; and milk and vitamin B12. The findings from the present study show that our sample population has an adequate intake of TWI and that there is a healthy association between beverages and dietary antioxidants.

Literature update week 15 (2018)

[5] *Shahsavari G, Raoufi A, Toolabi A et al.* **The effect of atorvastatin treatment duration on oxidative stress markers and lipid profile in patients with coronary artery diseases: A case series study**. ARYA atherosclerosis 2017; 13:282-287.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29643923

ABSTRACT
BACKGROUND: The major aim of this study was evaluating the effect of atorvastatin treatment on thiobarbituric acid reactive substances (TBARS), ferric reducing the ability of plasma (FRAP), small dense low-density lipoprotein cholesterol (sdLDL) and lipid profile in coronary artery disease (CAD) patients. METHODS: This study was carried out on 83 patients with angiographically proven coronary artery stenosis (52 men and 31 women) at Shahid Madani Hospital, Khorramabad, Iran, in 2015. The patients were divided into the 3 groups. 27 patients were classified statins consumption less than 6 days, 28 patients for 6 to 90 days, and 28 patients for more than 90 days. The level of sdLDL, lipid profile, TBARS and FRAP were assayed. RESULTS: FRAP levels of patients that received atorvastatin for more than 90 days (832 +/- 101) were significantly elevated (P = 0.01) compared to the patients received atorvastatin less than 6 days (688 +/- 75), whereas the levels of TBARS diminished significantly (P = 0.04). Also, the levels of total cholesterol (TC) and LDL-C were significantly decreased after 3 months of atorvastatin receiving (158 as compared to patients that consumed atorvastatin less than 6 days), (P = 0.02 and 0.03, respectively). The level of sdLDL was slightly increased with long-time consumption of atorvastatin (37 +/- 14) in patients in comparison with patients that received atorvastatin less than 6 days (32 +/- 15) (P = 0.06), but was not significant. CONCLUSION: The serum level of TBARS decreased and the serum level of FRAP increased in patients with long-time receiving atorvastatin. Therefore, atorvastatin contributes to the lowering oxidative stress in these patients.

[6] *Doonan LM, Fisher EA, Brodsky JL*. **Can modulators of apolipoproteinB biogenesis serve as an alternate target for cholesterol-lowering drugs?** Biochimica et biophysica acta 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627384

ABSTRACT
Understanding the molecular defects underlying cardiovascular disease is necessary for the development of therapeutics. The most common method to lower circulating lipids, which reduces the incidence of cardiovascular disease, is statins, but other drugs are now entering the clinic, some of which have been approved. Nevertheless, patients cannot tolerate some of these therapeutics, the drugs are costly, or the treatments are approved for only rare forms of disease. Efforts to find alternative treatments have focused on other factors, such as apolipoproteinB (apoB), which transports cholesterol in the blood stream. The levels of apoB are regulated by endoplasmic reticulum (ER) associated degradation as well as by a post ER degradation pathway in model systems, and we suggest that these events provide novel therapeutic targets. We discuss first how cardiovascular disease arises and how cholesterol is regulated, and then summarize the mechanisms of action of existing treatments for cardiovascular disease. We then review the apoB biosynthetic pathway, focusing on steps that might be amenable to therapeutic interventions.

[7] *Bays HE, Rosenson RS, Baccara-Dinet MT et al.* **Assessment of the 1% of Patients with Consistent < 15% Reduction in Low-Density Lipoprotein Cholesterol: Pooled Analysis of 10 Phase 3 ODYSSEY Alirocumab Trials**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627892

ABSTRACT

PURPOSE: Clinical trials of statins and other lipid-lowering therapies (LLTs) often report large inter-individual variations in their effects on low-density lipoprotein cholesterol (LDL-C). We evaluated apparent hyporesponsiveness to the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab (defined as < 15% LDL-C reduction from baseline at all timepoints) using data from 10 Phase 3 trials (3120 hypercholesterolemic patients). METHODS: This report assessed the LDL-C percent reduction from baseline at weeks 4-104 (depending on study), and alirocumab serum levels and antidrug antibodies, in patients with apparent hyporesponsiveness. RESULTS: Among the 3120 patients evaluated, 98.9% responded to alirocumab, and 33 (1.1%) had < 15% LDL C reduction at all measured timepoints. Pharmacokinetics data indicated that 13/33 apparent hyporesponders had not received alirocumab; no pharmacokinetics data were available for 14/33, and 6/33 had detectable alirocumab. For the six patients with confirmed alirocumab receipt, the degree of adherence to pre-study concurrent LLTs could not be determined after study start; one of these patients had persistent antidrug antibodies. CONCLUSIONS: Apparent hyporesponsiveness to alirocumab appeared to be due to lack of receipt of alirocumab determined by serum alirocumab levels, possible lack of adherence to concurrent LLTs, a theoretical and rare possibility of biological non-responsiveness due to persistent antidrug antibodies, or other causes, as yet unidentified.

[8] *Frayling TM, Beaumont RN, Jones SE et al.* **A Common Allele in FGF21 Associated with Sugar Intake Is Associated with Body Shape, Lower Total Body-Fat Percentage, and Higher Blood Pressure**. Cell Rep 2018; 23:327-336.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29641994

ABSTRACT

Fibroblast growth factor 21 (FGF21) is a hormone that has insulin-sensitizing properties. Some trials of FGF21 analogs show weight loss and lipid-lowering effects. Recent studies have shown that a common allele in the FGF21 gene alters the balance of macronutrients consumed, but there was little evidence of an effect on metabolic traits. We studied a common FGF21 allele (A:rs838133) in 451,099 people from the UK Biobank study, aiming to use the human allele to inform potential adverse and beneficial effects of targeting FGF21. We replicated the association between the A allele and higher percentage carbohydrate intake. We then showed that this allele is more strongly associated with higher blood pressure and waist-hip ratio, despite an association with lower total body-fat percentage, than it is with BMI or type 2 diabetes. These human phenotypes of variation in the FGF21 gene will inform research into FGF21's mechanisms and therapeutic potential.

[9] *Umeda T, Hayashi A, Harada A et al.* **Low-Density Lipoprotein Cholesterol Goal Attainment Rates by Initial Statin Monotherapy Among Patients With Dyslipidemia and High**

Cardiovascular Risk in Japan- A Retrospective Database Analysis. Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29628458
ABSTRACT
BACKGROUND: To understand the recent management status in Japan, we determined the low-density lipoprotein cholesterol (LDL-C) goal attainment (GA) rate of patients initiating statin monotherapy for dyslipidemia.Methods and Results:Dyslipidemic patients undergoing either primary prevention with high cardiovascular risk or secondary prevention (defined by 2012 Japan Atherosclerosis Society Guidelines) were retrospectively analyzed from a hospital-based claims database. In both groups, the LDL-C levels and GA rates of patients treated with intensive or standard statin monotherapy for >/=4 weeks (January 2012-August 2016) were evaluated. Among 1,501,013 dyslipidemic patients, 11,695 and 9,642 were included in the primary and secondary prevention groups, respectively. A total of 94% of patients underwent statin monotherapy as the initial lipid-lowering therapy, of which most (>/=80%) took intensive statins. The proportions of patients in the primary prevention group who achieved an LDL-C goal <120 mg/dL by intensive and standard statins were 81.1% and 61.2%, respectively, and the proportions of those who achieved a goal <100 mg/dL in the secondary prevention group were 73.3% and 48.1%, respectively. The GA rates were similar regardless of disease complications. CONCLUSIONS: Most patients (>70%) in both groups achieved LDL-C management goals using intensive statin monotherapy. Further treatment approaches are required for high-risk patients not achieving LDL-C goals by initial statin monotherapy. Continuous efforts are crucial for adherence and persistence of lipid-lowering therapies.

[10] *Herrington WG, Preiss D, Armitage J*. **Ezetimibe: Likely to Be Beneficial For All**. Circulation 2018; 137:1583-1584.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29632152
ABSTRACT

[11] *Shah A, Gray K, Figg N et al.* **Defective Base Excision Repair of Oxidative DNA Damage in Vascular Smooth Muscle Cells Promotes Atherosclerosis**. Circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29643057
ABSTRACT
Background -Atherosclerotic plaques demonstrate extensive accumulation of oxidative DNA damage, predominantly as 8-oxoguanine (8oxoG) lesions. 8oxoG is repaired by base excision repair (BER) enzymes; however, the mechanisms regulating 8oxoG accumulation in vascular smooth muscle cells (VSMCs) and its effects on their function and in atherosclerosis are unknown. Methods -We studied levels of 8oxoG and its regulatory enzymes in human atherosclerosis, the mechanisms regulating 8oxoG repair and the BER enzyme 8oxoG DNA glycosylase I (OGG1) in VSMCs in vitro, and the effects of reducing 8oxoG in VSMCs in atherosclerosis in ApoE(-/-) mice. Results -Human plaque VSMCs showed defective nuclear 8oxoG repair, associated with reduced acetylation of OGG1. OGG1 was a key regulatory enzyme of 8oxoG repair in VSMCs, and its acetylation was crucial to its repair function, through regulation of protein stability and expression. p300 and SIRT1 were identified as the OGG1 acetyltransferase and deacetylase regulators respectively, and both proteins interacted with

OGG1 and regulated OGG1 acetylation at endogenous levels. However, p300 levels were decreased in human plaque VSMCs and in response to oxidative stress, suggesting that ROS-induced regulation of OGG1 acetylation could be due to ROS-induced decrease in p300 expression. We generated mice that express VSMC-restricted OGG1 or an acetylation defective version (SM22alpha-OGG1 and SM22alpha-OGG1(K-R) mice) and crossed them with ApoE(-/-) mice. We also studied ApoE(-/-) mice deficient in OGG1 (OGG1(-/-)). OGG1(-/-) mice showed increased 8oxoG in vivo and increased atherosclerosis, whereas mice expressing VSMC-specific OGG1, but not the acetylation mutant OGG1(K-R), showed markedly reduced intracellular 8oxoG and reduced atherosclerosis. VSMC OGG1 reduced telomere 8oxoG accumulation, DNA strand breaks, cell death and senescence after oxidant stress, and activation of pro-inflammatory pathways. Conclusions -We identify defective 8oxoG BER in human atherosclerotic plaque VSMCs, OGG1 as a major 8oxoG repair enzyme in VSMCs, and p300/SIRT1 as major regulators of OGG1 through acetylation/deacetylation. Reducing oxidative damage by rescuing OGG1 activity reduces plaque development, indicating the detrimental effects of 8oxoG on VSMC function.

[12] *Danese MD, Sidelnikov E, Kutikova L*. **The prevalence, low-density lipoprotein cholesterol levels and treatment of patients at very high risk of cardiovascular events in the United Kingdom: a cross-sectional study**. Current medical research and opinion 2018:1-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627994

ABSTRACT

OBJECTIVE: To assess the prevalence of patients at very high risk of cardiovascular (CV) events in the United Kingdom (UK) and evaluate low-density lipoprotein cholesterol (LDL-C) values and treatment patterns in these patients. METHODS: This cross-sectional study used primary care data from UK electronic medical records in the Clinical Practice Research Datalink (CPRD) in 2013. Very high-risk patients were defined per European Society of Cardiology guidelines as those with hyperlipidemia (assessed by co-medication) and documented cardiovascular disease (CVD) or hyperlipidemia and type 2 diabetes (DM2) without CVD (DM2w/oCVD). All analyses were descriptive. RESULTS: Data from 4,940,226 patients were captured in the CPRD in 2013. Of these, 5% of patients had received >/=2 lipid-modifying therapy prescriptions and were at very high risk of CVD (3% [n = 138,536] had documented CVD, 2% [n=98,743] had DM2w/oCVD). In documented CVD patients, coronary artery disease (73%) was the most frequent type of event (25% had myocardial infarction [MI]), followed by cerebrovascular disease (18%) and peripheral arterial disease (9%); 21% had experienced multiple CV events, 25% had DM2 and 3% had MI within 1 year. In documented CVD and DM2w/oCVD patients, >95% received statin treatment; 24% received high-intensity statin and 1.5% statin plus ezetimibe. Across both populations, 64-66% had LDL-C levels >/=1.8 mmol/L, 27-28% >/=2.5 mmol/L, 6-7% >/=3.5 mmol/L and 3% had levels >/=4.0 mmol/L, respectively. CONCLUSION: A well-defined proportion of patients remain at very high-risk of CVD. Statin therapy needs optimization, but for some patients with high LDL-C levels, multiple CV events, MI within 1 year, or CVD and DM2, additional more intensive therapy may be needed.

[13] *Doggrell SA*. **What have we learnt from the clinical outcomes trials with the cetrapibs?** Current opinion in lipidology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29630000

ABSTRACT

PURPOSE OF REVIEW: The current review considers what we have learnt from the clinical outcome trials with the cetrapibs; the inhibitors of cholesteryl ester transfer protein that increase HDL cholesterol levels; torcetrapib, dalcetrapib, evacetrapib and anacetrapib. RECENT FINDINGS: Although an off-target increase in blood pressure may have contributed to the failure of torcetrapib in Investigation of Lipid Level Management to Understand its Impact in Atherosclerotics Events, recent evidence shows that torcetrapib also increased atherogenic apoproteins, and this may have contributed to its failure. Evacetrapib and anacetrapib also increase atherogenic apoproteins. This may have contributed to lack of effect of evacetrapib in Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes. The success of anacetrapib in Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification is more likely to have been due to lowering LDL cholesterol than to increasing HDL cholesterol. The lack of potency in increasing HDL cholesterol was initially considered as a reason for the failure of dalcetrapib in dal-OUTCOMES, but recent genomic studies suggest that dalcetrapib may be effective in subjects with a particular genotype, and this is being clinically tested. SUMMARY: Collectively, these clinical outcome trials do not support raising HDL cholesterol by inhibiting cholesteryl ester transfer protein, as a mechanism for improving cardiovascular outcomes, in the total population of subjects with coronary artery disease.

[14] *Zeng ZW, Zhang YN, Lin WX et al.* **A meta-analysis of pharmacological neuroprotection in noncardiac surgery: focus on statins, lidocaine, ketamine, and magnesium sulfate**. European review for medical and pharmacological sciences 2018; 22:1798-1811.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29630129

ABSTRACT

OBJECTIVE: Non-cardiac surgery is associated with perioperative cerebral complications (delirium, postoperative cognition dysfunction, stroke). While rare, these complications can lead to disabilities and deaths. Information is ambiguous as to whether pharmacological preoperative treatment exerts neuroprotection. We wished to systematically assess potential modulation by statins, lidocaine, ketamine or magnesium sulfate of the relative risk of cerebral complications in noncardiac surgery. Selection of these pharmacological agents was based on their known neuroprotective abilities. PATIENTS AND METHODS: By searching Medline, EMBASE and Cochrane databases, we identified 4 suitable publications that collectively enrolled 1358 patients (intent-to-treat population), of which 679 patients were treated preoperatively with statins (404 patients on atorvastatin and 275 on rosuvastatin) and 679 patients with preoperative placebo. The reported cerebral outcome was stroke, assessed either within 30 days (4 publications) or 6 months (2 publications) after surgery. RESULTS: Episodes of stroke within 30 days and 6 months postoperatively were observed in several publications, enabling aggregate analyses. No modulation by statins of the relative risk of stroke at 30 days was observed (risk ratio 1.59, 95% confidence interval 0.08-30.97; p = 0.76). At 6 months, statins showed an insignificant trend toward neuroprotection (risk ratio 0.33, 95% confidence interval 0.05-2.10; p = 0.24). CONCLUSIONS: The available clinical data are still scarce. Our analyses indicate no protective effects by statins against perioperative stroke but some favorable trends

toward delayed stroke. Further randomized trials are needed to unequivocally assess the neuroprotective potential of current pharmacological agents in non-cardiac surgery.

[15] *Maso Talou GD, Blanco PJ, Ares GD et al.* **Mechanical Characterization of the Vessel Wall by Data Assimilation of Intravascular Ultrasound Studies**. Front Physiol 2018; 9:292.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29643815
ABSTRACT
Atherosclerotic plaque rupture and erosion are the most important mechanisms underlying the sudden plaque growth, responsible for acute coronary syndromes and even fatal cardiac events. Advances in the understanding of the culprit plaque structure and composition are already reported in the literature, however, there is still much work to be done toward in-vivo plaque visualization and mechanical characterization to assess plaque stability, patient risk, diagnosis and treatment prognosis. In this work, a methodology for the mechanical characterization of the vessel wall plaque and tissues is proposed based on the combination of intravascular ultrasound (IVUS) imaging processing, data assimilation and continuum mechanics models within a high performance computing (HPC) environment. Initially, the IVUS study is gated to obtain volumes of image sequences corresponding to the vessel of interest at different cardiac phases. These sequences are registered against the sequence of the end-diastolic phase to remove transversal and longitudinal rigid motions prescribed by the moving environment due to the heartbeat. Then, optical flow between the image sequences is computed to obtain the displacement fields of the vessel (each associated to a certain pressure level). The obtained displacement fields are regarded as observations within a data assimilation paradigm, which aims to estimate the material parameters of the tissues within the vessel wall. Specifically, a reduced order unscented Kalman filter is employed, endowed with a forward operator which amounts to address the solution of a hyperelastic solid mechanics model in the finite strain regime taking into account the axially stretched state of the vessel, as well as the effect of internal and external forces acting on the arterial wall. Due to the computational burden, a HPC approach is mandatory. Hence, the data assimilation and computational solid mechanics computations are parallelized at three levels: (i) a Kalman filter level; (ii) a cardiac phase level; and (iii) a mesh partitioning level. To illustrate the capabilities of this novel methodology toward the in-vivo analysis of patient-specific vessel constituents, mechanical material parameters are estimated using in-silico and in-vivo data retrieved from IVUS studies. Limitations and potentials of this approach are exposed and discussed.

[16] *Hassan M*. **FOURIER & PCSK9 RNAi: Towards enhancing durability and efficacy of PCSK9 inhibitors**. Global cardiology science & practice 2017; 2017:13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29644225
ABSTRACT

[17] *Fuchs CD, Paumgartner G, Mlitz V et al.* **Colesevelam attenuates cholestatic liver and bile duct injury in Mdr2(-/-) mice by modulating composition, signalling and excretion of faecal bile acids**. Gut 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29636383
ABSTRACT

BACKGROUND AND AIMS: Interruption of the enterohepatic circulation of bile acids (BAs) may protect against BA-mediated cholestatic liver and bile duct injury. BA sequestrants are established to treat cholestatic pruritus, but their impact on the underlying cholestasis is still unclear. We aimed to explore the therapeutic effects and mechanisms of the BA sequestrant colesevelam in a mouse model of sclerosing cholangitis. METHODS: Mdr2(-/-) mice received colesevelam for 8 weeks. Gene expression profiles of BA homeostasis, inflammation and fibrosis were explored in liver, intestine and colon. Hepatic and faecal BA profiles and gut microbiome were analysed. Glucagon-like peptide 1 (GLP-1) levels in portal blood were measured by ELISA. Furthermore, Mdr2(-/-) mice as well as wild-type 3,5-diethoxy-carbonyl-1,4-dihydrocollidine-fed mice were treated with GLP-1-receptor agonist exendin-4 for 2 weeks prior to analysis. RESULTS: Colesevelam reduced serum liver enzymes, BAs and expression of proinflammatory and profibrogenic markers. Faecal BA profiling revealed increased levels of secondary BAs after resin treatment, while hepatic and biliary BA composition showed a shift towards more hydrophilic BAs. Colonic GLP-1 secretion, portal venous GLP-1 levels and intestinal messenger RNA expression of gut hormone Proglucagon were increased, while ileal Fgf15 expression was abolished by colesevelam. Exendin-4 treatment increased bile duct mass without promoting a reactive cholangiocyte phenotype in mouse models of sclerosing cholangitis. Microbiota analysis showed an increase of the phylum delta-Proteobacteria after colesevelam treatment and a shift within the phyla Firmicutes from Clostridiales to Lactobacillus. CONCLUSION: Colesevelam increases faecal BA excretion and enhances BA conversion towards secondary BAs, thereby stimulating secretion of GLP-1 from enteroendocrine L-cells and attenuates liver and bile duct injury in Mdr2(-/-) mice.

[18] *Kassner U, Hollstein T, Grenkowitz T et al.* **GENE THERAPY IN LIPOPROTEIN LIPASE DEFICIENCY (LPLD): CASE REPORT ON THE FIRST PATIENT TREATED WITH ALIPOGENE TIPARVOVEC UNDER DAILY PRACTICE CONDITIONS**. Human gene therapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29641318

ABSTRACT

We report one year results of the first lipoprotein lipase deficiency (LPLD) patient treated with alipogene tiparvovec, which is indicated for the treatment of patients with genetically confirmed LPLD suffering from acute and recurrent pancreatitis attacks despite dietary restrictions and expressing more than 5% of lipoprotein lipase (LPL) mass compared to a healthy control. During clinical development, alipogene tiparvovec has shown improvement of chylomicron (CM) metabolism and reduction of pancreatitis incidence up to 5.8 years post-treatment. A 43-year old female presented with severe hypertriglyceridemia (median triglyceride [TG] value of 3465 mg/dl) and a history of 37 pancreatitis attacks (PAs) within the last 25 years despite treatment with fibrates, omega 3 fatty acids and - since 2012 - twice weekly lipid apheresis. LPLD was confirmed by identification of two different pathogenic variants in the LPL gene located on separate alleles and therefore constituting a compound heterozygous state. With a detectable LPL mass level of 55.1 ng/ml, the patient was eligible for alipogene tiparvovec treatment and in September 2015 she receved 40 injections (1x1012 genome copies/kg) in the muscles of her upper legs under epidural anaesthesia and immunosuppressive therapy. Alipogene tiparvovec was well tolerated: no injection site or systemic reactions were observed. Median TG values decreased by 52%, dropping to 997 mg/dL

at month 3 and increasing thereafter. Within the first 18 months post-treatment the patient discontinued plasmapheresis and had no abdominal pain or PAs . In March 2017, the patient suffered from a PA due to diet violation. Within the first 12 months post treatment overall Quality of Life improved and no change in humoral or cellular immune response against LPL or AAV1 was observed.

[19] *Bimbova K, Bacova M, Kisucka A et al.* **A Single Dose of Atorvastatin Applied Acutely after Spinal Cord Injury Suppresses Inflammation, Apoptosis, and Promotes Axon Outgrowth, Which Might Be Essential for Favorable Functional Outcome**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29642434
ABSTRACT
The aim of our study was to limit the inflammatory response after a spinal cord injury (SCI) using Atorvastatin (ATR), a potent inhibitor of cholesterol biosynthesis. Adult Wistar rats were divided into five experimental groups: one control group, two Th9 compression (40 g/15 min) groups, and two Th9 compression + ATR (5 mg/kg, i.p.) groups. The animals survived one day and six weeks. ATR applied in a single dose immediately post-SCI strongly reduced IL-1beta release at 4 and 24 h and considerably reduced the activation of resident cells at one day post-injury. Acute ATR treatment effectively prevented the excessive infiltration of destructive M1 macrophages cranially, at the lesion site, and caudally (by 66%, 62%, and 52%, respectively) one day post-injury, whereas the infiltration of beneficial M2 macrophages was less affected (by 27%, 41%, and 16%). In addition, at the same time point, ATR visibly decreased caspase-3 cleavage in neurons, astrocytes, and oligodendrocytes. Six weeks post-SCI, ATR increased the expression of neurofilaments in the dorsolateral columns and Gap43-positive fibers in the lateral columns around the epicenter, and from day 30 to 42, significantly improved the motor activity of the hindlimbs. We suggest that early modulation of the inflammatory response via effects on the M1/M2 macrophages and the inhibition of caspase-3 expression could be crucial for the functional outcome.

[20] *Chiu CY, Wang LP, Liu SH, Chiang MT*. **Fish oil supplementation alleviates the altered lipid homeostasis in blood, liver and adipose tissues in high-fat diet-fed rats**. Journal of agricultural and food chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627983
ABSTRACT
This study investigated the effects of dietary supplementation of fish oil on the signals of lipid metabolism involved in hepatic cholesterol and triglyceride influx and excretion in high-fat diet (HFD)-fed rats. Fish oil (FO) repressed body (HFD: 533+/-18.2 g, HFD+FO: 488+/-28.0 g, $p<0.05$) and liver weights (HFD: 5.7+/-0.6 g/100 g body weight, HFD+FO: 4.8+/-0.4 g/100 g body weight, $p<0.05$) in HFD-fed rats. Fish oil could also improve HFD-induced imbalance of lipid metabolism in blood, liver, and adipose tissues including the significant decreases in plasma and liver total cholesterol (TC) (plasma-HFD: 113+/-33.6 mg/dL, HFD+FO: 50.0+/-5.95 mg/dL, $p<0.05$; liver-HFD: 102+/-13.0 mg/dL, HFD+FO: 86.6+/-7.81 mg/dL, $p<0.05$), blood, liver, and adipose triglyceride (TG) (blood-HFD: 52.5+/-20.4 mg/dL, HFD+FO: 29.8+/-4.30 mg/dL, $p<0.05$; liver-HFD: 56.2+/-10.0 mg/dL, HFD+FO: 30.3+/-5.28 mg/dL, $p<0.05$; adipose: HFD: 614+/-73.2 mg/dL,

HFD+FO: 409+/-334 mg/dL, p<0.05), low density (HFD: 79.8+/-40.9 mg/dL, HFD+FO: 16.6+/-5.47 mg/dL, p<0.05) and very-low-density (HFD: 49.7+/-33.3 mg/dL, HFD+FO: 10.4+/-3.45 mg/dL, p<0.05) lipoprotein, and the significant increases in fecal TC (HFD: 12.2+/-0.67 mg/dL, HFD+FO: 16.3+/-2.04 mg/dL, p<0.05) and TG (HFD: 2.09+/-0.10 mg/dL, HFD+FO: 2.38+/-0.22 mg/dL, p<0.05) and lipoprotein lipase activity of adipose tissues (HFD: 16.6+/-3.64 muM p-nitrophenol, HFD+FO: 24.5+/-4.19 muM p-nitrophenol, p<0.05). Moreover, fish oil significantly activated the protein expressions of hepatic lipid metabolism regulators (AMPKalpha and PPARalpha) and significantly regulated the lipid transport-related signaling molecules (ApoE, MTTP, ApoB, Angptl4, ApoCIII, ACOX1 and SREBPF1) in blood or liver of HFD-fed rats. These results suggest that fish oil supplementation improves HFD-induced imbalance of lipid homeostasis in blood, liver and adipose tissues in rats.

[21] *White CM*. **The Pharmacologic Role and Clinical Utility of PCSK9 Inhibitors for the Treatment of Hypercholesterolemia**. Journal of cardiovascular pharmacology and therapeutics 2018:1074248418769040.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29649884
ABSTRACT
In addition to monoclonal antibodies against proprotein convertase subtilisin-kexin type 9 (PCSK9), vaccines against PCSK9 and smaller molecule inhibitors as well as RNA inhibitors of PCSK9 production have been created. The monoclonal antibodies against PCSK9 and the PCSK9 RNA inhibitors can reduce low-density lipoproteins (LDLs) by over 50%, non-high-density lipoprotein (HDL) cholesterol and triglycerides, and increasing HDL. Although effective in several homozygous familial hypercholesterolemia patient types, PCSK9 inhibitors does not work in all patient types. Outcome trials show no effects on mortality but do show reductions in atherosclerotic events such as myocardial infarctions, strokes, and need for coronary revascularization. PCSK9 inhibitors have a very attractive safety profile with no significant elevations in measures of muscle or liver damage. The current and more advanced experimental agents all require subcutaneous dosing, and injection site reactions are among the most common adverse events. Therapy for the Food and Drug Administration (FDA) approved agents is markedly expensive, and this is the primary barrier to utilization. However, it is possible to identify patients with a number needed to treat to prevent an atherosclerotic event low enough to render it cost-effective and one such factor is whether or not you require a 50% reduction in LDL in order to achieve your LDL goal.

[22] *Zenti MG, Stefanutti C, Sanga V et al.* **Evolocumab and lipoprotein apheresis combination therapy may have synergic effects to reduce low-density lipoprotein cholesterol levels in heterozygous familial hypercholesterolemia: A case report**. Journal of clinical apheresis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29638018
ABSTRACT
A 49 years old woman (weight 68 kg, BMI 27.3 kg/m(2)) with heterozygous familial hypercholesterolemia (HeFH) and multiple statin intolerance with muscle aches and creatine kinase elevation, presented at the Outpatient Lipid Clinic of Verona University Hospital in May 2015. Hypercholesterolemia was firstly diagnosed during adolescence, followed in adulthood by a diagnosis of Cogan's syndrome, a rheumatologic disorder characterized by corneal and inner

ear inflammation. No xanthomas, corneal arcus, or vascular bruits were detectable at physical examination. Screening for macrovascular complications did not reveal relevant damages. Ongoing medical therapy included salicylic acid, methylprednisolone, methotrexate, and protonic-pump inhibitor. In the absence of specific lipid-lowering therapy, plasma lipid levels at first visit were: total-cholesterol = 522 mg/dL, LDL-cholesterol = 434 mg/dL, HDL-cholesterol = 84 mg/dL, triglycerides = 120 mg/dL, Lp(a) = 13 mg/dL. On December 2015, evolocumab 140 mg sc every 2 weeks was initiated. After a 24-week treatment, the LDL-cholesterol levels decreased by an average of 21.2% to 342 +/- 22 mg/dL (mean +/- SD). On May 2016, LDL-apheresis (H.E.L.P.system) was started as add-on therapy. Compared to the average levels obtained during the evolocumab monotherapy period, the LDL-cholesterol was reduced by 49.4%, thus reaching an inter-apheresis level (mean +/- SD) of 173 +/- 37 mg/dL. This report suggests that a combination therapy with evolocumab and lipoprotein-apheresis may have synergic effects on circulating lipid levels. Its relevance as a highly effective treatment option for hyperlipidemia in HeFH patients warrants further investigation in larger datasets.

[23] *Toth PP, Jones SR, Slee A et al.* **Relationship between lipoprotein subfraction cholesterol and residual risk for cardiovascular outcomes: A post hoc analysis of the AIM-HIGH trial**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627296
ABSTRACT
BACKGROUND: The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial failed to demonstrate incremental clinical benefit of extended-release niacin (ERN) in 3414 statin-treated patients with established cardiovascular (CV) disease who had low baseline levels of high-density lipoprotein cholesterol (HDL-C) as compared to placebo. A previous secondary analysis suggested that ERN provided outcome benefits in ERN-treated patients with high triglycerides (TGs; >200 mg/dL) and very low HDL-C (<32 mg/dL) at baseline. The current analysis sought to ascertain how changes in TG-enriched lipoproteins and HDL subfractions impact residual risk in the comparator treatment arms. OBJECTIVES: We evaluated the relationship between niacin treatment, lipoproteins and their subfractions, and CV outcomes in a non-prespecified, post hoc analysis of the AIM-HIGH trial. METHODS: Lipoprotein subfraction analysis was performed with zonal ultracentrifugation in 2457 AIM-HIGH participants at baseline and 1 year of treatment. Hazard ratios were estimated using Cox proportional hazards models for relationships between lipoproteins and the composite primary endpoint of CV death, myocardial infarction, acute coronary syndrome, ischemic stroke, or symptom-driven revascularization. Analyses were performed for the entire cohort and in participants with TGs > 200 mg/dL and HDL-C < 32 mg/dL. RESULTS: Apoprotein B-containing lipoproteins and their subfractions decreased significantly in both treatment arms but decreased more with ERN treatment. HDL-C and its subfractions increased significantly in both treatment groups, but more so in patients treated with ERN. For the entire study population, neither apoB- nor apoA1-containing lipoprotein subfractions predicted risk at baseline or at 1 year of follow-up. In the high TG and low HDL-C subgroup treated with placebo, changes at 1 year in HDL2-C, total cholesterol/HDL2-C, and non-HDL-C/HDL2-C may be associated with increased CV events, whereas in the ERN treatment arm, changes at 1 year in very low-density lipoprotein

cholesterol and very low-density lipoprotein subfractions, total remnant lipoproteins, and various risk ratios may be associated with increased CV events, while HDL2-C may be associated with reduced risk. CONCLUSIONS: We provide hypothesis-generating findings that ERN may confer benefit in patients with coronary heart disease who have high TGs and low HDL by reducing serum levels of remnant lipoprotein cholesterol and increasing HDL2-C.

[24] *Tsakiridou ED, Liberopoulos E, Giotaki Z, Tigas S*. **Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor use in the management of resistant hypercholesterolemia induced by mitotane treatment for adrenocortical cancer**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29650402
ABSTRACT
We report the case of a patient with probable heterozygous familial hypercholesterolemia and mitotane-induced resistant hypercholesterolemia, despite combination therapy with rosuvastatin and ezetimibe. The patient was managed with the addition of evolocumab. Use of a proprotein convertase subtilisin-kexin type 9 inhibitor, should be considered in patients who develop mitotane-related hypercholesterolemia that cannot be managed with conventional lipid-lowering treatment.

[25] *Uehara S, Sato KK, Koh H et al.* **The Association Between Metabolically Healthy Obesity and the Risk of Proteinuria: The Kansai Healthcare Study**. Journal of epidemiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29628481
ABSTRACT
BACKGROUND: Metabolically healthy obesity seems to be a unique phenotype for the risk of cardiometabolic diseases. However, it is not known whether this phenotype is associated with the risk of proteinuria. METHODS: Study subjects were 9,185 non-diabetic Japanese male workers aged 40-55 years who had no proteinuria, an estimated glomerular filtration rate >/=60 mL/min/1.73 m(2), no history of cancer, and no use of antihypertensive or lipid-lowering medications at baseline. Obesity was defined as body mass index >/=25.0 kg/m(2). Metabolic health was defined as the presence of no Adult Treatment Panel III components of the metabolic syndrome criteria, excluding waist circumference, and metabolic unhealth was defined as the presence of one or more metabolic syndrome components, excluding waist circumference. "Consecutive proteinuria" was considered positive if proteinuria was detected twice consecutively as 1+ or higher on urine dipstick at annual examinations to exclude chance proteinuria as much as possible. RESULTS: During the 81,660 person-years follow-up period, we confirmed 390 cases of consecutive proteinuria. Compared with metabolically healthy non-obesity, metabolically healthy obesity was not associated with the risk of consecutive proteinuria (multiple-adjusted hazard ratio [HR] 0.86; 95% confidence interval [CI], 0.37-1.99), but metabolically unhealthy non-obesity with >/=2 metabolic syndrome components (HR 1.77; 95% CI, 1.30-2.42), metabolically unhealthy obesity with one component (HR 1.71; 95% CI, 1.12-2.61), and metabolically unhealthy obesity with >/=2 metabolic syndrome components (HR 2.77; 95% CI, 2.01-3.82) were associated with an increased risk of consecutive proteinuria. CONCLUSIONS: Metabolically healthy obesity did not increase the risk of consecutive proteinuria in Japanese middle-aged men.

[26] *Wang K, Bao L, Zhou N et al.* **Structural Modification of Natural Product Ganomycin I Leading to Discovery of a alpha-Glucosidase and HMG-CoA Reductase Dual Inhibitor Improving Obesity and Metabolic Dysfunction in Vivo**. Journal of medicinal chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29634260
ABSTRACT
It is a great challenge to develop drugs for treatment of metabolic syndrome. With ganomycin I as a leading compound, 14 meroterpene derivatives were synthesized and screened for their alpha-glucosidase and HMG-CoA reductase inhibitory activities. As a result, a alpha-glucosidase and HMG-CoA reductase dual inhibitor ((R, E)-5-(4-(tert-butyl)phenyl)-3-(4,8-dimethylnona-3,7-dien-1-yl)furan-2(5 H)-one, 7d) with improved chemical stability and long-term safety was obtained. Compound 7d showed multiple and strong in vivo efficacies in reducing weight gain, lowering HbAlc level, and improving insulin resistance and lipid dysfunction in both ob/ob and diet-induced obesity (DIO) mice models. Compound 7d was also found to reduce hepatic steatosis in ob/ob model. 16S rRNA gene sequencing, SCFA, and intestinal mucosal barrier function analysis indicated that gut microbiota plays a central and causative role in mediating the multiple efficacies of 7d. Our results demonstrate that 7d is a promising drug candidate for metabolic syndrome.

[27] *Lee CH, Hsieh MJ, Liu SC et al.* **Novel bifurcation stents coated with bioabsorbable nanofibers with extended and controlled release of rosuvastatin and paclitaxel**. Materials science & engineering. C, Materials for biological applications 2018; 88:61-69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29636139
ABSTRACT
A novel bifurcation stent coated with bioabsorbable nanofibers that deliver the extended and controlled release of rosuvastatin and paclitaxel was developed. Bioabsorbable bifurcation stents, consisting of a double-slit tubular main body and two spiral branches, were manufactured. Bi-layered poly (lactic-co-glycolic acid) nanofibers that contained rosuvastatin and paclitaxel were used for treating the stents. Various properties of the fabricated stents, including compression strengths, collapse pressure, water contact angle and flow properties within a circulation model, were quantified. In vitro nanofibrous elution chromatography assays from the drug-loading bifurcation stents were carried out for the release patterns of pharmaceuticals. The effectiveness of eluted rosuvastatin and paclitaxel in inhibiting the adhesion of platelets as well as the proliferation of smooth muscle cells (SMCs) were studied, respectively. The experimental results suggest that bioabsorbable nanofibrous bifurcation stents released high concentrations of rosuvastatin and paclitaxel for 27 and 70days, respectively. The eluted drugs of rosuvastatin and paclitaxel effectively reduced adherent platelets and the proliferation of SMCs. The developed bioabsorbable nanofibrous bifurcation stents herein may provide a promising means of treating cardiovascular bifurcation lesions.

[28] *Gu Z, Sun C, Xiang D*. **Postoperative Adverse Cardiovascular Events Associated with Leptin and Adverse Age After Elective Major Non-Cardiac Surgery: An Asian Single-Center Study**. Medical science monitor : international medical journal of experimental and clinical research 2018; 24:2119-2125.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29630590

ABSTRACT
BACKGROUND The postoperative adverse cardiovascular events (PACE) after surgery can result in prolonged length of stay and poorer prognosis. The purpose of this Asian single-center study was to investigate the potential predicative role of leptin for PACE in elderly patients undergoing major non-cardiac surgery. MATERIAL AND METHODS The patients in the study were prospectively recruited from a series of elderly patients (>/=60 years) undergoing elective major non-cardiac surgery (>/=2 hours) in our hospital from June 2013 to June, 2016. The demographic and clinical data and the preoperative serum biomarkers of each participant were recorded in details. Suspected PACE were assessed by the same experienced expert based on clinical, blood, and other accessory tests. The univariate and multiple logistic regression analyses were plotted to evaluate the potential independent predictive factors for PACE. RESULTS A total of 270 elderly patients (145 males and 125 females), undergoing major elective non-cardiac surgery, were finally enrolled in this study. Older age, higher revised cardiac risk index score, higher levels of systolic blood pressure, B-type natriuretic peptide and leptin, the preoperative medication of beta blocker and lipid-lowering agents were positive predictors of PACE by univariate analyses ($p<0.05$). Our results indicated that preoperative leptin level (OR 1.84, 95% CI 1.08-3.42; p=0.015) and advanced age (OR 0.24, 95% CI 0.09-0.94; p=0.041) were significantly associated with the occurrence of PACE by multiple logistic regression analyses. CONCLUSIONS Preoperative serum leptin level and advanced age were two independent risk factors for PACE among elderly patients undergoing elective major non-cardiac surgery.

[29] *Srivastava RAK, Cornicelli JA, Markham B, Bisgaier CL*. **Gemcabene, a first-in-class lipid-lowering agent in late-stage development, down-regulates acute-phase C-reactive protein via C/EBP-delta-mediated transcriptional mechanism**. Molecular and cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29644527

ABSTRACT
Inflammation plays a key role in setting the stage leading to atherosclerosis progression, and high-sensitivity C-reactive protein (CRP) has been recognized as a predictor of cardiovascular risk. As a monotherapy and in combination with statins, gemcabene markedly reduced CRP in humans. Present investigation was undertaken to understand the mechanism of CRP reduction. In human hepatoma cells, gemcabene inhibited IL-6 plus IL-1beta-induced CRP production in a concentration-dependent manner, reaching 70% inhibition at 2 mM. In TNF-alpha-stimulated primary human coronary artery endothelial cells, both CRP and IL-6 productions were reduced by 70% at 2 mM gemcabene concentration. To investigate the mechanism of gemcabene-mediated reduction of CRP, transfection studies were performed with human CRP regulatory sequences in luciferase/beta-gal system that showed 25-fold increase in IL-6- and IL-6 plus IL-1beta-stimulated CRP transcription. Luciferase activity was reduced by 50% by gemcabene, suggesting transcriptional down-regulation of CRP. Site-directed mutagenesis of human CRP promoter revealed that the overlapping downstream C/EBP and NF-kappaB binding sites are important for gemcabene-mediated CRP transcription. Gel shift assays identified the transcription factor that binds to the downstream CRP promoter as C/EBP-delta. In conclusion, gemcabene decreases CRP by C/EBP-delta and NF-kappaB-mediated transcriptional mechanism and suppresses IL-6 and IL-1beta-induced CRP production.

[30] *Spannella F, Giulietti F, Cocci G et al.* **N-terminal pro B-Type natriuretic peptide is inversely correlated with low density lipoprotein cholesterol in the very elderly**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29650297
ABSTRACT
BACKGROUND AND AIMS: Laboratory studies on human adipose tissue and differentiated adipocytes indicate that natriuretic peptides (NPs) affect lipid metabolism and plasma cholesterol. Few previous clinical studies in non-elderly populations found associations between NPs in the physiological range and cholesterol. AIM: evaluate the association between NT-proBNP and lipid profile in very elderly hospitalized patients characterized by a wide range of NT-proBNP levels. METHODS AND RESULTS: Cross-sectional study on 288 very elderly patients hospitalized for medical conditions, in which increased NT-proBNP levels are very common. NT-proBNP, total cholesterol (TC), HDL cholesterol (HDLc) and triglycerides were collected just few days before discharge. Patients taking lipid-lowering drugs and patients with an admission diagnosis of acute heart failure were excluded. Calculated LDL-cholesterol (LDLc) was used for the analyses. Mean age: 87.7 +/- 6.2 years; female prevalence (57.3%). Median NT-proBNP: 2949 (1005-7335) pg/ml; mean TC: 145.1 +/- 40.3 mg/dl; mean HDLc: 38.4 +/- 18.6 mg/dl; median triglycerides: 100 (75-129) mg/dl; mean LDLc: 84.0 +/- 29.5 mg/dl. We found negative correlations between NT-proBNP and both TC and LDLc (Rho = -0.157; p = 0.008 and Rho = -0.166; p = 0.005, respectively), while no correlations emerged between NT-proBNP and HDLc (Rho = -0.065; p = 0.275) or triglycerides (Rho = -0.009; p = 0.874). These associations were confirmed considering NT-proBNP tertiles. The inverse association between NT-proBNP and LDLc was maintained even after adjusting for confounding factors. CONCLUSION: Our real-life clinical study supports the hypothesis that NPs play a role on cholesterol metabolism, given the association found between LDLc and NT-proBNP even in very elderly patients where NT-proBNP values are often in the pathological range.

[31] *Liang H, Lum H, Alvarez A et al.* **A low dose lipid infusion is sufficient to induce insulin resistance and a pro-inflammatory response in human subjects**. PloS one 2018; 13:e0195810.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29649324
ABSTRACT
OBJECTIVE: The root cause behind the low-grade inflammatory state seen in insulin resistant (obesity and type 2 diabetes) states is unclear. Insulin resistant subjects have elevations in plasma free fatty acids (FFA), which are ligands for the pro-inflammatory toll-like receptor (TLR)4 pathway. We tested the hypothesis that an experimental elevation in plasma FFA (within physiological levels) in lean individuals would upregulate TLR4 and activate downstream pathways (e.g., MAPK) in circulating monocytes. RESEARCH DESIGN AND METHODS: Twelve lean, normal glucose-tolerant subjects received a low dose (30 ml/h) 48 h lipid or saline infusion on two different occasions. Monocyte TLR4 protein level, MAPK phosphorylation, and expression of genes in the TLR pathway were determined before and after each infusion. RESULTS: The lipid infusion significantly increased monocyte TLR4 protein and phosphorylation of JNK and p38 MAPK. Lipid-mediated increases in TLR4 and p38 phosphorylation directly correlated with reduced peripheral insulin sensitivity (M value). Lipid increased levels of multiple genes linked to inflammation, including several TLRs, CD180, MAP3K7, and CXCL10.

Monocytes exposed in vivo to lipid infusion exhibited enhanced in vitro basal and LPS-stimulated IL-1beta secretion. CONCLUSIONS: In lean subjects, a small increase in plasma FFA (as seen in insulin resistant subjects) is sufficient to upregulate TLR4 and stimulate inflammatory pathways (MAPK) in monocytes. Moreover, lipids prime monocytes to endotoxin. We provide proof-of-concept data in humans indicating that the low-grade inflammatory state characteristic of obesity and type 2 diabetes could be caused (at least partially) by pro-inflammatory monocytes activated by excess lipids present in these individuals.

[32] *Moreau RA, Nystrom L, Whitaker BD et al.* **Phytosterols and their derivatives: Structural diversity, distribution, metabolism, analysis, and health-promoting uses**. Progress in lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627611
ABSTRACT
Phytosterols (plant sterols) occur in the cells of all plants. They are important structural components that stabilize the biological membranes of plants. Sterols can occur in the "free" unbound form or they can be covalently bound via an ester or glycosidic bond. Since our previous 2002 review on phytosterols and phytosterol conjugates, phytosterol glucosides have been found to be important structural components in the lipid rafts of the plasma membrane of plant cells, where they are thought to be essential to the function of plasma membrane enzymes and perhaps other proteins. Phytosterols also serve as precursors in the synthesis of important bioactive compounds such as steroidal saponins, steroidal glycoalkaloids, phytoecdysteroids, and brassinosteroids. Methods for the analysis of phytosterols range from traditional gas chromatography of free phytosterols to modern sophisticated forms of mass spectrometry which have been used for the new field of sterol lipidomics, sometimes called "sterolomics." Phytosterol-enriched functional foods first appeared about twenty years ago and many clinical studies have confirmed the low density lipoprotein (LDL) cholesterol-lowering properties of various types of phytosterols. In recent years additional clinical studies and more than ten important meta-analyses have provided insights to better understand the cholesterol-lowering and other biological effects of plant sterols.

[33] *Momo K, Takagi A, Miyaji A, Koinuma M*. **Assessment of statin-induced interstitial pneumonia in patients treated for hyperlipidemia using a health insurance claims database in Japan**. Pulmonary pharmacology & therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29627482
ABSTRACT
PURPOSE: This study aimed to determine the frequency and risk factors for statin-induced interstitial pneumonia (IP). METHOD: We conducted a retrospective cohort study using a large Japanese health insurance claims database. We determined the statin-induced IP incidence in patients treated with statins for hyperlipidemia (n=194,814) with 12-month screening and 3-month observation periods. Statin-induced IP was defined as: (1) diagnosis with IP (ICD-10 codes: J70.2-J70.4, J84.1, and J84.9) within 3 months after starting statins; (2) steroid administration starts after starting statins; (3) undergoing laboratory tests for sialylated carbohydrate antigen KL-6 or pulmonary surfactant protein-D; and (4) undergoing high-resolution computed tomography (HRCT). Risk factors for IP were defined as presence of lung-

related diseases including lung cancer and IP (ICD-10 codes: A16, J43-46, 60-70, and 80-89) that were known to the risk factors inducing IP during the screening period. RESULTS: Cohort 1 had no IP-inducing risk factors; based on lung-related disease history, we identified 4 cases (male/female: 0/4, 61+/-2.5 years) and 46,574 controls (male/female: 29,677/16,897, 51.3+/-9.5 years). In cohort 1, all cases were female and average age was older than that of controls ($p<0.01$). Cohort 2 had lung-related disease history that were known to the risk factors inducing IP; we identified 25 cases (male/female: 11/14, 52.8+/-11.3 years) and 4005 controls (male/female: 2305/1,700, 51.0+/-10.4 years). IP incidence was higher in cohort 2 than in cohort 1, who had no IP risk factors (0.6% vs. 0.009%, $p<0.01$). The adjusted case/control odds ratio in cohort 2 was 3.8-fold (1.7-8.5) in patients who had taken atorvastatin, respectively. DISCUSSION: We clarified the incidence (0.009% and 0.6% in patients without and with lung-related disease history that were known to the risk factors inducing IP, respectively) and risk factors for statin-induced IP (elderly females without lung-related disease history; atorvastatin administration in those with lung-related disease history). Physicians and pharmacists should pay close attention to female patients starting atorvastatin, especially those with past histories of lung-related diseases that were known to the risk factors for IP.

[34] *Yamagishi SI, Matsui T*. **Role of ligands of receptor for advanced glycation end products (RAGE) in peripheral artery disease**. Rejuvenation research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29644926
ABSTRACT
Atherosclerotic cardiovascular disease, including peripheral artery disease (PAD) is more common and severe in diabetic patients compared with non-diabetic individuals. Indeed, diabetes is associated with the increased risk of limb amputation and all-cause mortality in patients with symptomatic PAD. Proteins and lipids are non-enzymatically modified by sugars, resulting in the formation and accumulation of advanced glycation end products (AGEs), whose process is accelerated under diabetic conditions, especially patients with a long duration of diabetes. Accumulating evidence shows that non-enzymatic modification by sugars alters the structural integrity of collagens and lipoproteins in large vessels, thereby being involved in vascular stiffness and atherosclerotic plaque instability. Furthermore, engagement of receptor for AGEs (RAGE) with its ligands, such as AGEs, high mobility group box 1, and S100A proteins evokes inflammatory and thrombotic reactions, thus playing a central role in the development and progression of atherosclerotic cardiovascular disease. In this paper, we review the pathophysiological role of RAGE ligands in PAD and discuss the clinical utility of measurement of plasma, serum or tissue RAGE ligands for assessment of the severity and prognosis of PAD. This review suggests that RAGE ligands may be a novel biomarker and also a therapeutic target of PAD, especially in patients with diabetes.

[35] *Soulele K, Karalis V*. **On the Population Pharmacokinetics and the Enterohepatic Recirculation of Total Ezetimibe**. Xenobiotica 2018:1-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29629619
ABSTRACT
1. Ezetimibe is a potent cholesterol absorption inhibitor, with an erratic pharmacokinetic (PK) profile, attributed to an extensive enterohepatic recirculation (EHC). 2. The aim of this study

was to develop a population PK model able to adequately characterize the complex distribution processes of total ezetimibe. The analysis was performed on the individual concentration-time data obtained from 28 healthy subjects who participated in a bioequivalence study comparing two oral ezetimibe formulations. The population PK analysis was performed using nonlinear mixed effect modelling, where different EHC models were developed and evaluated for their performance. 3. Total ezetimibe pharmacokinetics was best described by a four-compartment model featuring EHC through the inclusion of an additional gallbladder compartment, which was assumed to release drug at specific time-intervals consistent with food intake. 4. The final PK model was able to adequately estimate the population pharmacokinetic parameters and to allow for a formal characterization of the pharmacokinetic profile and the secondary peaks due to enterohepatic recirculation.