Literature update week 35 (2018)

[1] *Shishikura D, Kataoka Y, Honda S et al.* **The Effect of Bromodomain and Extra-Terminal Inhibitor Apabetalone on Attenuated Coronary Atherosclerotic Plaque: Insights from the ASSURE Trial**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30155718
ABSTRACT
BACKGROUND: Apabetalone is a selective bromodomain and extra-terminal (BET) inhibitor which modulates lipid and inflammatory pathways implicated in atherosclerosis. The impact of apabetalone on attenuated coronary atherosclerotic plaque (AP), a measure of vulnerability, is unknown. METHODS: The ApoA-1 Synthesis Stimulation and intravascular Ultrasound for coronary atheroma Regression Evaluation (ASSURE; NCT01067820) study employed serial intravascular ultrasound (IVUS) measures of coronary atheroma in 281 patients treated with apabetalone or placebo for 26 weeks. AP was measured at baseline and follow-up. Factors associated with changes in AP were investigated. RESULTS: AP was observed in 31 patients (11%) [27 (13.0%) in the apabetalone group and four (5.5%) in the placebo group]. The apabetalone group demonstrated reductions in AP length by - 1 mm [interquartile range (IQR) - 4, 1] (p = 0.03), AP arc by - 37.0 degrees (IQR - 59.2, 8.2) (p = 0.003) and the AP index by - 34.6 mm degrees (IQR - 52.6, 10.1) (p = 0.003) from baseline. The change in AP index correlated with on-treatment concentration of high-density lipoprotein (HDL) particles (r = - 0.52, p = 0.006), but not HDL cholesterol (r = - 0.11, p = 0.60) or apolipoprotein A-1 (r = - 0.16, p = 0.43). Multivariable analysis revealed that on-treatment concentrations of HDL particles (p = 0.03) and very low-density lipoprotein particles (p = 0.01) were independently associated with changes in AP index. CONCLUSIONS: Apabetalone favorably modulated ultrasonic measures of plaque vulnerability in the population studied, which may relate to an increase in HDL particle concentrations. The clinical implications are currently being investigated in the phase 3 major adverse cardiac event outcomes trial BETonMACE.

[2] *Sedgeman LR, Beysen C, Allen RM et al.* **Intestinal bile acid sequestration improves glucose control by stimulating hepatic miR-182-5p in type 2 diabetes**. American journal of physiology. Gastrointestinal and liver physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30160993
ABSTRACT
Colesevelam is a bile acid sequestrant approved to treat both hyperlipidemia and type 2 diabetes, but the mechanism for its glucose lowering effects is not fully understood. The aim of this study was to investigate the role of hepatic microRNA's as regulators of metabolic disease and to investigate the link between the cholesterol and glucose lowering effects of colesevelam. To quantify the impact of colesevelam treatment in rodent models of diabetes, metabolic studies were performed in Zucker Diabetic Fatty (ZDF) rats and db/db mice. Colesevelam treatments significantly decreased plasma glucose levels and increased glycolysis in the absence of changes to insulin levels in ZDF rats and db/db mice. High-throughput sequencing and real-time PCR were used to quantify hepatic miRNA and mRNA changes, and the cholesterol-sensitive miR-96/182/183 cluster was found to be significantly increased in livers from ZDF rats treated with colesevelam compared to vehicle controls. Inhibition of miR-182 in vivo attenuated colesevelam-mediated improvements to glycemic control in db/db mice.

Hepatic expression of mediator complex subunit 1 (MED1), a nuclear receptor coactivator, was significantly decreased with colesevelam treatments in db/db mice and Med1 was experimentally validated to be a direct target of miR-96/182/183 in humans and mice. In summary, these results support that colesevelam likely improves glycemic control through hepatic miR-182-5p, a mechanism that directly links cholesterol and glucose metabolism.

[3] *Bouillet B, Buffier P, Smati S et al.* **Expert opinion on the metabolic complications of mTOR inhibitors**. Annales d'endocrinologie 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30144939
ABSTRACT
Using mTOR inhibitors (mTORi) as anticancer drugs led to hyperglycemia (12-50%) and hyperlipidemia (7-73%) in phase-III trials. These high rates require adapted treatment in cancer patients. Before initiating mTORi treatment, lipid profile screening should be systematic, with fasting glucose assay in non-diabetic patients and HbA1C in diabetic patients. After initiation, lipid profile monitoring should be systematic, with fasting glucose assay in non-diabetic patients, every 2 weeks for the first month and then monthly. The HbA1C target is</=8%, before and after treatment initiation in known diabetic patients and in case of onset of diabetes under mTORi. LDL-cholesterol targets should be adapted to general health status and cardiovascular and oncologic prognosis. If treatment is indicated, pravastatin should be prescribed in first line; atorvastatin and simvastatin are contraindicated. Fenofibrate should be prescribed for hypertriglyceridemia>5g/l resisting dietary measures adapted to oncologic status. In non-controllable hypertriglyceridemia exceeding 10g/l, mTORi treatment should be interrupted and specialist opinion should be sought.

[4] *Klosiewicz-Latoszek L, Cybulska B, Bialobrzeska-Paluszkiewicz J et al.* **Clinical management of heterozygous familial hypercholesterolemia in a Polish outpatient metabolic clinic: a retrospective observational study**. Archives of medical science : AMS 2018; 14:962-970.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30154876
ABSTRACT
Introduction: There are currently no reports available from a Polish clinical practice on heterozygous familial hypercholesterolemia (HeFH) management. The aim of this study was to test the efficacy of HeFH hypolipidemic treatment in a Polish outpatient metabolic clinic according to treatment targets outlined in the European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) guidelines. Material and methods: This retrospective, observational study was performed on HeFH patients who attended their routine follow-up visits in the metabolic outpatient clinic in the period between April and September 2016. According to EAS/ESC guidelines, the goal and intensity of therapy were assigned individually for every patient based on cardiovascular (CV) risk (high or very high). The treatment target was achievement of low-density lipoprotein cholesterol (LDL-C) levels < 1.8 mmol/l for very high CV risk patients and < 2.6 mmol/l for high CV risk patients. A >/= 50% decrease in LDL-C over the observation period was an additional outcome measure. Results: In the overall group of 222 HeFH patients (mean age: 55.2 +/-16.2 years, 72% women), LDL-C levels decreased on average by 52.6% ($p < 0.001$). More than half of the patients were treated with the maximum tolerated dose of statins. A total of 25.2% of patients attained target levels of LDL-C and 55.9% attained a

>/= 50% reduction in its concentration. Despite therapy, significantly elevated post-follow-up levels of LDL-C (> 4.1 mmol/l) remained in 14% of all patients. Conclusions: Hypolipidemic therapy according to EAS/ESC guidelines was suboptimal for a significant number of HeFH patients. Additional clinical management should be considered.

[5] *Cao YX, Liu HH, Sun D et al.* **The different relations of PCSK9 and Lp(a) to the presence and severity of atherosclerotic lesions in patients with familial hypercholesterolemia**. Atherosclerosis 2018; 277:7-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30170223
ABSTRACT
BACKGROUND AND AIMS: The relation of lipoprotein (a) [Lp(a)] and proprotein convertase substilisin/kexin type 9 (PCSK9) levels to coronary artery disease (CAD) has been well established in the general population, while little is known about the association between Lp(a) or PCSK9 and atherosclerotic lesions of different artery sites in patients with familial hypercholesterolemia (FH). METHODS: One hundred and fifty-one patients with verified genotyped heterozygous FH (HeFH) were enrolled. There were available data regarding coronary angiography and carotid ultrasonography in 151 patients and femoral ultrasonography in 55 patients. Coronary and carotid severity was evaluated by Gensini score and Crouse score. PCSK9 and Lp(a) concentrations were determined by ELISA and immunoturbidimetry, respectively. Finally, the correlation of PCSK9 and Lp(a) with the presence and severity of CAD and peripheral artery disease (PAD) was assessed. RESULTS: The distributions of PCSK9 and Lp(a) were skewed and a close correlation between them in HeFH patients was found. PCSK9 levels were significantly higher in patients with coronary and carotid atherosclerotic lesions compared to their non-atherosclerotic groups, while no difference was found in femoral atherosclerotic lesions groups. Lp(a) levels only differed between patients with or without coronary atherosclerotic lesions. Patients with highest PCSK9 and Lp(a) concentrations had the highest prevalence and severity of atherosclerotic lesions. Multivariate regression analysis showed that PCSK9 was independently associated with CAD and PAD, while Lp(a) was only associated with CAD. CONCLUSIONS: Circulating PCSK9 concentrations were associated with an increased risk of CAD and PAD, while Lp(a) was only a marker for CAD in HeFH patients.

[6] *Navarese EP, Raggi P*. **PCSK9 inhibition for patients with and without prior coronary revascularization: Potential additional benefit of a novel therapeutic agent**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30150083
ABSTRACT

[7] *Waldmann E, Vogt A, Crispin A et al.* **Corrigendum to: "Effect of mipomersen on LDL-cholesterol in patients with severe LDL-hypercholesterolaemia and atherosclerosis treated by lipoprotein apheresis (The MICA-Study)" [Atherosclerosis 259 (2017 Apr) 20-25]**. Atherosclerosis 2018; 275:461-462.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30153939
ABSTRACT

[8] *Balestrino M, Adriano E*. **Statin-induced myopathy prevented by creatine administration**. BMJ case reports 2018; 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30150340
ABSTRACT
A 66-year-old woman with chronic myeloid leukaemia in nilotinib-induced remission was diagnosed with amaurosis fugax, caused by carotid stenosis. Serum cholesterol was 316 mg/dL (Low-Density Lipoprotein (LDL) cholesterol 213 mg/dL). Nilotinib was discontinued and replaced by interferon. Antiplatelet therapy and atorvastatin 40 mg/day were prescribed. Muscle pain and elevation of serum creatine kinase (CK) occurred; thus, atorvastatin was replaced by ezetimibe. Afterwards, muscle pain subsided and CK reverted to normal, but 2 years later serum cholesterol was still elevated at 218 mg/dL with LDL cholesterol 126 mg/dL. Simvastatin 5 mg/day was then started, but again muscle pain occurred and CK rose to 267 U/L. Simvastatin was stopped and serum cholesterol climbed to 252 mg/dL. Creatine was prescribed and simvastatin was reintroduced. Two months later, cholesterol was 171 mg/dL, CK was 72 U/L and there was no muscle pain. This case supports the view that creatine may prevent statin-induced myopathy.

[9] *Coombes JA, Rowett D, Whitty JA, Cottrell WN*. **Use of a patient-centred educational exchange (PCEE) to improve patient's self-management of medicines after a stroke: a randomised controlled trial study protocol**. BMJ open 2018; 8:e022225.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30166304
ABSTRACT
INTRODUCTION: National and international guidelines make recommendations for secondary prevention of stroke including the use of medications. A strategy which engages patients in a conversation to personalise evidence-based educational material (patient-centred educational exchange; PCEE) may empower patients to better manage their medications. METHODS AND ANALYSIS: This protocol outlines a non-blinded randomised controlled trial. Consenting patients admitted with a diagnosis of stroke or transient ischaemic attack will be randomised 1:1 to receive either a PCEE composed of two sessions, one at the bedside before discharge and one by telephone at least 10 days after discharge from hospital in addition to usual care (intervention) or usual care alone (control). The primary aim of this study is to determine whether a PCEE improves adherence to antithrombotic, antihypertensive and lipid-lowering medications prescribed for secondary prevention of stroke over the 3 months after discharge, measured using prescription-refill data. Secondary aims include investigation of the impact of the PCEE on adherence over 12 months using prescription-refill data, self-reported medication taking behaviour, self-reported clinical outcomes (blood pressure, cholesterol, adverse medication events and readmission), quality of life, the cost utility of the intervention and changes in beliefs towards medicines and illness. ETHICS AND DISSEMINATION: Communication of the trial results will provide evidence to aid clinicians in conversations with patients about medication taking behaviour related to stroke prevention. The targeted audiences will be health practitioners and consumers interested in medication taking behaviour in chronic diseases and in particular those interested in secondary prevention of stroke.The trial has ethics approval from Metro South Human Research Ethics Committee (HREC/15/QPAH/531) and The

University of Queensland Institutional Human Research Ethics (2015001612). TRIAL REGISTRATION NUMBER: ACTRN12615000888561; Pre-results.

[10] *Donald Harvey R, Aransay NR, Isambert N et al.* **Effect of multiple-dose osimertinib on the pharmacokinetics of simvastatin and rosuvastatin**. British journal of clinical pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30171779
ABSTRACT
AIM: We report on two phase I, open-label, single-arm studies assessing the effect of osimertinib on simvastatin (CYP3A substrate) and rosuvastatin (breast cancer resistance protein substrate [BCRP] substrate) exposure in patients with advanced epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer who have progressed after treatment with an EGFR tyrosine kinase inhibitor, to determine, upon coadministration, whether osimertinib could affect the exposure of these agents. METHODS: 52 patients in the CYP3A study (pharmacokinetic [PK] analysis, N = 49), and 44 patients in the BCRP study were dosed (PK analysis, N = 44). In the CYP3A study, patients received single doses of simvastatin 40 mg on Days 1 and 31, and osimertinib 80 mg once daily on Days 3-32. In the BCRP study, single doses of rosuvastatin 20 mg were given on Days 1 and 32, and osimertinib 80 mg once daily on Days 4-34. RESULTS: Geometric least squares mean (GLSM) ratios (90% confidence intervals) of simvastatin plus osimertinib for area under the plasma concentration-time curve from zero to infinity (AUC) were 91% (77-108): entirely contained within the pre-defined no relevant effect limits, and Cmax of 77% (63, 94) which was not contained within the limits. GLSM ratios of rosuvastatin plus osimertinib for AUC were 135% (115-157) and Cmax were 172 (146, 203): outside the no relevant effect limits. CONCLUSIONS: Osimertinib is unlikely to have any clinically relevant interaction with CYP3A substrates and has a weak inhibitory effect on BCRP. No new safety concerns were identified in either study.

[11] *Ormazabal V, Nair S, Elfeky O et al.* **Association between insulin resistance and the development of cardiovascular disease**. Cardiovascular diabetology 2018; 17:122.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30170598
ABSTRACT
For many years, cardiovascular disease (CVD) has been the leading cause of death around the world. Often associated with CVD are comorbidities such as obesity, abnormal lipid profiles and insulin resistance. Insulin is a key hormone that functions as a regulator of cellular metabolism in many tissues in the human body. Insulin resistance is defined as a decrease in tissue response to insulin stimulation thus insulin resistance is characterized by defects in uptake and oxidation of glucose, a decrease in glycogen synthesis, and, to a lesser extent, the ability to suppress lipid oxidation. Literature widely suggests that free fatty acids are the predominant substrate used in the adult myocardium for ATP production, however, the cardiac metabolic network is highly flexible and can use other substrates, such as glucose, lactate or amino acids. During insulin resistance, several metabolic alterations induce the development of cardiovascular disease. For instance, insulin resistance can induce an imbalance in glucose metabolism that generates chronic hyperglycemia, which in turn triggers oxidative stress and causes an inflammatory response that leads to cell damage. Insulin resistance can also alter systemic lipid metabolism

which then leads to the development of dyslipidemia and the well-known lipid triad: (1) high levels of plasma triglycerides, (2) low levels of high-density lipoprotein, and (3) the appearance of small dense low-density lipoproteins. This triad, along with endothelial dysfunction, which can also be induced by aberrant insulin signaling, contribute to atherosclerotic plaque formation. Regarding the systemic consequences associated with insulin resistance and the metabolic cardiac alterations, it can be concluded that insulin resistance in the myocardium generates damage by at least three different mechanisms: (1) signal transduction alteration, (2) impaired regulation of substrate metabolism, and (3) altered delivery of substrates to the myocardium. The aim of this review is to discuss the mechanisms associated with insulin resistance and the development of CVD. New therapies focused on decreasing insulin resistance may contribute to a decrease in both CVD and atherosclerotic plaque generation.

[12] *Yang N, Song Y, Dong B et al.* **Elevated Interleukin-38 Level Associates with Clinical Response to Atorvastatin in Patients with Hyperlipidemia**. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2018; 49:653-661.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30165364
ABSTRACT
BACKGROUND/AIMS: Hyperlipidemia is a risk factor for various cardiovascular and metabolic disorders. And it is tightly related to chronic inflammation. Interleukin-38 (IL-38) represents a new member of anti-inflammatory cytokines. Thus we studied the important role of IL-38 in hyperlipidemia development and treatment. METHODS: The mRNA level of IL-38 in PBMCs (peripheral blood mononuclear cells) and serum IL-38 levels in hyperlipidemia patients and healthy controls were measured by real-time polymerase chain reaction (RT-PCR) and enzyme-linked immunoassay (ELISA). The hyperlipidemia patients were further divided into two groups (Sensitive and Resistant Group) according to their clinical response to Atorvastatin therapy. Finally, the effects of IL-38 on hyperlipidemia was evaluated in the mice model. RESULTS: Data showed that the IL-38 mRNA and serum protein levels were higher in patients with hyperlipidemia compared with healthy controls. And the IL-38 mRNA and serum protein levels were higher in patients sensitive to Atorvastatin therapy than the resistant group. In vitro, IL-38 inhibited the production of IL-6, IL-1beta and CRP in PBMCs of patients with hyperlipidemia. In the mice model of hyperlipidemia, IL-38 was also elevated during the hyperlipidemia development. Furthermore, the IL-38 over-expressed by adeno-associated virus significantly inhibited the hyperlipidemia development, inflammatory factor secretion and also the atherosclerosis process. CONCLUSION: Thus our data showed that IL-38 might present protective effects on hyperlipidemia treatment.

[13] *Sabico S, Al-Mashharawi A, Al-Daghri NM et al.* **Effects of a 6-month multi-strain probiotics supplementation in endotoxemic, inflammatory and cardiometabolic status of T2DM patients: A randomized, double-blind, placebo-controlled trial**. Clinical nutrition (Edinburgh, Scotland) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30170781
ABSTRACT

OBJECTIVE: The aim of this trial was to characterize the beneficial effects of probiotics on decreasing endotoxin levels and other cardiometabolic parameters in Arab patients with type 2 diabetes mellitus (T2DM). METHODS: Saudi adults with naive T2DM (n = 30; 12 males and 18 females) were randomly allocated to receive twice daily placebo or 2.5 x 10(9) cfu/g of Ecologic((R))Barrier (multi-strain probiotics; n = 31; 14 males and 17 females) in a double-blind manner over a 6 month period, respectively. Anthropometrics were measured and fasting blood samples were collected to analyze endotoxin, glycemic parameters [glucose, insulin, c-peptide and homeostasis model assessment for insulin resistance (HOMA-IR)], lipids [triglycerides, total cholesterol, low and high-density lipoprotein (LDL and HDL, respectively) cholesterol and total/HDL-cholesterol ratio], inflammatory markers [tumor-necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and C-reactive protein (CRP)] and adipocytokines [leptin, adiponectin and resistin] at baseline and after 3 and 6 months of intervention. RESULTS: Multi-strain probiotics supplementation for 6 months caused a significant decrease in circulating levels of endotoxin by almost 70% over 6 months, as well as glucose (38%), insulin (38%), HOMA-IR (64%), triglycerides (48%), total cholesterol (19%), total/HDL-cholesterol ratio (19%), TNF-alpha (67%), IL-6 (77%), CRP (53%), resistin (53%), and a significant increase in adiponectin (72%) as compared with baseline. Only HOMA-IR had a clinically significant reduction (-3.4, 64.2%) in the probiotics group as compared to placebo group at all time points. No other clinically significant changes were observed between the probiotic or placebo group at 3 and 6 months in other markers. CONCLUSION: Multi-strain probiotic supplementation over 6 months as a monotherapy significantly decreased HOMA-IR in T2DM patients, with the probiotic treatment group highlighting reduced inflammation and improved cardiometabolic profile. As such, multi-strain probiotics is a promising adjuvant anti-diabetes therapy. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01765517.

[14] *Santos HO, da Silva GAR*. **To what extent does cinnamon administration improve the glycemic and lipid profiles?** Clinical nutrition ESPEN 2018; 27:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30144878

ABSTRACT

BACKGROUND & AIMS: Cinnamon is a condiment used in cooking and by some in large quantities as a supplement with purported hypoglycemic and lipid-lowering potential. The current literature review aims to discuss the evidence of cinnamon administration regarding its hypoglycemic and lipid-lowering effects, summarizing clinical recommendations. METHODS: Electronic databases including PubMed, Cochrane library, Science Direct and Web of Science were searched with the scientific name of the plant as well as the common name. The search for articles was based on following keywords: "cinnamon diabetes", "cinnamon diabetes type 2", "cinnamon and diabetes type 2", "Cinnamomum aromaticum", "Cinnamomum cassia", "Cinnamomum verum", "Cinnamomum zeylanicum". We carried out inclusion criteria between 2003 and 2018 focusing on human studies. RESULTS: Concerning glycemic profile, in individuals with type II diabetes mellitus the fasting blood glucose reduced from 12.9 to 52.2 mg/dL and HbA1c from 0.27 to 0.83%, whereas serum insulin decreased in few studies. Research papers ranged from 6 to 17 weeks in duration. The lipid lowering potential, in turn, is most controversial compared to anti-hyperglycemic potential. Also cinnamon administration has been claimed to reduce fat mass and raise serum antioxidants, but the studies used inaccurate

methods. Two species are most investigated, C. cassia/aromaticum, and C.zeylanicum/verum. CONCLUSIONS: About 1-6 g of these cinnamon species mainly in powder seems to be an adjunct drug treatment for type 2 diabetes mellitus and other conditions of glycemic impairment. However, more controlled clinical trials are needed.

[15] *Yorek MA*. **The Potential Role of Fatty Acids in Treating Diabetic Neuropathy**. Current diabetes reports 2018; 18:86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30145729
ABSTRACT
PURPOSE OF REVIEW: This review will summarize recent findings of the effect of supplemental fatty acids, with an emphasis on omega-3 polyunsaturated fatty acids, as a treatment for diabetic peripheral neuropathy. RECENT FINDINGS: Pre-clinical studies have provided evidence that treating diabetic rodents with delta linolenic acid (omega-6 18:3) and to a greater extent with eicosapentaenoic and docosahexaenoic acids (omega-3 20:5 and 22:6, respectively) improve and even reverse vascular and neural deficits. Additional studies have shown resolvins, metabolites of eicosapentaenoic and docosahexaenoic acids, can induce neurite outgrowth in neuron cultures and that treating type 1 or type 2 diabetic mice with resolvin D1 or E1 provides benefit for peripheral neuropathy similar to fish oil. Omega-3 polyunsaturated fatty acids derived from fish oil and their derivatives have anti-inflammatory properties and could provide benefit for diabetic peripheral neuropathy. However, clinical trials are needed to determine whether this statement is true.

[16] *Mamo JC, Lam V, Brook E et al.* **Probucol prevents blood-brain barrier dysfunction and cognitive decline in mice maintained on pro-diabetic diet**. Diabetes & vascular disease research 2018:1479164118795274.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30156119
ABSTRACT
An emerging body of evidence consistently suggests that compromised blood-brain barrier integrity may be causally associated with cognitive decline induced by type-2 diabetes. Our previous studies demonstrated that selected anti-inflammatory/anti-oxidative agents can preserve the integrity of blood-brain barrier and prevent neuroinflammation in mouse models of dysfunctional blood-brain barrier. Therefore, we have tested whether the previously proven blood-brain barrier protective agent, probucol, can prevent blood-brain barrier breakdown and cognitive decline in a dietary-induced murine model of diabetic insulin resistance. After 6-month chronic ingestion of a diet high in fat and fructose, the mice became insulin resistant. The high-fat and high-fructose-fed mice showed significant cognitive decline assessed by Morris water maze, concomitant with significant elevations in cortical and hippocampal glial acidic fibrillary protein and Fluoro Jade-C staining, indicating heightened neuroinflammation and neurodegeneration, respectively. The integrity of blood-brain barrier in high-fat and high-fructose-fed mice was substantially compromised, and this showed a significant association with heightened neurodegeneration. Co-provision of probucol with high-fat and high-fructose diet completely prevented the cognitive decline and blood-brain barrier dysfunction. Similarly, metformin was able to restore the cognitive function in high-fat and high-fructose-fed mice, while its blood-brain barrier protective effects were modest. These data suggest that probucol

may prevent cognitive decline induced by insulin resistance by preserving the integrity of blood-brain barrier, whereas metformin's neuroprotective effects may be mediated through a separate pathway.

[17] *Ridker PM, Libby P, MacFadyen JG et al.* **Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30165610
ABSTRACT
Aims: Canakinumab, a monoclonal antibody targeting interleukin (IL)-1beta, reduces rates of recurrent cardiovascular events without lowering lipids. It is uncertain, however, to what extent these beneficial cardiovascular outcomes are mediated through interleukin-6 (IL-6) signalling, an issue with substantial pathophysiologic consequences and therapeutic implications. Methods and results: A total of 4833 stable atherosclerosis patients in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) had IL-6 levels measured before randomization and after treatment with placebo or one of three doses of canakinumab (50 mg, 150 mg, or 300 mg) given subcutaneously once every 3 months. Participants were followed for up to 5 years (median follow-up 3.7 years). Compared with those allocated to placebo, CANTOS participants receiving canakinumab who achieved on-treatment IL-6 levels below the study median value of 1.65 ng/L experienced a 32% reduction in major adverse cardiovascular events [MACE, multivariable adjusted hazard ratio (HRadj) 0.68, 95% confidence interval (CI) 0.56-0.82; P < 0.0001], a 30% reduction in MACE plus the additional endpoint of hospitalization for unstable angina requiring urgent revascularization (MACE+, HRadj 0.70, 95% CI 0.59-0.84; P < 0.0001), a 52% reduction in cardiovascular mortality (HRadj 0.48, 95% CI 0.34-0.68; P < 0.0001), and a 48% reduction in all-cause mortality (HRadj 0.52, 95% CI 0.40-0.68; P < 0.0001) with prolonged treatment. In contrast, those with on-treatment IL-6 levels equal to or above 1.65 ng/L after taking the first dose of canakinumab had no significant benefit for any of these endpoints. These differential findings based on the magnitude of IL-6 response were seen in analyses alternatively based on tertiles of on-treatment IL-6 levels, and in analyses using a statistical inference approach to estimate the effect of treatment among individuals who would achieve a targeted IL-6 level. Conclusion: CANTOS provides proof of concept evidence in humans that modulation of the IL-6 signalling pathway, at least with canakinumab, associates with reduced cardiovascular event rates, independent of lipid lowering. Clinical trial registration: ClinicalTrials.gov NCT01327846.

[18] *Isilay Ozdogan A, Akca G, Senel S*. **Development and in vitro evaluation of chitosan based system for local delivery of atorvastatin for treatment of periodontitis**. Eur J Pharm Sci 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30171985
ABSTRACT
In recent years, statin group drugs have been widely investigated in treatment of periodontal diseases due to their anti-inflammatory effect. The efficacy of statins can be enhanced by local administration into the periodontal pocket by appropriate delivery systems. The aim of our study was to develop a bioadhesive delivery system for local delivery of atorvastatin in

treatment of periodontal disease. For this purpose, gel formulations were prepared using different types of chitosan (base and water soluble) and viscosity, bioadhesivity and syringeability of the gels as well as in vitro drug release properties were investigated vitro. Furthermore, anti-inflammatory effect of the formulations was studied in vitro using tumor necrosis factor (TNF)-alfa induced human gingival fibroblast (hGF) cells. Release of proinflammatory (IL-1beta, IL-6, IL-8) and anti-inflammatory (TGF-beta1, TGF-beta2, TGF-beta3, IL-10) cytokines were measured after incubating the hGF cells with the formulations. The viscosity of the formulations was found to be suitable for a local application into periodontal pocket. In presence of drug, bioadhesive property of the formulations was found to increase, and bioadhesion force was within the range, which would retain the delivery system at the application site, subsequently maintain drug levels at desired amount for longer period of time. The release of atorvastatin from the gels was found to be slower than that of the solution. The cytokine levels were found to decrease following application of the formulations, and anti-inflammatory effect was observed to enhance in presence of chitosan. No significant differences were found between base and water-soluble chitosan.

[19] *Krysiak R, Szkrobka W, Okopien B*. **The Relationship Between Statin Action On Thyroid Autoimmunity And Vitamin D Status: A Pilot Study**. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30149415
ABSTRACT
BACKGROUND: Both vitamin D preparations and high-dose statin therapy were found to reduce thyroid antibody titers. OBJECTIVE: The purpose of this study was to assess whether vitamin D status determines the effect of statin therapy on thyroid autoimmunity. METHODS: The study population consisted of 39 euthyroid women with Hashimoto's thyroiditis and moderate or moderately high cardiovascular risk divided into two groups: women with vitamin D deficiency or insufficiency (group A; n=19) and women with normal vitamin D status (group B, n=20). All patients received atorvastatin therapy (20-40 mg daily) for the following 6 months. Plasma lipids, circulating levels of thyrotropin, free thyroid hormones, prolactin and 25-hydroxyvitamin D, titers of thyroid peroxidase and thyroglobulin antibodies, as well as Jostel's, the SPINA-GT and the SPINA-GD indices were assessed at the beginning and at the end of the study. RESULTS: The study completed all women. At baseline, with the exception of 25-hydroxyvitamin D, there were no significant differences between both study groups in plasma lipids, circulating hormone levels and titers of thyroid peroxidase and thyroglobulin antibodies. Despite improving plasma lipids in both study groups, atorvastatin reduced thyroid antibody titers only in women with normal vitamin D status. Moreover, in this group of patients, atorvastatin increased the SPINA-GT index. Circulating levels of the measured hormones, Jostel's thyrotropin index and the SPINA-GD index remained at a similar level throughout the study. CONCLUSIONS: The results of the study suggest that the effect of atorvastatin therapy on thyroid autoimmunity depends on vitamin D status.

[20] *Godoy JC, Niesman IR, Busija AR et al.* **Atorvastatin, but not pravastatin, inhibits cardiac Akt/mTOR signaling and disturbs mitochondrial ultrastructure in cardiac myocytes**. FASEB

journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201800876R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30169110

ABSTRACT

Statins, which reduce LDL-cholesterol by inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, are among the most widely prescribed drugs. Skeletal myopathy is a known statin-induced adverse effect associated with mitochondrial changes. We hypothesized that similar effects would occur in cardiac myocytes in a lipophilicity-dependent manner between 2 common statins: atorvastatin (lipophilic) and pravastatin (hydrophilic). Neonatal cardiac ventricular myocytes were treated with atorvastatin and pravastatin for 48 h. Both statins induced endoplasmic reticular (ER) stress, but only atorvastatin inhibited ERK1/2(T202/Y204), Akt(Ser473), and mammalian target of rapamycin signaling; reduced protein abundance of caveolin-1, dystrophin, epidermal growth factor receptor, and insulin receptor-beta; decreased Ras homolog gene family, member A activation; and induced apoptosis. In cardiomyocyte-equivalent HL-1 cells, atorvastatin, but not pravastatin, reduced mitochondrial oxygen consumption. When male mice underwent atorvastatin and pravastatin administration per os for up to 7 mo, only long-term atorvastatin, but not pravastatin, induced elevated serum creatine kinase; swollen, misaligned, size-variable, and disconnected cardiac mitochondria; alteration of ER structure; repression of mitochondria- and endoplasmic reticulum-related genes; and a 21% increase in mortality in cardiac-specific vinculin-knockout mice during the first 2 months of administration. To our knowledge, we are the first to demonstrate in vivo that long-term atorvastatin administration alters cardiac ultrastructure, a finding with important clinical implications.-Godoy, J. C., Niesman, I. R., Busija, A. R., Kassan, A., Schilling, J. M., Schwarz, A., Alvarez, E. A., Dalton, N. D., Drummond, J. C., Roth, D. M., Kararigas, G., Patel, H. H., Zemljic-Harpf, A. E. Atorvastatin, but not pravastatin, inhibits cardiac Akt/mTOR signaling and disturbs mitochondrial ultrastructure in cardiac myocytes.

[21] *Deepti S, Bansal R, Singh S*. **ST segment elevation myocardial infarction with normal coronary arteries**. Heart Asia 2018; 10:e011084.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30167000

ABSTRACT

Case presentation: A middle-aged patient presented to the emergency department with intermittent chest pain of 4-hour duration. The patient had been recently diagnosed with metastatic adenocarcinoma of the colon and was receiving 5-fluorouracil (5-FU)-based chemotherapy at the time of presentation. The ECG at presentation showed 1 mm ST segment elevation in leads II, III and aVF, with reciprocal changes in leads aVL, V1 and V2 (figure 1A). Serum cardiac troponin I level was elevated at 0.11 ng/mL (normal: 0.00-0.02 ng/mL). The patient was given sublingual nitrate and loading doses of aspirin, clopidogrel and atorvastatin, and was taken up for coronary angiography with an intent to perform primary percutaneous coronary intervention.Figure 1(A) 12-lead ECG done at presentation to the emergency department. (B) 12-lead ECG done 30 min after coronary angiography.The images of the coronary angiogram are shown in figure 2. The patient was angina-free by this time. A repeat ECG done 30 min after coronary angiography is shown in figure 1B. Two-dimensional transthoracic echocardiogram revealed normal left ventricle (LV) systolic function and no

regional wall motion abnormality.Figure 2Images of the coronary angiogram of the patient. (A) Right anterior oblique view with a caudal angulation showing left anterior descending (LAD) artery and left circumflex (LCx) artery. (B) Left anterior oblique view with a cranial angulation showing right coronary artery (RCA). Question: What is the likely mechanism of myocardial infarction in this patient?In situ coronary artery thrombosis with spontaneous recanalisation.Epicardial coronary artery vasospasm.Coronary artery embolism.Coronary microvascular dysfunction.

[22] *Bostanitis I, Tsalidou M*. **Atorvastatin induced gynecomastia in a dyslipidemic patient. A case report**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30145234
ABSTRACT

[23] *Arany I, Fulop T, Dixit M*. **Chronic Nicotine Exposure Reduces Antioxidant Function of Simvastatin in Renal Proximal Tubule Cells**. In Vivo 2018; 32:1033-1037.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30150424
ABSTRACT
BACKGROUND/AIM: We have previously reported that simvastatin exhibits antioxidant properties via extracellular signal-regulated kinase (ERK)/cAMP-response element binding (CREB) protein-dependent induction of heme oxygenase-1 (HO1) and chronic nicotine exposure inhibits ERK/CREB signaling in renal proximal tubule cells (through p66shc). Herein, whether nicotine dampens simvastatin-dependent HO1 induction was determined. MATERIALS AND METHODS: Renal proximal tubule (NRK52E) cells were pre-treated with 200 muM nicotine for 24 h followed by 10 muM simvastatin. Promoter activity of HO1 and manganese superoxide dismutase (MnSOD) and activation of CREB and ERK (via ELK1) were determined in luciferase reporter assays. CREB and p66shc were modulated via genetic means. RESULTS: Nicotine suppressed simvastatin-dependent activation of HO1 and MnSOD promoters and activity of CREB and ELK1 via p66shc. Overexpression of CREB or knockdown of p66shc restored simvastatin-dependent induction of HO1 and MnSOD in the presence of nicotine. CONCLUSION: Antioxidant efficiency of simvastatin might be significantly lessened in smokers/E-cigarette users.

[24] *Yuan H, Hu H, Sun J et al.* **Ultrasound Microbubble Delivery Targeting Intraplaque Neovascularization Inhibits Atherosclerotic Plaque in an APOE-deficient Mouse Model**. In Vivo 2018; 32:1025-1032.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30150423
ABSTRACT
BACKGROUND/AIM: Intraplaque neovascularization is often associated with plaque formation, development and instability, and clinical symptoms in atherosclerosis. The aim of the present study was to investigate a new strategy for treating athrosclerosis by ultrasound-targeted microbubble delivery (UTMD) targeting intraplaque neovascularization in an APOE-deficient mouse model of atherosclerosis. MATERIALS AND METHODS: A mouse model of atherosclerosis was induced by feeding Apoe(-/-) mice a hypercholesterolemic diet and was verified with hematoxylin and eosin staining and intercellular adhesion molecule 1 (ICAM-1) expression.

Targeted microbubbles (MB) were prepared by conjugating microbubbles with biotinylated antibody to ICAM1 (MBi) or with both biotinylated anti-ICAM1 and the angiogenesis inhibitor Endostar (MBie). The targeted microbubbles were analyzed with epifluorescence microscopy and flow cytometry. The animals with induced atherosclerotic plaques received MBi or MBie followed by UTMD treatment. Endostar treatment alone was given to other animals for comparison. Morphological assessment of atherosclerotic plaques was performed after treatment. The expression of angiogenesis marker CD31 was detected by immunohistochemical analysis. RESULTS: Atherosclerotic plaques developed in the entire aorta with significant intraplaque ICAM-1 expression in the APOE-deficient mice following a 30-week hypercholesterolemic diet. Microbubbles were successfully conjugated with anti-ICAM-1 and Endostar, with a conjugation rate of 98.3% and 63.5%, respectively. UTMD with MBie significantly reduced the area of atherosclerotic plaque as compared to the model control ($p<0.05$). Treatment with Endostar and UTMD with MBie significantly reduced CD31 expression compared with the model control group ($p<0.01$). Greater significant inhibitory effect on CD31 expression was found in the group treated with UTMD and MBie compared to the Endostar- and UTMD with MBi groups ($p<0.01$). CONCLUSION: UTMD targeting intraplaque neovascularization was found to inhibit atherosclerotic plaque in a mouse model of atherosclerosis, suggesting the potential of microbubble-mediated ultrasound technology in aiding drug delivery for atherosclerosis treatment.

[25] *Riaz R, Merchant AZ, Ul Haq MS et al.* **Statins everyday versus alternate days: Is there a difference in myalgia rates?** Indian Heart J 2018; 70:492-496.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30170642

ABSTRACT

OBJECTIVE: Statins are widely used drugs, known to cause myalgia, leading to high discontinuation rates. The objective of our study was to determine the frequency of myalgia in patients on everyday-dose (EDD) regimen with those on alternate-day dose (ADD) regimen. METHODS: This cross sectional study was conducted in a tertiary care hospital of Pakistan. A sample size of 400 patients between the age of 40-70 years, taking simvastatin 40mg for at least 6 months or more were selected. Patients with prior musculoskeletal or neuromuscular complains, and family history of muscular disorders were excluded. Subjects were evaluated for myalgia via a self-administered questionnaire, and those complaining of myalgia were then evaluated for serum vitamin D levels. Data was analyzed through SPSS 16.0 and compared using chi square test. RESULTS: The overall prevalence of myalgia was 7% (28/400). Frequency of myalgia in patients taking simvastatin everyday (n=20, 10%) was significantly higher compared to those taking it every alternate day (n=8, 4%) ($p=0.02$). There was no significant difference between the time of onset, nature, severity, type, or location of myalgia between the 2 groups. The most common cited triggering factor for pain was physical exercise. Of the patients experiencing myalgia, 13 (6.5%) from the EDD group and 6 (3%) from the ADD group had low levels of vitamin D. CONCLUSIONS: ADD regime was better tolerated by the patients than EDD regime. Alternate day therapy, with or without vitamin D supplementation, may be used by the physicians for troublesome muscular complains.

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[26] *Nakano K, Matoba T, Koga JI et al.* **Safety, Tolerability, and Pharmacokinetics of NK-104-NP**. Int Heart J 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30158384
ABSTRACT
Pulmonary hypertension (PH) is a disease with poor prognosis, caused by the obstruction/stenosis of small pulmonary arteries. Statin is known to have vasodilating and anti-inflammatory property and is considered to be a candidate of therapeutic agents for the treatment of PH, but its efficacy has not been verified in clinical trials. We have formulated pitavastatin incorporating nanoparticles composed of poly (lactic-co-glycolic acid) (NK-104-NP) to improve drug delivery to the pulmonary arteries and evaluated their safety and pharmacokinetics in healthy volunteers. To accomplish this purpose, phase I clinical trials were conducted. In the single intravenous administration regimen, 40 healthy subjects were enrolled and PK (pharmacokinetic) parameters in 4 groups (1, 2, 4, and 8 mg as pitavastatin calcium) were as follows: 1.00 hour after the administration, the plasma concentration of pitavastatin reached Cmax (the maximum drug concentration) in all groups. Cmax, AUC0-t (area under the curve from time 0 to the last measurable concentration) and AUC0-infinity (area under the curve from time 0 extrapolated to infinite time) were increased in a dose-dependent manner. Population pharmacokinetic analysis based on these results indicated no accumulation of pitavastatin after repeated administration of NK-104-NP for 7 days. In this 7-day administration trial, the mean Cmax and AUC0-infinity of pitavastatin were not significantly different between days 1 and 7, suggesting that pitavastatin is unlikely to accumulate after repeated administration. In these trials, three adverse events (AEs) were reported, but they were resolved without any complications and judged to have no causal relationships with NK-104-NP. These results indicate that the innovative nanotechnology-based medicine NK-104-NP exhibited dose-dependent pharmacokinetics and was well tolerated with no significant AEs in healthy volunteers.

[27] *Chernonosov A*. **The Use of Dried Blood Spots for the Quantification of Antihypertensive Drugs**. International journal of analytical chemistry 2018; 2018:3235072.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30154849
ABSTRACT
Hypertension or high blood pressure is a harbinger of cardiovascular diseases. There are several classes of drugs used to treat hypertension. This review discusses the use of dried blood spots (DBSs) for the quantification by mass spectrometry (MS), tandem mass spectrometry (MS/MS), or, in some cases, by fluorescence detection methods the following antihypertensive medications: angiotensin-converting enzyme inhibitors (ramipril, ramiprilat, captopril, and lisinopril); angiotensin II receptor antagonists (valsartan, irbesartan, losartan, and losartan carboxylic acid); calcium channel blockers (verapamil, amlodipine, nifedipine, pregabalin, and diltiazem); alpha blockers (guanfacine, doxazosin, and prazosin); beta blockers (propranolol, bisoprolol, atenolol, and metoprolol); endothelin receptor antagonists (bosentan and ambrisentan); and statins (simvastatin, atorvastatin, and rosuvastatin).

[28] *Verdoia M, Nardin M, Negro F et al.* **Impact of statin therapy on the immature platelet count in patients with coronary artery disease: A single centre cohort study**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30150123
ABSTRACT
BACKGROUND: Statins represent a pivotal therapy among patients with coronary artery disease (CAD), providing both lipid-lowering and pleiotropic, anti-thrombotic and anti-inflammatory benefits. Immature platelet count (IPC) has been proposed as the fraction of younger and potentially more reactive platelets, therefore potentially affecting the risk of major cardiovascular ischemic events. The aim of the present study was to evaluate the impact of statin therapy on IPC in patients with CAD. METHODS: Patients undergoing coronary angiography in a single centre were included. IPC levels were measured by routine blood cells count (A Sysmex XE-2100) as the product of immature platelet fraction (IPF) and platelet count, in patients naive or chronically treated with statins at admission. RESULTS: We included in our study 642 patients, 61.2% treated with statins at admission. Patients on chronic statins were more often males, with a worse metabolic profile, but for lower total and LDL cholesterol, and a higher prevalence of major cardiovascular risk factors. The mean levels of IPC did not differ between statin treated and naive patients (7.9+/-4.7 vs 7.7+/-5, p=0.60) and neither the distribution of IPC across tertiles (p=0.36). In fact, at multivariate regression analysis, statin use was not independently associated with the rate of IPC above the 3rd tertile (adjusted OR[95%CI]=1.19[0.80-1.79], p=0.39). Moreover, among the 190 patients that introduced the therapy with statins at admission, the levels of IPC and major platelet parameters did not differ at a median follow-up of 32days, as compared to chronically treated or non-treated patients. CONCLUSION: The present study shows that among patients with CAD the use of statins does not affect the immature platelet count or main platelet parameters.

[29] *Paw M, Wnuk D, Kadziolka D et al.* **Fenofibrate Reduces the Asthma-Related Fibroblast-To-Myofibroblast Transition by TGF-Beta/Smad2/3 Signaling Attenuation and Connexin 43-Dependent Phenotype Destabilization**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30158495
ABSTRACT
The activation of human bronchial fibroblasts by transforming growth factor-beta(1) (TGF-beta(1)) leads to the formation of highly contractile myofibroblasts in the process of the fibroblast(-)myofibroblast transition (FMT). This process is crucial for subepithelial fibrosis and bronchial wall remodeling in asthma. However, this process evades current therapeutic asthma treatment strategies. Since our previous studies showed the attenuation of the TGF-beta(1)-induced FMT in response to lipid-lowering agents (e.g., statins), we were interested to see whether a corresponding effect could be obtained upon administration of hypolipidemic agents. In this study, we investigated the effect of fenofibrate on FMT efficiency in populations of bronchial fibroblasts derived from asthmatic patients. Fenofibrate exerted a dose-dependent inhibitory effect on the FMT, even though it did not efficiently affect the expression of alpha-smooth muscle actin (alpha-SMA; marker of myofibroblasts); however, it considerably reduced its incorporation into stress fibers through connexin 43 regulation. This effect was accompanied by disturbances in the actin cytoskeleton architecture, impairments in the maturation of focal

adhesions, and the fenofibrate-induced deactivation of TGF-beta(1)/Smad2/3 signaling. These data suggest that fenofibrate interferes with myofibroblastic differentiation during asthma-related subepithelial fibrosis. The data indicate the potential application of fenofibrate in the therapy and prevention of bronchial remodeling during the asthmatic process.

[30] *Silvestre OM, Nadruz W, Jr., Querejeta Roca G et al.* **Declining Lung Function and Cardiovascular Risk: The ARIC Study**. Journal of the American College of Cardiology 2018; 72:1109-1122.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30165982
ABSTRACT
BACKGROUND: Pulmonary dysfunction predicts incident cardiovascular disease (CVD). OBJECTIVES: The purpose of this study was to evaluate whether longitudinal decline in lung function is associated with incident heart failure (HF), coronary heart disease (CHD), and stroke. METHODS: Among 10,351 participants in the ARIC (Atherosclerosis Risk In Communities) study free of CVD, rapid lung function decline was defined as the greatest quartile (n = 2,585) of decline in either forced expiratory volume in 1 s (FEV1) (>1.9% decline/year) or forced vital capacity (FVC) (>2.1% decline/year) over 2.9 +/- 0.2 years. The relationship between rapid decline in FEV1 or FVC and subsequent incident HF, CHD, stroke, or a composite of these was assessed using multivariable Cox regression adjusting for the baseline spirometry value, demographics, height, body mass index, heart rate, diabetes, hypertension, low-density lipoprotein, use of lipid-lowering medication, N-terminal fragment of prohormone for B-type natriuretic peptide, and smoking. RESULTS: The mean age was 54 +/- 6 years, 56% were women, and 81% were white. At 17 +/- 6 years of follow-up, HF occurred in 14%, CHD 11%, stroke 6%, and the composite in 24%. Rapid decline in FEV1 and in FVC were both associated with a heightened risk of incident HF (hazard ratio [HR]: 1.17; 95% confidence interval [CI]: 1.04 to 1.33; p = 0.010; and HR: 1.27; 95% CI: 1.12 to 1.44; p < 0.001; respectively), with rapid decline in FEV1 most prognostic in the first year of follow-up (HR: 4.22; 95% CI: 1.34 to 13.26; p = 0.01). Rapid decline in FEV1 was also associated with incident stroke (HR: 1.25; 95% CI: 1.04 to 1.50; p = 0.015). CONCLUSIONS: A rapid decline in lung function, assessed by serial spirometry, is associated with a higher incidence of subsequent CVD, particularly incident HF.

[31] *Lai M, Yan X, Jin Z*. **The response of bone cells to titanium surfaces modified by simvastatin-loaded multilayered films**. Journal of biomaterials science. Polymer edition 2018:1-26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30156968
ABSTRACT
The aim of this study was to enhance cytocompatibility of titanium substrates by loading a multilayer film of chitosan (Chi), gelatin (Gel) and simvastatin (SV). This was fabricated using a spin-assisted layer-by-layer (LBL) technique. The surface properties of the different substrates were characterized by field emission scanning electron microscopy (FE-SEM), atomic force microscope (AFM), X-ray photoelectron spectroscopy (XPS) and contact angle measurement, respectively. Simvastatin release in vitro was measured by ultraviolet-visible spectrophotometer. A well morphology with filopodia extensions was observed in mesenchymal stem cells (MSCs) grown on simvastatin loaded multilayered films-modified

titanium substrates. After 7, 14 and 21 days of culture, the simvastatin loaded multilayered films increased cell proliferation, improved osteoblastic differentiation of alkaline phosphatase (ALP) and mineralization. Additionally, osteoclast diffentiation marker tartrate-resistant acid phosphatase (TRAP) was decreased in simvastatin loaded multilayered films. This study provides a new insight for the fabrication of titanium-based implants to enhance osseointegration especially for osteoporosis patients in orthopedic application.

[32] *Lohani M, Dhasmana A, Haque S et al.* **Niacin deficiency modulates genes involved in cancer: Are smokers at higher risk?** Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30171725
ABSTRACT
The role of niacin's metabolite, nicotinamide adenine dinucleotide (NAD), in DNA repair via base-excision repair pathway is well documented. We evaluated if niacin deficiency results in genetic instability in normal human fetal lung fibroblasts (MRC-5), and further, does it leads to enhanced accumulation of cigarette smoke-induced genetic damage? MRC-5 cells were grown discretely in niacin-proficient/deficient media, and exposed to nicotine-derived nitrosamine ketone (NNK, a cigarette smoke carcinogen). Niacin deficiency abated the NAD polymerization, augmented the spontaneous induction of micronuclei (MN) and chromosomal aberrations (CA) and raised the expression of 10 genes and suppressed 12 genes involved in different biological functions. NNK exposure resulted in genetic damage as measured by the induction of MN and CA in cells grown in niacin-proficient medium, but the damage became practically marked when niacin-deficient cells were exposed to NNK. NNK exposure raised the expression of 16 genes and suppressed the expression of 56 genes in cells grown in niacin-proficient medium. NNK exposure to niacin-deficient cells raised the expression of eight genes including genes crucial in promoting cancer such as FGFR3 and DUSP1 and suppressed the expression of 33 genes, including genes crucial in preventing the onset and progression of cancer like RASSF2, JUP, and IL24, in comparison with the cells grown in niacin-proficient medium. Overall, niacin deficiency interferes with the DNA damage repair process induced by chemical carcinogens like NNK, and niacin-deficient population are at the higher risk of genetic instability caused by cigarette smoke carcinogen NNK.

[33] *Balasubramanian H, Kumar RS, Anireddy JS, Rao DV*. **Development of a Simple, Highly Selective RP-LC Method for the Quantification of Diastereomers and Other Related Substances of Ezetimibe Using Multivariate Analysis**. Journal of chromatographic science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30165615
ABSTRACT
A simple reverse phase method for the selective quantification of ezetimibe (EZM), its diastereomers and other related substances was developed. The method demonstrated an excellent separation between each of the 14 impurities (including diastereomers, specified impurities and degradation products) and EZM within a runtime of 45 min. The developed method was evaluated against the reported USP method, other literature methods found that none of them was able to separate/show the absence of all the diastereomers and degradation products. The critical method parameters were optimized using central composite design. Forced degradation studies proved the method to be highly specific and the structure of all the

major degradation products were confirmed by LC-MS study. The results of validation proved the method to be precise (% RSD < 4), accurate (recoveries in range of 100 +/- 6%), linear (R2 > 0.999) and sensitive (LOQ </= 0.04% and LOD </= 0.01%) for all the impurities and drug. The method is suitable for both drug substance and oral solid dosage form.

[34] *Holm Nielsen S, Tengryd C, Edsfeldt A et al.* **A biomarker of collagen type I degradation is associated with cardiovascular events and mortality in patients with atherosclerosis**. Journal of internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30156050
ABSTRACT
OBJECTIVE: Atherosclerosis is characterized by accumulation of lipids, cells and extracellular matrix (ECM) proteins in the arterial wall. Collagen type I (COL1), a component of the arterial ECM, is cleaved by matrix metalloproteinases (MMPs) and known to be remodelled in atherosclerosis. We explored whether the MMP-mediated COL1 biomarker, C1M, was associated with cardiovascular events, cardiovascular mortality and all-cause mortality in a large prospective cohort of patients with known atherosclerosis. METHODS: Serum from 787 patients who underwent a carotid endarterectomy was included. Circulating levels of C1M were measured in serum. A total of 473 patients were followed for 6 years after surgery. Associations between C1M and incidence of cardiovascular events, cardiovascular mortality and all-cause mortality were assessed by Kaplan-Meier curves and Cox regression analysis. RESULTS: A total of 101 (21.4%) patients suffered from nonfatal cardiovascular events during the follow-up period, and 64 (13.5%) patients died. Of these, 39 (60.9%) died from cardiovascular diseases. Patients with C1M levels above the median were significantly associated with cardiovascular events, cardiovascular mortality and all-cause mortality (P < 0.001, P = 0.004 and P < 0.001, respectively). C1M was included in the final model for prediction of cardiovascular events (HR 2.15, 95% CI 1.40-3.32, P = 0.001), cardiovascular mortality (HR 2.20, 95% CI 1.07-4.51, P = 0.031) and all-cause mortality (HR 2.98 95% CI 1.67-5.33, P = < 0.001). CONCLUSIONS: In patients with atherosclerotic carotid lesions, high levels of C1M predicted cardiovascular events, cardiovascular mortality and all-cause mortality. These findings emphasize the importance of remodelling mechanisms in atherosclerosis that are now becoming more and more explored.

[35] *Nagm A, Horiuchi T, Hongo K*. **Letter to the Editor. Carotid atherosclerotic plaque instability and cognition: collecting additional data**. Journal of neurosurgery 2018:1-2.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30168736
ABSTRACT

[36] *Shah MH, Roshan R, Desai R, Kadam SS*. **Neonatal hyperlipidemia with pancreatitis: Novel gene mutation of lipoprotein lipase**. Journal of postgraduate medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30147083
ABSTRACT
Lipoprotein lipase (LPL) deficiency is an autosomal recessive metabolic disorder with varying presentation in infancy and childhood, whereas clinical manifestations are rare in neonatal period. The estimated prevalence is one in a million births. A 23-day-old baby was admitted

with complaints of fever, vomiting, and lethargy. Blood sample drawn appeared lipemic. Lipemia retinalis was noted on funduscopic examination. Biochemical analysis revealed abnormal lipid profile with severe hypertriglyceridemia (10,300 mg/dL) and elevated serum lipase level (517 IU/L) indicative of LPL deficiency with acute pancreatitis. LPL deficiency was suspected and was confirmed by molecular genetic testing, which revealed a novel mutation in LPL gene. Dietary management and gemfibrozil were started following which serum triglyceride level decreased and serum lipase level normalized. The patient is following up regularly for growth and development monitoring.

[37] *Liu D, Chu X, Wang H et al.* **The changes of immunoglobulin G N-glycosylation in blood lipids and dyslipidaemia**. Journal of translational medicine 2018; 16:235.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30157878
ABSTRACT
BACKGROUND: Alternative N-glycosylation has significant structural and functional consequences on immunoglobulin G (IgG) and can affect immune responses, acting as a switch between pro- and anti-inflammatory IgG functionality. Studies have demonstrated that IgG N-glycosylation is associated with ageing, body mass index, type 2 diabetes and hypertension. METHODS: Herein, we have demonstrated patterns of IgG glycosylation that are associated with blood lipids in a cross-sectional study including 598 Han Chinese aged 20-68 years. The IgG glycome composition was analysed by ultra-performance liquid chromatography. RESULTS: Blood lipids were positively correlated with glycan peak GP6, whereas they were negatively correlated with GP18 ($P < 0.05/57$). The canonical correlation analysis indicated that initial N-glycan structures, including GP4, GP6, GP9-12, GP14, GP17, GP18 and GP23, were significantly correlated with blood lipids, including total cholesterol, total triglycerides (TG) and low-density lipoprotein ($r = 0.390$, $P < 0.001$). IgG glycans patterns were able to distinguish patients with dyslipidaemia from the controls, with an area under the curve of 0.692 (95% confidence interval 0.644-0.740). CONCLUSIONS: Our findings indicated that a possible association between blood lipids and the observed loss of galactose and sialic acid, as well as the addition of bisecting GlcNAcs, which might be related to the chronic inflammation accompanying with the development and procession of dyslipidaemia.

[38] *Qato K, Conway AM, Mondry L et al.* **Management of isolated femoropopliteal in-stent restenosis**. Journal of vascular surgery 2018; 68:807-810.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30144908
ABSTRACT
OBJECTIVE: The optimal catheter-directed therapy for femoropopliteal in-stent restenosis (ISR) remains controversial with limited durability. The natural history of untreated ISR is not well characterized. We evaluated the midterm outcomes of patients with asymptomatic isolated femoropopliteal ISR who were observed under a surveillance program. METHODS: Patients treated with isolated femoropopliteal stents from January 2009 to December 2013 were retrospectively investigated for the development of ISR. ISR was classified on the basis of duplex ultrasound criteria, with >50% defined as peak systolic velocity (PSV) twice that of the normal vessel and >75% as PSV >400 cm/s or four times the normal PSV. Asymptomatic patients with ISR of >50% were tracked for progression to high-grade (>75%) stenosis,

occlusion, need for reintervention, and amputation. RESULTS: Asymptomatic ISR of >50% was identified in 62 (15.3%) of 402 patients with isolated femoropopliteal stents. The mean time for development of ISR was 22.1 (+/-20.1) months. The mean age was 72 (+/-9.7) years, and 34 (55.7%) patients were female. Thirty-one (50%) patients were diabetic, 18 (29.1%) were smokers, and 8 (12.9%) had chronic kidney disease. Indications for treatment were claudication in 49 (79.0%), tissue loss in 9 (14.5%), and rest pain in 4 (6.4%) patients. TransAtlantic Inter-Society Consensus (TASC) A lesions were treated in 13 (21%) patients, TASC B lesions in 24 (38.7%), and TASC C lesions in 25 (40.3%). Three-vessel runoff was identified in 25 (40.3%) patients, two-vessel runoff in 18 (29.0%), and one-vessel runoff in 19 (30.6%). Under surveillance, ISR of >50% progressed to >75% or occlusion in 20 (32.3%) patients. The mean time to progression was 17.4 months, and the mean overall follow-up was 33.1 months. Reintervention was required in 22 (35.0%) patients, with an average of 1.95 (range, 1-4) interventions per patient. Reintervention was undertaken in 19 (86%) patients for claudication and in 3 (18%) patients for critical limb ischemia. One patient required an amputation despite previous reintervention for progression. Progression to >75% stenosis was predictive of need for reintervention (P = .004). CONCLUSIONS: Under a surveillance program, asymptomatic patients with femoropopliteal ISR of >50% may be observed with a low risk of limb loss. Given the slow rate of progression and the poor durability of reintervention, surveillance with delayed intervention may be warranted.

[39] *Gupta A, Mackay J, Whitehouse A et al.* **Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomised factorial trial**. Lancet 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30158072
ABSTRACT
BACKGROUND: In patients with hypertension, the long-term cardiovascular and all-cause mortality effects of different blood pressure-lowering regimens and lipid-lowering treatment are not well documented, particularly in clinical trial settings. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy Study reports mortality outcomes after 16 years of follow-up of the UK participants in the original ASCOT trial. METHODS: ASCOT was a multicentre randomised trial with a 2 x 2 factorial design. UK-based patients with hypertension were followed up for all-cause and cardiovascular mortality for a median of 15.7 years (IQR 9.7-16.4 years). At baseline, all patients enrolled into the blood pressure-lowering arm (BPLA) of ASCOT were randomly assigned to receive either amlodipine-based or atenolol-based blood pressure-lowering treatment. Of these patients, those who had total cholesterol of 6.5 mmol/L or lower and no previous lipid-lowering treatment underwent further randomisation to receive either atorvastatin or placebo as part of the lipid-lowering arm (LLA) of ASCOT. The remaining patients formed the non-LLA group. A team of two physicians independently adjudicated all causes of death. FINDINGS: Of 8580 UK-based patients in ASCOT, 3282 (38.3%) died, including 1640 (38.4%) of 4275 assigned to atenolol-based treatment and 1642 (38.1%) of 4305 assigned to amlodipine-based treatment. 1768 of the 4605 patients in the LLA died, including 903 (39.5%) of 2288 assigned placebo and 865 (37.3%) of 2317 assigned atorvastatin. Of all deaths, 1210 (36.9%) were from cardiovascular-related causes. Among patients in the BPLA, there was no

overall difference in all-cause mortality between treatments (adjusted hazard ratio [HR] 0.90, 95% CI 0.81-1.01, p=0.0776]), although significantly fewer deaths from stroke (adjusted HR 0.71, 0.53-0.97, p=0.0305) occurred in the amlodipine-based treatment group than in the atenolol-based treatment group. There was no interaction between treatment allocation in the BPLA and in the LLA. However, in the 3975 patients in the non-LLA group, there were fewer cardiovascular deaths (adjusted HR 0.79, 0.67-0.93, p=0.0046) among those assigned to amlodipine-based treatment compared with atenolol-based treatment (p=0.022 for the test for interaction between the two blood pressure treatments and allocation to LLA or not). In the LLA, significantly fewer cardiovascular deaths (HR 0.85, 0.72-0.99, p=0.0395) occurred among patients assigned to statin than among those assigned placebo. INTERPRETATION: Our findings show the long-term beneficial effects on mortality of antihypertensive treatment with a calcium channel blocker-based treatment regimen and lipid-lowering with a statin: patients on amlodipine-based treatment had fewer stroke deaths and patients on atorvastatin had fewer cardiovascular deaths more than 10 years after trial closure. Overall, the ASCOT Legacy study supports the notion that interventions for blood pressure and cholesterol are associated with long-term benefits on cardiovascular outcomes. FUNDING: Pfizer.

[40] *Chang WH, Ting HC, Chen WW et al.* **Omega-3 and omega-6 fatty acid differentially impact cardiolipin remodeling in activated macrophage**. Lipids in health and disease 2018; 17:201.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30153842
ABSTRACT
BACKGROUND: The macrophage plays an important role in innate immunity to induce immune responses. Lipid replacement therapy has been shown to change the lipid compositions of mitochondria and potentially becomes an alternative to reduce the inflammatory response. METHODS: We examined the effects of omega-6 arachidonic acid (AA), omega-3 eicosapentaenoic acid (EPA), and omega-3 docosahexaenoic acid (DHA) supplementation on the activated the macrophage cell line RAW264.7 via KdO2-lipid A (KLA). The mitochondrial cardiolipin (CL) and monolysocardiolipin (MLCL) were analyzed by LC-MS. RESULTS: After macrophage activation by KLA, CL shifted to saturated species, but did not affect the quantity of CL. Inhibition of delta 6 desaturase also resulted in the same trend of CL species shift. We further examined the changes in CL and MLCL species induced by polyunsaturated fatty acid supplementation during inflammation. After supplementation of AA, EPA and DHA, the MLCL/CL ratio increased significantly in all treatments. The percentages of the long-chain species highly elevated and those of short-chain species reduced in both CL and MLCL. CONCLUSIONS: Comparisons of AA, EPA and DHA supplementation revealed that the 20-carbon EPA (20:5) and AA (20:4) triggered higher incorporation and CL remodeling efficiency than 22-carbon DHA (22:6). EPA supplementation not only efficiently extended the chain length of CL but also increased the unsaturation of CL.

[41] *Martinez-Jimenez C, Cruz-Angeles J, Videa M, Martinez LM*. **Co-Amorphous Simvastatin-Nifedipine with Enhanced Solubility for Possible Use in Combination Therapy of Hypertension and Hypercholesterolemia**. Molecules (Basel, Switzerland) 2018; 23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30154310
ABSTRACT

The high index of simultaneous incidence of hypertension and hypercholesterolemia in the population of many countries demands the preparation of more efficient drugs. Therefore, there is a significant area of opportunity to provide as many alternatives as possible to treat these illnesses. Taking advantage of the solubility enhancement that can be achieved when an active pharmaceutical ingredient (API) is obtained and stabilized in its amorphous state, in the present work, new drug-drug co-amorphous formulations (Simvastatin SIM- Nifedipine NIF) with enhanced solubility and stability were prepared and characterized. Results show that the co-amorphous system (molar ratio 1:1) is more soluble than the pure commercial APIs studied separately. Aqueous dissolution profiles showed increments of solubility of 3.7 and 1.7 times for SIM and NIF, correspondingly, in the co-amorphous system. The new co-amorphous formulations, monitored in time, (molar fractions 0.3, 0.5 and 0.7 of SIM) remained stable in the amorphous state for more than one year when stored at room temperature and did not show any signs of crystallization when re-heating. Inspection on the remainder of a sample after six hours of dissolution showed no recrystallization, confirming the stability of co-amorphous system. The enhanced solubility of the co-amorphous formulations makes them promising for simultaneously targeting of hypertension and hypercholesterolemia through combination therapy.

[42] *Kobayashi E, Nishijima C, Sato Y et al.* **The Prevalence of Dietary Supplement Use Among Elementary, Junior High, and High School Students: A Nationwide Survey in Japan**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30154316
ABSTRACT
The prevalence of dietary supplement use, such as vitamins, minerals, or fish oil, has increased among children in Japan; however, whether children are using dietary supplements appropriately remains unclear. This study aimed to determine dietary supplement use among children. In August 2017, a nationwide internet preliminary survey of 265,629 mothers aged from 25 to 59 years old was undertaken. Of these, 19,041 mothers of children attending either elementary school, junior high school, or high school were selected. Among them, 16.4% were currently providing their children with dietary supplements and 5.2% had previously given dietary supplements to their children. The prevalence of dietary supplement use was higher in boys than in girls, and the prevalence increased according to their grade. A total of 2439 participants were eligible to undertake a targeted survey on dietary supplement use. Dietary supplements were being taken to maintain health, supplement nutrients, and enhance growth in both boys and girls, and many children (37.5%) were provided with vitamin and mineral supplements. Mothers mainly obtained information concerning dietary supplements via the internet, and supplements were purchased in drug stores or via the internet. The prevalence of dietary supplement use in mothers was 65.4% and may be associated with the prevalence rates in children. Some mothers reported adverse events (3.6%) in their children, such as stomachache, diarrhea, nausea and vomiting, and constipation. The cause-and-effect relationships for adverse events were not clear, but some children were given products for adults. Children are more influenced by dietary supplements compared to adults. To prevent adverse events due to inappropriate use, parental education concerning dietary supplements is essential.

Literature update week 35 (2018)

[43] *Haimeur A, Meskini N, Mimouni V et al.* **A comparative study on the effect of argan oil versus fish oil on risk factors for cardio-vascular disease in high-fat-fed rats**. Nutrition 2018; 57:32-39.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30153577
ABSTRACT
OBJECTIVES: The aim of this study was to investigate the effects of two different sources of polyunsaturated fatty acid-fish oil (FO) and argan oil (AO)-on some risk factors for cardiovascular disease, such as platelet aggregation, dyslipidemia, and oxidative stress. METHODS: To explore this, four groups of six male rats were fed with different diets: The first group received a standard diet (control); the second group received a high-fat diet; the third was fed with a high-fat diet supplemented with 5% FO, and the last group received a high-fat diet supplemented with 5% AO. RESULTS: After 8 wk of the diet, AO showed a decrease in plasma lipids similar to that of FO. However, unlike FO, AO had no significant effect on hepatic lipid levels. On the other hand, supplementation with AO and FO similarly reduced platelet hyperactivity induced by high-fat diet. Concerning the results of oxidative stress, AO showed an antioxidant effect in the tissues and platelets greater than that observed in the high-fat FO group. CONCLUSIONS: For rats, the consumption of FO prevented the development of adiposity, restored insulin sensitivity, decreased plasma and liver lipid levels, and also prevented the prothrombotic effect. Intake of AO as a food supplement did not affect adiposity or liver lipid levels but decreased plasma lipid levels and improved oxidative status and platelet activity. FO and, to a lesser degree, AO thus represent promising nutritional tools in the prevention of cardiovascular disease.

[44] *Fouhse J, Yang K, Li J et al.* **Establishing a model for childhood obesity in adolescent pigs**. Obesity science & practice 2018; 4:396-406.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30151234
ABSTRACT
Objective: Rising worldwide prevalence of obesity and metabolic diseases in children has accentuated the importance of developing prevention and management strategies. The objective of this study was to establish a model for childhood obesity using high-fat feeding of adolescent pigs, as pigs have a longer developmental period and are physiologically more similar to humans than rodents. Methods: Crossbred pigs were fed a high-fat diet (HFD) or low-fat diet (n = 6/treatment) from postnatal day 49 to 84. On postnatal day 84, an oral glucose tolerance test was performed, jugular blood sampled to determine lipopolysaccharide levels and plasma lipids, intestinal digesta collected to characterize microbial and metabolite composition and back fat and intestinal tissue assayed for gene expression. Results: Five-week HFD increased weight gain and back fat thickness, caused dyslipidaemia and impaired glucose tolerance and increased expression of genes in back fat suggesting inflammation. HFD pigs had distinct proximal colon microbiota with 48% reduction ($P < 0.05$) in Bacteroidetes and increased expression of pro-inflammatory genes interleukin-18 and tumour necrosis factor in ileum ($P < 0.05$). Conclusions: These findings indicate that adolescent pigs should be considered a suitable model for childhood obesity, because short-term HFD feeding is sufficient to induce obesity and glucose intolerance, recapitulating disease characteristics in adolescent pigs.

[45] *Masafi S, Saadat SH, Tehranchi K et al.* **Effect of Stress, Depression and Type D Personality on Immune System in the Incidence of Coronary Artery Disease**. Open access Macedonian journal of medical sciences 2018; 6:1533-1544.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30159090
ABSTRACT
BACKGROUND: Psychoneuroimmunology (PNI) is the study of the interaction between psychological processes and the nervous and immune systems of the human body. The impact of psychological factors on the immune system and the role of this system in Coronary Artery Disease (CAD) are confirmed. Coronary Heart Disease (CHD) is arisen due to the failure of blood and oxygen to the heart tissues. AIM: The present study aimed to describe psychoneuroimmunological processes which contribute to CAD and CHD progression. METHOD: Such psychological risk factors like stress, depression and type D personality were investigated here. Psychoneuroimmunological pathways of all three mentioned risk factors were described for CAD. RESULTS: The studies review indicated that stress could be accompanied with myocardial ischemia and help to rupture. The depression involves in the transfer of stable atherosclerotic plaque to unstable, and type D personality is effective in the initial stages of a CAD. CONCLUSION: As more information on cardiovascular immunity becomes available, this will provide a better understanding and thus act as the foundation for the potential development of new treatment strategies for treatment of cardiovascular disorders.

[46] *Myasoedova VA, Ravani AL, Frigerio B et al.* **Novel pharmacological targets for calcific aortic valve disease: Prevention and treatments**. Pharmacological research : the official journal of the Italian Pharmacological Society 2018; 136:74-82.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30149054
ABSTRACT
Calcific aortic valve disease (CAVD) is the most common valvular disorder in the elderly, with the incidence of 3% in general population of Western countries. The initial phase of CAVD is characterized by leaflet thickening and possible spotty calcification (i.e. aortic valve sclerosis (AVSc)), while advanced stages have leaflets structure degeneration (i.e. aortic valve stenosis (AS)). The pathological cellular and molecular mechanisms, involved in CAVD, are extracellular matrix degradation, aberrant matrix deposition, fibrosis, mineralization, inflammation, lipid accumulation, and neo-angiogenesis. CAVD clinical risk shares considerable overlap with those of atherosclerosis and they include hypertension, smoking habits, and hyperlipidemia. Unfortunately, surgical aortic valve replacement and transcatheter aortic valve implantation are the only available treatments when the disease become severe and symptoms occur. Indeed, no approved pharmacological approach is available for CAVD patients. In this review, we describe the current literature evidence on possible future therapeutic targets for this debilitating and fatal disease such as PCSK9, P2Y2 receptor, cadherin 11, and DDP-4.

[47] *Lacy M, Atzler D, Liu R et al.* **Interactions between dyslipidemia and the immune system and their relevance as putative therapeutic targets in atherosclerosis**. Pharmacology & therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30149100

ABSTRACT
Cardiovascular disease (CVD) continues to be a leading cause of death worldwide with atherosclerosis being the major underlying pathology. The interplay between lipids and immune cells is believed to be a driving force in the chronic inflammation of the arterial wall during atherogenesis. Atherosclerosis is initiated as lipid particles accumulate and become trapped in vessel walls. The subsequent immune response, involving both adaptive and immune cells, progresses plaque development, which may be exacerbated under dyslipidemic conditions. Broad evidence, especially from animal models, clearly demonstrates the effect of lipids on immune cells from their development in the bone marrow to their phenotypic switching in circulation. Interestingly, recent research has also shown a long-lasting epigenetic signature from lipids on immune cells. Traditionally, cardiovascular therapies have approached atherosclerosis through lipid-lowering medications because, until recently, anti-inflammatory therapies have been largely unsuccessful in clinical trials. However, the recent Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) provided pivotal support of the inflammatory hypothesis of atherosclerosis in man spurring on anti-inflammatory strategies to treat atherosclerosis. In this review, we describe the interactions between lipids and immune cells along with their specific outcomes as well as discuss their future perspective as potential cardiovascular targets.

[48] *Feng Q, Wei WQ, Chung CP et al.* **Relationship between very low low-density lipoprotein cholesterol concentrations not due to statin therapy and risk of type 2 diabetes: A US-based cross-sectional observational study using electronic health records**. PLoS medicine 2018; 15:e1002642.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30153257
ABSTRACT
BACKGROUND: Observations from statin clinical trials and from Mendelian randomization studies suggest that low low-density lipoprotein cholesterol (LDL-C) concentrations may be associated with increased risk of type 2 diabetes mellitus (T2DM). Despite the findings from statin clinical trials and genetic studies, there is little direct evidence implicating low LDL-C concentrations in increased risk of T2DM. METHODS AND FINDINGS: We used de-identified electronic health records (EHRs) at Vanderbilt University Medical Center to compare the risk of T2DM in a cross-sectional study among individuals with very low (</=60 mg/dl, N = 8,943) and normal (90-130 mg/dl, N = 71,343) LDL-C levels calculated using the Friedewald formula. LDL-C levels associated with statin use, hospitalization, or a serum albumin level < 3 g/dl were excluded. We used a 2-phase approach: in 1/3 of the sample (discovery) we used T2DM phenome-wide association study codes (phecodes) to identify cases and controls, and in the remaining 2/3 (validation) we identified T2DM cases and controls using a validated algorithm. The analysis plan for the validation phase was constructed at the time of the design of that component of the study. The prevalence of T2DM in the very low and normal LDL-C groups was compared using logistic regression with adjustment for age, race, sex, body mass index (BMI), high-density lipoprotein cholesterol, triglycerides, and duration of care. Secondary analyses included prespecified stratification by sex, race, BMI, and LDL-C level. In the discovery cohort, phecodes related to T2DM were significantly more frequent in the very low LDL-C group. In the validation cohort (N = 33,039 after applying the T2DM algorithm to identify cases and controls),

the risk of T2DM was increased in the very low compared to normal LDL-C group (odds ratio [OR] 2.06, 95% CI 1.80-2.37; P < 2 x 10-16). The findings remained significant in sensitivity analyses. The association between low LDL-C levels and T2DM was significant in males (OR 2.43, 95% CI 2.00-2.95; P < 2 x 10-16) and females (OR 1.74, 95% CI 1.42-2.12; P = 6.88 x 10-8); in normal weight (OR 2.18, 95% CI 1.59-2.98; P = 1.1x 10-6), overweight (OR 2.17, 95% CI 1.65-2.83; P = 1.73x 10-8), and obese (OR 2.00, 95% CI 1.65-2.41; P = 8 x 10-13) categories; and in individuals with LDL-C < 40 mg/dl (OR 2.31, 95% CI 1.71-3.10; P = 3.01x 10-8) and LDL-C 40-60 mg/dl (OR 1.99, 95% CI 1.71-2.32; P < 2.0x 10-16). The association was significant in individuals of European ancestry (OR 2.67, 95% CI 2.25-3.17; P < 2 x 10-16) but not in those of African ancestry (OR 1.09, 95% CI 0.81-1.46; P = 0.56). A limitation was that we only compared groups with very low and normal LDL-C levels; also, since this was not an inception cohort, we cannot exclude the possibility of reverse causation. CONCLUSIONS: Very low LDL-C concentrations occurring in the absence of statin treatment were significantly associated with T2DM risk in a large EHR population; this increased risk was present in both sexes and all BMI categories, and in individuals of European ancestry but not of African ancestry. Longitudinal cohort studies to assess the relationship between very low LDL-C levels not associated with lipid-lowering therapy and risk of developing T2DM will be important.

[49] *Khiaosa-Ard R, Zebeli Q*. **Diet-induced inflammation: From gut to metabolic organs and the consequences for the health and longevity of ruminants**. Research in veterinary science 2018; 120:17-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30170184
ABSTRACT
Dietary shifts play an important role in decreased longevity in ruminant livestock. Ruminants evolved as cellulose fermenters adapt to fiber-rich diets. Instead, high-producing ruminants nowadays are commonly fed with grain-based diets to increase intake and productivity. Such diets, however, trade off the health of the animal. One negative aspect of such feeding is related to elevated levels of bacterial endotoxin (lipopolysaccharide, LPS) in the gut lumen and the likelihood of LPS translocation across the gut causing systemic and local (tissue) inflammation with consequences for production and longevity. However, the view for toxicity of gut LPS is oversimplified, overlooking the physicochemistry of LPS and the translocation route that determine the fate and immune reactive activity of LPS within the host. The barrier and defensive mechanisms of rumen morphology and intestinal mucus are understated. LPS cross the epithelial barrier paracellularly through impaired tight-junction and transcellularly through receptor-mediated transcytosis and the lipoprotein pathway transporting lipids. The lipoprotein pathway delivers LPS to the circulation before reaching the liver for detoxification and is believed to be the major natural route of gut LPS translocation at least in non-ruminants. Ruminant research has focused on endotoxemia and systemic inflammation but with little success and conflicting results, not to mention that low-grade inflammation is not easy to detect. In fact, LPS in the circulation must be effectively removed to avoid an adverse effect of rising level of LPS in the circulation. Circulating LPS could be transported towards target tissues in various organs, leading to local inflammation and altered metabolic activity in the tissues. Therefore, it might be feasible to capture tissue inflammation, especially in the metabolic organs including the liver, adipose tissues, and mammary gland. The present review gathers

research updates and presents a comprehensive view of the physicochemical properties and bioactivity of LPS and the possibilities of translocation as well as other possible fate of LPS at each gut site in ruminants. Furthermore, we describe the involvement of three key metabolic organs including the liver, adipose tissue, and mammary gland in response to gut-derived LPS that lead to inflammation in the tissue posing consequences for the health and longevity of dairy cows.

[50] *Lekuona I*. **PCSK9 Inhibitors: From Innovation to Sustainable Clinical Application**. Revista espanola de cardiologia (English ed.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30150140
ABSTRACT

[51] *Vieira Barbosa J, Vionnet J, Sciarra A et al.* **[Primary biliary cholangitis : an update]**. Revue medicale suisse 2018; 14:1489-1494.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30156781
ABSTRACT
Primary biliary cholangitis (PBC) is an autoimmune liver disease which affects primarily women and is characterized by progressive destruction of small intrahepatic bile ducts. Most common symptoms are fatigue and pruritus. Diagnostic hallmarks are cholestasis and positive antimitochondrial antibodies. The first-line therapy is ursodeoxycholic acid (UDCA), with excellent results when started at an early stage. Nevertheless, 3040 % of patients do not achieve a complete biochemical response with UDCA. In these cases, the adjunction of obeticholic acid can be discussed. Fibrates appear to be a promising alternative. Liver transplantation yields excellent outcomes in advanced cases.

[52] *Li N, Wen C, Huang P et al.* **Atorvastatin reduces alcohol-induced endoplasmic reticulum stress in AC16 cardiomyocytes**. Scandinavian cardiovascular journal : SCJ 2018:1-20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30160187
ABSTRACT
OBJECTIVES: To investigate the effects of atorvastatin on the ultrastructure and lipid metabolism of AC16 cardiomyocytes in response to alcohol-induced endoplasmic reticulum stress (ERS). DESIGN: The expression of the ERS-related factor GRP78 in the established ERS model was determined by western blotting. Alcohol-exposed cardiomyocytes were treated with various concentrations of atorvastatin, and GRP78 expression was measured. Cardiomyocyte ultrastructure was observed and SREBP-1c and triglyceride (TG) levels were evaluated. RESULTS: Exposure to ethanol for 0, 12, 24, and 48 h significantly affected GRP78 expression (0.19 +/- 0.02, 0.27 +/- 0.03, 0.39 +/- 0.01, and 0.64 +/- 0.02, respectively). GRP78 expression in the 1, 10, and 100 mumol L(-1) atorvastatin-treated groups was 0.50 +/- 0.04, 0.38 +/- 0.03, and 0.24 +/- 0.01, respectively, and significantly different from control group expression (0.19 +/- 0.02); the expression in the alcohol group was 0.64 +/- 0.02. Alcohol-treated AC16 cells had significantly larger and fewer mitochondria and disorganized cristae, often replaced by vacuoles. These aberrations decreased with increasing atorvastatin concentrations. SREBP-1c expression also differed significantly among all atorvastatin-treated and control groups (0.47 +/- 0.04, 0.39 +/- 0.03, and 0.31 +/- 0.02; normal 0.25 +/- 0.02; alcohol 0.56 +/- 0.03). TG

expression differed significantly between the 10 and 100 mumol L(-1) groups (26.84 +/- 1.63, 23.11 +/- 2.05) and the alcohol group (36.35 +/- 2.41). CONCLUSIONS: Atorvastatin inhibited the expression of the ERS-related factor GRP78 in response to alcohol exposure, improved cell morphology, and enhanced lipid metabolism in a cellular model of alcoholic cardiomyopathy.

[53] *Santiago P, Scheinberg AR, Levy C*. **Cholestatic liver diseases: new targets, new therapies**. Therapeutic advances in gastroenterology 2018; 11:1756284818787400.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30159035
ABSTRACT
Cholestatic liver diseases result from gradual destruction of bile ducts, accumulation of bile acids and self-perpetuation of the inflammatory process leading to damage to cholangiocytes and hepatocytes. If left untreated, cholestasis will lead to fibrosis, biliary cirrhosis, and ultimately end-stage liver disease. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are the two most common chronic cholestatic liver diseases affecting adults, and their etiologies remain puzzling. While treatment with ursodeoxycholic acid (UDCA) has significantly improved outcomes and prolonged transplant-free survival for patients with PBC, treatment options for UDCA nonresponders remain limited. Furthermore, there is no available medical therapy for PSC. With recent advances in molecular biochemistry specifically related to bile acid regulation and understanding of immunologic pathways, novel pharmacologic treatments have emerged. In this review, we discuss the standard of care and emphasize the various emerging treatments for PBC and PSC.