Literature update week 09 (2018)

[1] *Oliveira JB, Soares A, Sposito AC*. **Inflammatory Response During Myocardial Infarction**. Advances in clinical chemistry 2018; 84:39-79.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29478516
ABSTRACT
The occlusion of a coronary artery by a thrombus generated on a ruptured atherosclerotic plaque has been pursued in the last decades as a determining event for the clinical outcome after myocardial infarction (MI). Yet, MI causes a cell death wave front, which triggers an inflammatory response to clear cellular debris, and which in excess can double the myocardial lesion and influence the clinical prognosis in the short and long term. Accordingly, proper, timely regulated inflammatory response has now been considered a second pivotal player in cardiac recovery after MI justifying the search for pharmacological strategies to modulate inflammatory effectors. This chapter reviews the key events and the main effectors of inflammation after myocardial ischemic insult, as well as the contribution of this phenomenon to the progression of atherosclerosis.

[2] *Bird RP*. **The Emerging Role of Vitamin B6 in Inflammation and Carcinogenesis**. Advances in food and nutrition research 2018; 83:151-194.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29477221
ABSTRACT
Vitamin B6 serves as a coenzyme catalyzing more than 150 enzymes regulating metabolism and synthesis of proteins, carbohydrates, lipids, heme, and important bioactive metabolites. For several years vitamin B6 and its vitamers (B6) were recognized as antioxidant and antiinflammatory and in modulating immunity and gene expression. During the last 10 years, there were growing reports implicating B6 in inflammation and inflammation-related chronic illnesses including cancer. It is unclear if the deficiency of B6 or additional intake of B6, above the current requirement, should be the focus. Whether the current recommended daily intake for B6 is adequate should be revisited, since B6 is important to human health beyond its role as a coenzyme and its status is affected by many factors including but not limited to age, obesity, and inflammation associated with chronic illnesses. A link between inflammation B6 status and carcinogenesis is not yet completely understood. B6-mediated synthesis of H2S, a gasotransmitter, and taurine in health and disease, especially in maintaining mitochondrial integrity and biogenesis and inflammation, remains an important area to be explored. Recent developments in the molecular role of B6 and its direct interaction with inflammasomes, and nuclear receptor corepressor and coactivator, receptor-interacting protein 140, provide a strong impetus to further explore the multifaceted role of B6 in carcinogenesis and human health.

[3] *Kirkland JB, Meyer-Ficca ML*. **Niacin**. Advances in food and nutrition research 2018; 83:83-149.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29477227
ABSTRACT
Nicotinic acid and nicotinamide, collectively referred to as niacin, are nutritional precursors of the bioactive molecules nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). NAD and NADP are important cofactors for most cellular redox

reactions, and as such are essential to maintain cellular metabolism and respiration. NAD also serves as a cosubstrate for a large number of ADP-ribosylation enzymes with varied functions. Among the NAD-consuming enzymes identified to date are important genetic and epigenetic regulators, e.g., poly(ADP-ribose)polymerases and sirtuins. There is rapidly growing knowledge of the close connection between dietary niacin intake, NAD(P) availability, and the activity of NAD(P)-dependent epigenetic regulator enzymes. It points to an exciting role of dietary niacin intake as a central regulator of physiological processes, e.g., maintenance of genetic stability, and of epigenetic control mechanisms modulating metabolism and aging. Insight into the role of niacin and various NAD-related diseases ranging from cancer, aging, and metabolic diseases to cardiovascular problems has shifted our view of niacin as a vitamin to current views that explore its potential as a therapeutic.

[4] *Yamada Y, Terauchi Y, Watada H et al.* **Efficacy and Safety of GPR119 Agonist DS-8500a in Japanese Patients with Type 2 Diabetes: a Randomized, Double-Blind, Placebo-Controlled, 12-Week Study**. Adv Ther 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29488152
ABSTRACT
INTRODUCTION: G protein-coupled receptor 119 (GPR119) is a promising target for the treatment of type 2 diabetes mellitus (T2DM), as both insulin and glucagon-like peptide-1 secretion can be promoted with a single drug. We compared the efficacy and safety of the GPR119 agonist DS-8500a with placebo and sitagliptin 50 mg in Japanese patients with T2DM. METHODS: This randomized, double-blind, parallel-group comparison study was conducted in Japan (trial registration NCT02628392, JapicCTI-153068). Eligible patients aged >/= 20 years with T2DM and hemoglobin A1c (HbA1c) >/= 7.0% and < 10.0% were randomized to receive placebo, DS-8500a (25, 50, or 75 mg), or sitagliptin 50 mg once daily for 12 weeks. The primary efficacy endpoint was change in HbA1c from baseline to week 12. Secondary endpoints included change in fasting plasma glucose (FPG), glucose AUC0-3h during a meal tolerance test, 2-hour postprandial glucose (2hr-PPG), and changes in lipid parameters (total, low-density lipoprotein (LDL-) and high-density lipoprotein (HDL-) cholesterol, and triglycerides) at week 12. Safety endpoints included adverse events, hypoglycemia, and clinical/laboratory variables. RESULTS: DS-8500a demonstrated dose-dependent HbA1c lowering compared with placebo at week 12: change from baseline - 0.23% (p = 0.0173), - 0.37% (p = 0.0001), and - 0.44% (p < 0.0001) in the 25-mg, 50-mg, and 75-mg groups, respectively. At 50- and 75-mg doses, DS-8500a significantly lowered FPG, glucose AUC0-3h, and 2hr-PPG compared with placebo. The glucose-lowering effect was maintained up to 12 weeks. DS-8500a did not lower any of the above parameters to a greater extent than sitagliptin. Compared with placebo and sitagliptin, DS-8500a 50 and 75 mg significantly reduced total cholesterol, LDL-cholesterol, and triglycerides, and significantly increased HDL-cholesterol. All DS-8500a doses were well tolerated. Two cases of clinically relevant drug-related hypoglycemia occurred in the DS-8500a 50-mg group. CONCLUSION: DS-8500a was well tolerated and demonstrated significant glucose-lowering effects and favorable changes in lipid profiles up to 12 weeks in Japanese patients with T2DM. FUNDING: Daiichi Sankyo Co. Ltd.

[5] *Gregg LP, Hedayati SS*. **Management of Traditional Cardiovascular Risk Factors in CKD: What Are the Data?** American journal of kidney diseases : the official journal of the National Kidney Foundation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29478869
ABSTRACT
Patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) are 10 times more likely to die of cardiovascular (CV) diseases than the general population, and dialysis-dependent patients are at even higher risk. Although traditional CV risk factors are highly prevalent in individuals with CKD, these patients were often excluded from studies targeting modification of these risks. Although treatment of hypertension is beneficial in CKD, the best target blood pressure has not been established. Trial data showed that renin-angiotensin-aldosterone blockade may prevent CV events in patients with CKD. The risks of aspirin may equal the benefits in NDD-CKD samples, and there are no trials testing aspirin in dialysis-dependent patients. Lipid-lowering therapy improves CV outcomes in NDD-CKD, but not in dialysis-dependent patients. Strict glycemic control prevents CV events in nonalbuminuric individuals, but showed no benefit in those with baseline albuminuria with albumin excretion > 300mg/g, and there are no data in dialysis-dependent patients. Data for lifestyle modifications, such as weight loss, physical activity, and smoking cessation, are mostly observational and extrapolated from non-CKD samples. This comprehensive review summarizes the best existing evidence and current clinical guidelines for modification of traditional risk factors for the prevention of CV events in patients with CKD and identifies knowledge gaps.

[6] *Melnik MV, Afonicheva, II, Beloborodova AV*. **[THE ROLE PLEIOTROPIC EFFECTS OF CALCIUM CHANNEL BLOCKER LERCANIDIPINE IN PERIOPERATIVE THERAPY OF ARTERIAL HYPERTENSION.]**. Anesteziologiia i reanimatologiia 2016; 61:395-398.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29489111
ABSTRACT
This review presents the data of assessing antihypertensive efficacy and tolerability vasoselective high-lipophilic the 3d generations calcium channel blocker lercanidpine. The inhibition of the calcium ions flow through the membranes of smooth muscle cells of blood vessels causes peripheral, cerebral, renal and coronary vasodilation decreasing total peripheral vascular resistance and, consequently, blood pressure (BP) lowering and improve regional circulation. During reception of lercanidipine the level of norepinephrine remains the same even when using high doses of the drug. Negative inotropic effect does not occur therefore, lercanidipine can be used in the treatment of myocardial ischemia. Renal protection properties slow down the development and progression ofchronic renalfailure (CRF). The drug can be successfully used in patients with arterial hypertension, chronic renalfailure, diabetic and non-diabetic nephropathy. Lercanidpine also may be effectively used in the treatment of hypertension with associated clinical conditions: bronchial asthma, chronic obstructive pulmonary disease, bradiarrythmias, atrioventricular blockade 2-3 degree, sinus node dysfunction, peripheral arteries deseases with symptoms of the extremities ischemia, sleep disturbance, depression, dystonia, asthenic and cephalgic syndme in the frame of the cerebrovascular insufficiency manifestations. Therapy with lercanidpine, in addition to lowering blood pressure, can help to nephroprotection, neuroprotection, antianginal effect, the

regression of left ventricular hypertrophy, improvement of lipid metabolism and glucose tolerance. With over 30 years experience in the application and modification of the molecular structure, slow the onset of action and superior long-lasting effect reception of letranidipine well-tolerated and provides a high adherence ofpatients to the treatment of hypertension.

[7] *Fraz S, Lee AH, Wilson JY*. **Gemfibrozil and carbamazepine decrease steroid production in zebrafish testes (Danio rerio)**. Aquatic toxicology (Amsterdam, Netherlands) 2018; 198:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29494825
ABSTRACT
Gemfibrozil (GEM) and carbamazepine (CBZ) are two environmentally relevant pharmaceuticals and chronic exposure of fish to these compounds has decreased androgen levels and fish reproduction in laboratory studies. The main focus of this study was to examine the effects of GEM and CBZ on testicular steroid production, using zebrafish as a model species. Chronic water borne exposures of adult zebrafish to 10mug/L of GEM and CBZ were conducted and the dosing was confirmed by chemical analysis of water as 17.5+/-1.78 and 11.2+/-1.08mug/L respectively. A 67day exposure led to reduced reproductive output and lowered whole body, plasma, and testicular 11-ketotestosterone (11-KT). Testicular production of 11-KT was examined post exposure (42days) using ex vivo cultures to determine basal and stimulated steroid production. The goal was to ascertain the step impaired in the steroidogenic pathway by each compound. Ex vivo 11-KT production in testes from males chronically exposed to GEM and CBZ was lower than that from unexposed males. Although hCG, 25-OH cholesterol, and pregnenolone stimulation increased 11-KT production in all treatment groups over basal levels, hCG stimulated 11-KT production remained significantly less in testes from exposed males compared to controls. 25-OH cholesterol and pregnenolone stimulated 11-KT production was similar between GEM and control groups but the CBZ group had lower 11-KT production than controls with both stimulants. We therefore propose that chronic GEM and CBZ exposure can reduce production of 11-KT in testes through direct effects independent of mediation through HPG axis. The biochemical processes for steroid production appear un-impacted by GEM exposure; while CBZ exposure may influence steroidogenic enzyme expression or function.

[8] *Yamada S, Senokuchi T, Matsumura T et al.* **Inhibition of Local Macrophage Growth Ameliorates Focal Inflammation and Suppresses Atherosclerosis**. Arteriosclerosis, thrombosis, and vascular biology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29496659
ABSTRACT
OBJECTIVE: Macrophages play a central role in various stages of atherosclerotic plaque formation and progression. The local macrophages reportedly proliferate during atherosclerosis, but the pathophysiological significance of macrophage proliferation in this context remains unclear. Here, we investigated the involvement of local macrophage proliferation during atherosclerosis formation and progression using transgenic mice, in which macrophage proliferation was specifically suppressed. APPROACH AND RESULTS: Inhibition of macrophage proliferation was achieved by inducing the expression of cyclin-dependent kinase inhibitor 1B, also known as p27(kip) (cyclin-dependent kinase inhibitor 1B), under the regulation of a scavenger receptor promoter/enhancer. The macrophage-specific human

p27(kip) Tg mice were subsequently crossed with apolipoprotein E-deficient mice for the atherosclerotic plaque study. Results showed that a reduced number of local macrophages resulted in marked suppression of atherosclerotic plaque formation and inflammatory response in the plaque. Moreover, fewer local macrophages in macrophage-specific human p27(kip) Tg mice helped stabilize the plaque, as evidenced by a reduced necrotic core area, increased collagenous extracellular matrix, and thickened fibrous cap. CONCLUSIONS: These results provide direct evidence of the involvement of local macrophage proliferation in formation and progression of atherosclerotic plaques and plaque stability. Thus, control of macrophage proliferation might represent a therapeutic target for treating atherosclerotic diseases.

[9] *Martinez TA, Zeybek ND, Muftuoglu S*. **Evaluation of the Cytotoxic and Autophagic Effects of Atorvastatin on Mcf-7 Breast Cancer Cells**. Balkan medical journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29485098
ABSTRACT
BACKGROUND: Recently, cytotoxic effects of statins on breast cancer cells have been reported. However, the mechanism of anti-proliferative effects is currently unknown. Autophagy is a non-apoptotic programmed cell death, which is characterized by degradation of cytoplasmic components and with a role in cancer pathogenesis. AIMS: To investigate the anti-proliferative effects of atorvastatin was on MCF-7 human breast adenocarcinoma cells in aspect of autophagy and apoptosis. STUDY DESIGN: Cell culture study. METHODS: Cell viability was analyzed using WST-1 cell proliferation assay. Apoptosis was determined by TUNEL method, whereas autophagy was assessed by Beclin-1 and LC3B immunofluorescence staining. Ultrastructural analysis of cells was performed by electron microscopy. RESULTS: Atorvastatin reduced MCF-7 cell proliferation in a dose- and time-dependent manner inducing TUNEL, Beclin-1, and LC3B positive cells. Moreover, ultrastructural analysis showed apoptotic, autophagic and necrotic morphological changes in treatment groups. Statistically significant increase in apoptotic index was detected with increased concentrations of atorvastatin at 24h and 48h ($p<0.05$). CONCLUSION: The anti-proliferative effects of atorvastatin on breast cancer cells is mediated by induction of apoptosis and autophagy which shows statins as a potential treatment option for breast cancer.

[10] *Chen Y, Chen L, Zhang H et al.* **Interaction of Sulfonylureas with Liver Uptake Transporters OATP1B1 and OATP1B3**. Basic & clinical pharmacology & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498478
ABSTRACT
Sulfonylureas (SUs) such as glibenclamide, gliclazide, glimepiride, glipizide and gliquidone are one of the first oral medicines available for the treatment of type 2 diabetes, and are widely used for the treatment of hyperglycaemia. The hepatic transporters, organic anion transporting polypeptide 1B1 (OATP1B1) and organic anion transporting polypeptide 1B3 (OATP1B3), play an important role in the disposition of a variety of drugs by mediating their uptake from blood into hepatocytes. Drug-drug interactions mediated by OATP1B1/1B3 may result in the hepatic transporting change for drug substrates. The inhibitory effects of glibenclamide and glimepiride on sulfobromophthalein (BSP) uptake have been previously studied, and glibenclamide has been reported as the substrate of OATP1B3, but it remains unclear whether other SUs such as

gliclazide, glipizide and gliquidone are substrates of OATP1B1 and OATP1B3. Here, we investigated the relationship between the five most commonly applied SUs (glibenclamide, gliclazide, glimepiride, glipizide, gliquidone) and OATP1B1 and OATP1B3. We performed uptake and inhibition assays in HEK293T cells stably expressing OATP1B1 or OATP1B3, respectively, and established a liquid chromatography mass spectrometry (LC-MS) method for the simultaneous measurement of five SUs. We demonstrated that gliclazide and glimepiride are substrates of OATP1B1 and glibenclamide and glipizide are substrates of OATP1B3. We also confirmed the interaction between these SUs and rosuvastatin. No transporting was observed for gliquidone, suggesting that it is not a substrate of either transporter.

[11] *Royo J, Villain N, Champeval D et al.* **Effects of n-3 polyunsaturated fatty acid supplementation on cognitive functions, electrocortical activity and neurogenesis in a non-human primate, the grey mouse lemur (Microcebus murinus)**. Behavioural brain research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29486268
ABSTRACT
Among environmental factors that may affect on brain function, some nutrients and particularly n-3 polyunsaturated fatty acids (n-3 PUFA) are required for optimal brain development. Their effects on cognitive functions, however, are still unclear, and studies in humans and rodents have yielded contradictory results. We used a non-human primate model, the grey mouse lemur, phylogenetically close to human. The aim of this study was to demonstrate the impact of n-3 PUFA supplementation on cognitive functions, neuronal activity and neurogenesis. Two groups of animals whose diet was supplemented with either fish oil (rich in n-3 PUFA) or olive oil as a control. These two groups were subjected to a visual discrimination task and to a test of anxiety in the open-field. In parallel, cortical activity was measured with telemetric ECoG recordings. Finally, adult neurogenesis was investigated ex vivo by means of immunohistochemistry. Animals supplemented with fish oil exhibited better visual discrimination performance and tended to have lower anxiety levels. Furthermore, supplementation increased the power of alpha, beta and gamma frequency bands in the EEG, which are related to various aspects of memory and decision-making. This study also provides the first evidence of the existence of adult neurogenesis process in a prosimian primate. Notably, lemurs supplemented with n-3 PUFAs for 21 months exhibited a higher number of newly born neurons in brain areas related to memory and emotions, compared to control animals. Altogether, these results point to long-term positive effects of dietary n-3 PUFAs on various functions of the primate brain. Further studies will be needed to determine a formal causal link between behavioral improvement and creation of new neurons.

[12] *Rezk MR, Badr KA*. **Quantification of amlodipine and atorvastatin in human plasma by UPLC-MS/MS method and its application to a bioequivalence study**. Biomedical chromatography : BMC 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498757
ABSTRACT

A robust, rapid and sensitive UPLC-MS/MS method has been developed, optimized and validated for determination of amlodipine (AML) and atorvastatin (ATO) in human plasma using eplerenone as an internal standard (IS). Multiple-reaction monitoring in positive electrospray ionization mode was utilized in Xevo TQD LC-MS/MS. Double extraction was used in sample preparation using diethyl ether and ethyl acetate. The prepared samples were analyzed using Acquity UPLC BEH C18 (50 x 2.1 mm, 1.7 mum) column. Ammonium formate and acetonitrile, pumped isocraticaly at a flow rate of 0.25 ml/min., were used as a mobile phase. Method validation was done as per the FDA guidelines. Linearity was achieved in the range of 0.1-10 ng/ml for AML and 0.05-50 ng/ml for ATO. Intra-day and inter-day accuracy and precision were calculated and found to be within the acceptable range. A short run time, of less than 1.5 minutes, permits analysis of a large number of plasma samples per batch. The developed and validated method was applied to estimate AML and ATO in a bioequivalence study in healthy human volunteers.

[13] *Lucas BD, Elhabyan AK, Lucas KH*. **Rationale for Increasing the Starting Dose of Simvastatin**. Clinical drug investigation 2002; 22:639.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29492858
ABSTRACT

[14] *Peng C, Ding Y, Yi X et al.* **Polymorphisms in CYP450 Genes and the Therapeutic Effect of Atorvastatin on Ischemic Stroke: A Retrospective Cohort Study in Chinese Population**. Clinical therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29500141
ABSTRACT
PURPOSE: Ischemic stroke (IS) is one of the most common neurologic diseases and is the main cause of death and disability in the Chinese population. This retrospective cohort study was performed to elucidate the relationship between single nucleotide polymorphisms (SNPs) in cytochrome P450 genes and the therapeutic effect of atorvastatin. METHODS: A total of 192 cases of IS were enrolled in the study. All patients were treated with atorvastatin, and their lipid levels and proportions were measured. Six SNPs in 4 cytochrome P450 genes (CYP2C19, CYP2D6, CYP3A4, and CYP4F2) related to drug metabolism were selected to be genotyped and analyzed. FINDINGS: Data were analyzed for 192 patients (sex, male/female, 122/70; mean age, 69.81 [9.35] years; Hypertension, 163[84.90%]; Cigarette smoking, 34[17.71%]). Among the 192 patients with IS treated with atorvastatin, it was found that the G allele of rs1065852 (CYP2D6) had a better effect on lowering of DeltaLDL ($P < 0.001$), DeltaLDL/LDL ($P < 0.001$), Delta(LDL/HDL) ($P < 0.001$), and Delta(LDL/HDL)/(LDL/HDL) ($P < 0.001$). We also found that rs2242480 (CYP3A4) showed marginal association with DeltaLDL ($P = 0.049$) under the dominant model. In addition, rs2242480 and rs1065852 exhibited cumulative effects on the lipid-lowering (DeltaLDL, DeltaLDL/LDL, and Delta[LDL/HDL]) efficacy of atorvastatin ($P < 0.001$). IMPLICATIONS: The results suggest that CYP2D6 and CYP3A4 affect treatment with atorvastatin in patients with IS.

[15] *Ghasemi Fard S, Wang F, Sinclair AJ et al.* **How does high DHA fish oil affect health? A systematic review of evidence**. Critical reviews in food science and nutrition 2018:1-44.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29494205

ABSTRACT

The health benefits of fish oil, and its omega-3 long chain polyunsaturated fatty acid content, have attracted much scientific attention in the last four decades. Fish oils that contain higher amounts of eicosapentaenoic acid (EPA; 20:5n-3) than docosahexaenoic acid (DHA; 22:6n-3), in a distinctive ratio of 18/12, are typically the most abundantly available and are commonly studied. Although the two fatty acids have traditionally been considered together, as though they were one entity, different physiological effects of EPA and DHA have recently been reported. New oils containing a higher quantity of DHA compared with EPA, such as fractionated and concentrated fish oil, tuna oil, calamari oil and microalgae oil, are increasingly becoming available on the market, and other oils, including those extracted from genetically modified oilseed crops, soon to come. This systematic review focuses on the effects of high DHA fish oils on various human health conditions, such as the heart and cardiovascular system, the brain and visual function, inflammation and immune function and growth/Body Mass Index. Although inconclusive results were reported in several instances, and inconsistent outcomes observed in others, current data provides substantiated evidence in support of DHA being a beneficial bioactive compound for heart, cardiovascular and brain function, with different, and at times complementary, effects compared with EPA. DHA has also been reported to be effective in slowing the rate of cognitive decline, while its possible effects on depression disorders are still unclear. Interestingly, gender- and age- specific divergent roles for DHA have also been reported. This review provides a comprehensive collection of evidence and a critical summary of the documented physiological effects of high DHA fish oils for human health.

[16] *Karasulu HY, Gundogdu E, Turk UO et al.* **Enhancing Solubility and Bioavailability of Rosuvastatin into Self Emulsifying Drug Delivery System**. Current drug delivery 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29484996

ABSTRACT

The aim of this study was to develop new Rosuvastatin calcium (RCa) self emulsifying drug delivery system (SEDDS) and to evaluate the bioavailability and pharmacodynamic effect of RCa-SEDDS in Yorkshire pigs. Firstly, SEDDS was developed and prepared then RCa was incorporated into SEDDS which was evaluated regarding their characterization, stability properties, drug release profiles, permeation and cytotoxicity studies. Finally, in vivo performance of RCa-SEDDS (F1-RCa-SEDDS) was examined by pharmacokinetic and pharmacodynamics studies. The average droplet size of RCa-SEDDS ranged between 200 and 250 nm. RCa-SEDDS that contained 12.8% Oleic acid, 11 % Labrafil M, 3.3 % Labrasol and 4.4 % Transcutol HP were found to be stable and exhibited approximately 4-fold higher permeation than commercial tablet (Crestor(R) 20 mg tablet). In pharmacokinetic studies, when F1-RCa-SEDDS and commercial tablet were administered orally, F1-RCa-SEDDS showed higher bioavailability of RCa than commercial tablet. Respectively, in pharmacodynamic studies, triglyceride and total cholesterol levels were significantly reduced with F1-RCa-SEDDS formulation by 37% and 19% when compared to baseline values. However, these decreases with commercial formulation were only 6% and 2% respectively. According to these findings, development formulation could be potentially used to enhance the oral absorption of RCa.

[17] *Hermans MP, Valensi P*. **Elevated triglycerides and low high-density lipoprotein cholesterol level as marker of very high risk in type 2 diabetes**. Current opinion in endocrinology, diabetes, and obesity 2018; 25:118-129.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29493554

ABSTRACT
PURPOSE OF REVIEW: The aim of this review is to describe in diabetic patients the determinants underlying atherogenic dyslipidemia, a complex dyslipidemia defined as the coexistence of fasting hypertriglyceridemia and low high-density lipoprotein cholesterol level. Atherogenic dyslipidemia is often comorbid with hyperglycemia in patients with the common form of type 2 diabetes mellitus (T2DM), namely that associated with obesity, insulin resistance, hyperinsulinemia and the metabolic syndrome phenotype. RECENT FINDINGS: The role of triglyceride-rich lipoproteins, both fasting and nonfasting, is increasingly considered as a direct driver of atherosclerosis in diabetic patients, even in those receiving best standards of care, including low-density lipoprotein cholesterol level adequately controlled by statins and/or ezetimibe. The residual cardiovascular risk related to atherogenic dyslipidemia in T2DM patients can be inferred from subgroup analysis of diabetic patients within landmark lipid-lowering trials, or from T2DM-only trials, such as Fenofibrate Intervention and Event Lowering in Diabetes study or Action to Control Cardiovascular Risk in Diabetes-Lipid trial. SUMMARY: The presence of atherogenic dyslipidemia markedly increases cardiovascular risk, and there is evidence that part of the residual cardiovascular risk in T2DM can be safely and effectively reduced by fibrates. Ongoing trials will determine whether new classes of drugs or dietary intervention targeting hypertriglyceridemia (such as n-3 fatty acids or SPPARMalpha) will reduce macro and microvascular residual risk in T2DM patients with atherogenic dyslipidemia at inclusion.

[18] *Blanco F, Heinonen SE, Gurzeler E et al.* **In vivo inhibition of nuclear factor of activated T-cells leads to atherosclerotic plaque regression in IGF-II/LDLR(-/-)ApoB(100/100) mice**. Diabetes & vascular disease research 2018:1479164118759220.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29499628

ABSTRACT
AIMS: Despite vast clinical experience linking diabetes and atherosclerosis, the molecular mechanisms leading to accelerated vascular damage are still unclear. Here, we investigated the effects of nuclear factor of activated T-cells inhibition on plaque burden in a novel mouse model of type 2 diabetes that better replicates human disease. METHODS & RESULTS: IGF-II/LDLR(-/-)ApoB(100/100) mice were generated by crossbreeding low-density lipoprotein receptor-deficient mice that synthesize only apolipoprotein B100 (LDLR(-/-)ApoB(100/100)) with transgenic mice overexpressing insulin-like growth factor-II in pancreatic beta cells. Mice have mild hyperglycaemia and hyperinsulinaemia and develop complex atherosclerotic lesions. In vivo treatment with the nuclear factor of activated T-cells blocker A-285222 for 4 weeks reduced atherosclerotic plaque area and degree of stenosis in the brachiocephalic artery of IGF-II/LDLR(-/-)ApoB(100/100) mice, as assessed non-invasively using ultrasound biomicroscopy prior and after treatment, and histologically after termination. Treatment had no impact on plaque composition (i.e. muscle, collagen, macrophages). The reduced plaque area could not be explained by effects of A-285222 on plasma glucose, insulin or lipids. Inhibition of nuclear factor

of activated T-cells was associated with increased expression of atheroprotective NOX4 and of the anti-oxidant enzyme catalase in aortic vascular smooth muscle cells. CONCLUSION: Targeting the nuclear factor of activated T-cells signalling pathway may be an attractive approach for the treatment of diabetic macrovascular complications.

[19] *Henry RR, Muller-Wieland D, Taub PR et al.* **Effect of alirocumab on lipids and lipoproteins in individuals with metabolic syndrome and without diabetes: Pooled data from 10 phase 3 trials**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29493859
ABSTRACT
AIMS: This analysis assessed efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, in patients with or without metabolic syndrome (MetS) using pooled data from 10 phase 3 ODYSSEY trials. MATERIALS AND METHODS: Data from 4983 randomized patients (1940 with MetS; 1642 with diabetes excluded) were assessed in subgroups by MetS status. Efficacy data were analysed in 4 pools per study design: 2 placebo-controlled pools (1 using alirocumab 150 mg every 2 weeks [Q2W], 1 using 75/150 mg Q2W) with background statin, and 2 ezetimibe-controlled pools (both alirocumab 75/150 mg Q2W), 1 with and 1 without background statin. Alirocumab 75/150 mg indicates possible dose increase from 75 to 150 mg at Week 12 based on Week 8 LDL-C. RESULTS: LDL-C percentage reduction from baseline at Week 24 with alirocumab was 63.9% (MetS) and 56.8% (non-MetS) in the pool of alirocumab 150 mg Q2W, and 42.2-52.2% (MetS) and 45.0-52.6% (non-MetS) in 3 pools using 75/150 mg Q2W. Levels of other lipid and lipoprotein parameters were also improved with alirocumab treatment, including apolipoprotein B, non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein(a) and HDL-C. Overall, the percentage change at Week 24 in LDL-C and other lipids and lipoproteins did not vary by MetS status. Adverse event rates were generally similar between treatment groups, regardless of MetS status; injection-site reactions occurred more frequently in alirocumab vs control groups. CONCLUSIONS: Across study pools, alirocumab-associated reductions in LDL-C, apolipoprotein B, and non-HDL-C were significant versus control, and did not vary by MetS status.

[20] *Hopstock LA, Eggen AE, Lochen ML et al.* **Secondary prevention care and effect: Total and low-density lipoprotein cholesterol levels and lipid-lowering drug use in women and men after incident myocardial infarction - The Tromso Study 1994-2016**. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology 2018:1474515118762541.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29488799
ABSTRACT
BACKGROUND: Secondary prevention guidelines after myocardial infarction (MI) are gender neutral, but underutilisation of treatment in women has been reported. DESIGN: We investigated the change in total and low-density lipoprotein (LDL) cholesterol levels and lipid-lowering drug (LLD) use after first-ever MI in a population-based study. METHODS: We followed 10,005 participants (54% women) attending the Tromso Study 1994-1995 and 8483 participants (55% women) attending the Tromso Study 2007-2008 for first-ever MI up to their participation in 2007-2008 and 2015-2016, respectively. We used linear and logistic regression models to

investigate sex differences in change in lipid levels. RESULTS: A total of 395 (MI cohort I) and 132 participants (MI cohort II) had a first-ever MI during 1994-2008 and 2007-2013, respectively. Mean change in total cholesterol was -2.34 mmol/L (SD 1.15) in MI cohort I, and in LDL cholesterol was -1.63 mmol/L (SD 1.12) in MI cohort II. Men had a larger decrease in lipid levels compared to women: the linear regression coefficient for change was -0.33 (95% confidence interval [CI] -0.51 to -0.14) for total cholesterol and -0.21 (95% CI -0.37 to -0.04) for LDL cholesterol, adjusted for baseline lipid value, age and cohort. Men had 73% higher odds (95% CI 1.15-2.61) of treatment target achievement compared to women, adjusted for baseline lipid value, age and cohort. LLD use was reported in 85% of women and 92% of men in MI cohort I, and 80% in women and 89% in men in MI cohort II. CONCLUSIONS: Compared to men, women had significantly less decrease in lipid levels after MI, and a smaller proportion of women achieved the treatment target.

[21] *Doggrell SA*. **Cardiovascular outcomes trial with anacetrapib in subjects with high cardiovascular risk - are major benefits REVEALed?** Expert opinion on pharmacotherapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498299
ABSTRACT
INTRODUCTION: The actions of the cholesteryl ester transfer protein (CETP) inhibitors (torcetrapib, dalcetrapib and evacetrapib) include increasing high-density lipoprotein (HDL) cholesterol, but they do not reduce cardiovascular outcomes in subjects with high cardiovascular risk. Anacetrapib also inhibits CETP, increases HDL cholesterol and lowers low-density lipoprotein (LDL) cholesterol. Areas Covered: This evaluation is of the REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification) trial, which was a cardiovascular outcomes trial with anacetrapib in subjects with high cardiovascular risk. Consideration is given as to whether increasing HDL cholesterol, lowering LDL cholesterol or other mechanisms/factors underlying the positive outcome with this CETP inhibitor. Expert opinion: After three years, the REVEAL trial with anacetrapib, demonstrated cardiovascular benefits, but not a reduction in coronary artery deaths. The reductions were not significant in years one and two. Thus, in my opinion, the benefits of anacetrapib were not major, and may not apply in 'real' world populations where adherence to medicines is lower than in REVEAL. Also, lowering LDL cholesterol and off-target mechanisms of anacetrapib may have contributed to any beneficial and/or toxic effects. Anacetrapib has a good safety profile.

[22] *Sidharta SL, Baillie TJ, Howell S et al.* **Evaluation of human coronary vasodilator function predicts future coronary atheroma progression**. Heart 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29496901
ABSTRACT
OBJECTIVE: Coronary vasodilator function and atherosclerotic plaque progression have both been shown to be associated with adverse cardiovascular events. However, the relationship between these factors and the lipid burden of coronary plaque remains unknown. These experiments focus on investigating the relationship between impaired coronary vasodilator function (endothelium dependent (salbutamol) and endothelium independent (glyceryl trinitrate)) and the natural history of atheroma plaque progression and lipid burden using dual modality intravascular ultrasound (IVUS) and near-infrared spectroscopy (NIRS) imaging.

METHODS: 33 patients with stable chest pain or acute coronary syndrome underwent serial assessment of coronary vasodilator function and intracoronary plaque IVUS and NIRS imaging. Coronary segmental macrovascular response (% change segmental lumen volume (DeltaSLV)), plaque burden (per cent atheroma volume (PAV)), lipid core (lipid-rich plaque (LRP) and lipid core burden index (LCBI)) were measured at baseline and after an interval of 12-18 months (n=520 segments). RESULTS: Lipid-negative coronary segments which develop into LRP over the study time period demonstrated impaired endothelial-dependent function (-0.24+/-2.96 vs 5.60+/-1.47%, P=0.04) and endothelial-independent function (13.91+/-4.45 vs 21.19+/-3.19%, P=0.036), at baseline. By multivariate analysis, endothelial-dependent function predicted LCBI (beta coefficient: -3.03, 95% CI (-5.81 to -0.25), P=0.033) whereas endothelial-independent function predicted PAV (beta coefficient: 0.07, 95% CI (0.04 to 0.10), P<0.0001). CONCLUSIONS: Epicardial coronary vasodilator function is a determinant of future atheroma progression and composition irrespective of the nature of clinical presentation. TRIAL REGISTRATION NUMBER: ACTRN12612000594820, Post-results.

[23] *Najjari M, Vaezi G, Hojati V et al.* **Involvement of IL-1beta and IL-6 in antiarrhythmic properties of atorvastatin in ouabain-induced arrhythmia in rats**. Immunopharmacology and immunotoxicology 2018:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29486618
ABSTRACT
PURPOSE: Evidence show that statins possess wide beneficial cardioprotective and anti-inflammatory effects; therefore, in the present experiment, we investigated the antiarrhythmic properties of atorvastatin in ouabain-induced arrhythmia in isolated rat atria and the role of several inflammatory cytokines in this effect. MATERIALS AND METHODS: Male rats were pretreated with either of atorvastatin (10 mg/kg) or vehicle, orally once daily for 6 weeks. After induction of anesthesia, we isolated the atria and after incubation with ouabain, time of onset of arrhythmia and asystole as well as atrial beating rate and contractile force were recorded. We also measured the atrial levels of IL-1beta, IL-6, and TNF-alpha after the injection of ouabain to animals. RESULTS: Pretreatment with atorvastatin significantly delayed the onset of arrhythmia and asystole compared with vehicle-treated group ($p < .01$, $p < .001$, respectively). Incubation of ouabain boosted both atrial beating rate and contractile force in vehicle-treated group ($p < .05$), while these responses in atorvastatin-treated group were not significant ($p > .05$). Injection of ouabain elevated the atrial levels of IL-1beta, IL-6, and TNF-alpha, while pretreatment of animals with atorvastatin could reverse the ouabain-induced increase in atrial IL-1beta and IL-6 ($p < .01$ and $p < .05$, respectively). CONCLUSIONS: It is concluded that observed antiarrhythmic effects of atorvastatin might be attributed to modulation of some inflammatory cytokines, at least IL-1beta and IL-6.

[24] *Fang M, Qian Q, Zhao Z et al.* **High-Sensitivity C-Reactive Protein Combined with Low-Density Lipoprotein Cholesterol as the Targets of Statin Therapy in Patients with Acute Coronary Syndrome**. Int Heart J 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29479010
ABSTRACT

To investigate the combination of high-sensitivity C-reactive protein (hs-CRP) and Low-density lipoprotein (LDL)-C as the targets for statin treatment in patients with acute coronary syndrome (ACS). This single-center, prospective, randomized study was performed in 400 patients treated with atorvastatin 40 mg/day for 1 month and then with atorvastatin 20 mg/day as maintenance. The patients were randomized to the LDL group (LDL-C target of < 2.07 mmol/L according to the Chinese dyslipidemia guidelines) and to the LDL-CRP group (LDL-C target of < 2.07 mmol/L and hs-CRP target of < 3 mg/L). The patients were followed up for major adverse cardiac events (MACE) at 6, 12, and 18 months. The two groups had similar baseline characteristics and 391 patients completed the follow-up. No differences were found in LDL-C between the two groups, but a difference was found in hs-CRP at 12 and 18 months. There was a significant difference in revascularization (8.7% versus 3.6%, P = 0.04) and MACE (16.8% versus 9.7%; P = 0.04) between the LDL and LDL-CRP groups at 18 months. Compared to LDL-C as the single target, targeting both LDL-C and hs-CRP by statin therapy in patients with ACS could further reduce the incidence of MACE and the residual cardiovascular risk.

[25] *Li B, Lu X, Wang J et al.* **The metabonomics study of P-selectin glycoprotein ligand-1 (PSGL-1) deficiency inhibiting the progression of atherosclerosis in LDLR(-/-) mice**. International journal of biological sciences 2018; 14:36-46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29483823
ABSTRACT
Atherosclerosis (AS) is a multi-factorial chronic disease commonly associated with the mechanisms of metabolism disorder, endothelial dysfunction and chronic inflammation. AS an inflammatory molecule, p-selectin glycoprotein ligand-1 (PSGL-1) played an important role in the inflammatory process of atherogenesis involving the recruitment of leukocyte and transmitting signals to activate leukocyte during the adhesion process. So far, there has been little study regarding the effects of PSGL-1 on AS progression and the metabolic regulation. In this report, we studied the effect of PSGL-1 deficiency on the formation and progression of AS and the metabolic regulation by use of LDLR(-/-), PSGL-1(-/-) transgenic mice based on metabonomics. It was found that the PSGL-1 deficiency reduced the atherosclerotic plaque area, inflammatory cells infiltration and fiber hyperplasia during the AS development. The serum metabonomics study showed that the LDLR(-/-) ,PSGL-1(-/-) mice had higher levels of HDL, valine, acetate, pyruvate, choline, PC, GPC and glycine, and lower levels of LDL+VLDL and lactate at the early stage of atherosclerosis, while lactate, citrate and glutamine showed statistical significance at the late stage of atherosclerosis. These results showed that the PSGL-1 deficiency inhibited the AS progression and regulated glucose metabolism, lipid metabolism, amino acid and phospholipid metabolism in LDLR(-/-) mice.

[26] *Jiang C, Nischal H, Sun H et al.* **Non-Native Conformational Isomers of the Catalytic Domain of PCSK9 Induce an Immune Response, Reduce Lipids and Increase LDL Receptor Levels**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29495280
ABSTRACT
PCSK9 (Proprotein convertase subtilisin/kexin type 9) increases plasma cholesterol levels by promoting LDL receptor degradation. Current antibody inhibitors block the interaction between

PCSK9 and LDL receptors, significantly decrease plasma cholesterol levels, and provide beneficial clinical outcomes. To reduce the action of PCSK9 in plasma, a novel strategy that will produce a panel of non-native, conformationally-altered isomers of PCSK9 (X-PCSK9) to develop active immunotherapy targeting of native PCSK9 and inhibiting/blocking the interaction of PCSK9 with LDL receptor, thus decreasing plasma cholesterol levels is proposed. The authors used the scrambled disulfide bond technique to generate conformationally-altered isomers of the catalytic domain of mouse PCSK9. The focus was on the immune response of four X-isomers and their effects on plasma cholesterol and triglyceride levels in both C57BL/6J and Apoe-/- mice. The authors showed that the four immunogens produced significant immunogenicity against native PCSK9 to day 120 after immunization of C57BL/6J and Apoe-/- mice. This resulted in significantly decreased plasma cholesterol levels in C57BL/6J mice, and to a lesser degree in Apoe-/- mice. The X-PCSK9-B1 treated mice had increased LDL receptor mRNA and protein levels at day 120 after treatment. Thus, this study provides a new, potentially promising approach that uses long-term immunotherapy for a treatment of hypercholesterolemia.

[27] *Shi R, Zhao L, Wang F et al.* **Effects of lipid-lowering agents on diabetic retinopathy: a Meta-analysis and systematic review**. International journal of ophthalmology 2018; 11:287-295.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29487821
ABSTRACT
AIM: To clarify this controversy and to provide evidence for application of lipid lowering agents in treatment of diabetic retinopathy (DR). METHODS: We searched the databases of PubMed, Embase and Cochrane Library Central Register of Controlled Trials (CENTRAL) and abstracts from main annual meetings up to January 1, 2017. Google scholar and ClinicalTrials.gov were also searched for unpublished relevant studies. We included randomized controlled trials (RCTs) that studied lipid-lowering agents in type 1 or type 2 diabetes in this Meta-analysis. The primary endpoint was the progression of DR, and the secondary endpoints included vision loss, development of diabetic macular edema (DME) and aggravation of hard exudates. The pooled odds ratios (OR) with corresponding 95% confidence intervals (95%CIs) were calculated. RESULTS: After systemic and manual literature search by two independent investigators, we included 8 RCTs from 7 published articles with 13 454 participants in this Meta-analysis. The results revealed that lipid-lowering drugs were associated with reduced risk in DR progression [OR=0.77 (95%CI: 0.62, 0.96), P=0.02]. Lipid-lowering agents might have protective effect on DME compared to placebo, although the difference was not statistically significant [OR=0.60 (95%CI: 0.34, 1.08), P=0.09]. However, no significant differences in the worsening of vision acuity [OR=0.96 (95%CI: 0.81,1.14), P=0.64] and hard exudates [OR=0.50 (95%CI:0.15, 1.74), P=0.28] were found between the lipid-lowering drugs and the placebo groups. CONCLUSION: In DR patients, lipid-lowering agents show a protective effect on DR progression and might be associated with reduced risk in the development of DME. However, lipid-lowering agents have no effects on vision loss and hard exudates aggravation. Further clinical trials in larger scale are required to confirm the conclusion of this study and thus justify the use of intensive control lipids with anti-lipid agents at the early stages of DR.

[28] *Girelli D, Busti F, Marchi G et al.* **Therapeutic oligonucleotides in cardiovascular and metabolic diseases: insights for the internist**. Internal and emergency medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498010
ABSTRACT
The idea of using small RNA fragments (oligonucleotides) for therapeutic purposes dates back to the 1990s, following the landmark discoveries on the mechanisms of gene silencing and RNA-interference (RNA-i). However, the first applications in medicine were hampered by difficulties in chemical stabilization and efficient delivery to target tissues. Recent advances in chemical manipulation of oligonucleotides have, at least partially, bypassed such obstacles. In particular, conjugation with ligands for specific receptors allows the selective uptake of oligonucleotides by critical cells (e.g., hepatocytes), where they inhibit the synthesis of the target protein by binding the complementary mRNA and inducing its degradation. In parallel, next-generation sequencing (NGS) studies at population levels have identified a number of key molecular targets, mainly through the discovery of "human knock-outs," i.e., subjects lacking a given protein because of nonsense mutations in the corresponding gene. Such highly informative individuals are often healthy, or even protected from the development of certain diseases. Indeed, subjects with null mutations in certain genes controlling lipoprotein metabolism like PCSK9 or ANGPTL-3 have a lower risk of cardiovascular disease. Since the complete absence of such proteins does not appear to carry any negative health effect, the corresponding genes are ideal candidates for the silencing approach. Pilot clinical trials with long acting anti-PCSK9 or anti-ANGPTL-3 oligonucleotides have yielded very promising results, so that their use as "vaccines" against atherosclerosis has been suggested in the future. As therapeutic oligonucleotides can virtually target innumerable proteins, their increasing development is predicted to substantially expand the repertoire of the "biological drugs," in addition to, or even substituting, more consolidated approaches like monoclonal antibodies.

[29] *Hsu RH, Lin WD, Chao MC et al.* **Congenital generalized lipodystrophy in Taiwan**. Journal of the Formosan Medical Association = Taiwan yi zhi 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29478747
ABSTRACT
BACKGROUND: Congenital generalized lipodystrophy (CGL) is a rare disorder characterized by scarce adipose tissue. This disease is distributed worldwide, but little is known about these patients in the Chinese population. Here, we delineate the phenotype and prognosis of CGL in our cohort. METHODS: Patients diagnosed with CGL from 8 medical centers were reviewed. The initial presentation, laboratory findings, and molecular testing were retrospectively analyzed. RESULTS: A total of 16 patients were analyzed, and the current median age was 3.5 years (range, 9 months-17.5 years). In all patients, molecular results confirmed BSCL2 mutation. c.782dupG (p.Ile262Hisfs*12) was the most common genotype identified. All patients had triangular faces and muscular hypertrophy. In addition, 75% presented with hepatomegaly, 19% had cardiomegaly, and 44% exhibited acanthosis nigricans. Developmental delay was noted in 5 out of 9 patients (56%) with a median developmental quotient (DQ)/intelligence quotient (IQ) of 61. Thirteen patients (81.3%) had high triglyceride levels. Eight patients received leptin analysis, and 7 of them (88%) had low leptin levels. One patient exclusively received a lipid-lowering drug, 4 patients were exclusively placed on a fat-restricted diet, 5 patients were

administered combination therapy, and 5 patients received no treatment. Three patients (19%) who developed diabetes mellitus received both oral hypoglycemic agents and insulin. Three patients (19%) experienced loss of ambulation and died prematurely. CONCLUSIONS: Our findings highlight the uniqueness of the genotype and phenotype in our cohort. Further long-term surveillance for comorbidities is necessary for early detection and management of these patients.

[30] *Obaid DR, Calvert PA, Bennett MR, West NEJ*. **High-Risk Atherosclerotic Plaque in Aberrant Circumflex Coronary Artery**. J Invasive Cardiol 2018; 30:E26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29493517
ABSTRACT
A 45-year-old man presented after an episode of central chest pain. Catheter angiography revealed an aberrant circumflex artery and high-grade stenosis in the mid RCA and proximal CX arteries. Previous case series have suggested that the retroaortic portion of aberrant circumflex arteries may be particularly prone to the development of atherosclerosis.

[31] *Shrestha S, Wu BJ, Guiney L et al.* **Cholesteryl Ester Transfer Protein and its Inhibitors**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29487091
ABSTRACT
Most of the cholesterol in plasma is in an esterified form that is generated in potentially cardioprotective high density lipoproteins (HDLs). Cholesteryl ester transfer protein (CETP) mediates bidirectional transfers of cholesteryl esters (CE) and triglycerides (TG) between plasma lipoproteins. Since CE originates in HDLs, and TG enters the plasma as a component of very low density lipoproteins (VLDLs), activity of CETP results in a net mass transfer of CE from HDLs to VLDLs and low density lipoproteins (LDLs), and of TG from VLDLs to LDLs and HDLs. As inhibition of CETP activity increases the concentration of HDL cholesterol and decreases the concentration of VLDL and LDL cholesterol, it has the potential to reduce atherosclerotic cardiovascular disease. This has led to the development of anti-CETP neutralising monoclonal antibodies, vaccines and anti-sense oligonucleotides. Small molecule inhibitors of CETP have also been developed and four of them have been studied in large scale cardiovascular clinical outcome trials. This review describes the structure of CETP and its mechanism of action. Details of its regulation and non-lipid transporting functions are discussed, and the results of the large scale clinical outcome trials of small molecule CETP inhibitors are summarised.

[32] *Xu R, Shi G, Xu L et al.* **Simvastatin improves oral implant osseointegration via enhanced autophagy and osteogenesis of BMSCs and inhibited osteoclast activity**. Journal of tissue engineering and regenerative medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498229
ABSTRACT
Dental implants have become a widely accepted and successful treatment for fully and partially edentulous patients. Simvastatin has been applied to improve and accelerate the osseointegration of implants by increasing the quantity and quality of bone tissue. However, its potential mechanism has not been elucidated completely. Here, we found that simvastatin

significantly enhanced the autophagy level of jaw-derived bone marrow stromal cells (BMSCs) and alleviated production of reactive oxygen species under unfavourable conditions. Simvastatin promoted osteogenic differentiation of BMSCs via enhanced autophagy. Furthermore, simvastatin inhibited the bone resorption activity of osteoclasts. With the use of a rat model of oral implant osseointegration, we found local injection of simvastatin displayed more new bone formation at the interface of the bone and implant compared with that of oral administration. Fluorochrome labelling histomorphometrical analysis and micro-CT also showed that simvastatin promoted the osseointegration of implants. Notably, fewer activated osteoclasts were observed in the region of osseointegration of implants from the simvastatin treatment groups, especially the local delivery of simvastatin. Collectively, our results revealed that simvastatin can increase osteoblastic differentiation of BMSCs via enhanced autophagy and decreased osteoclast activity. Thus, simvastatin could be a viable and promising drug to improve and even accelerate the osseointegration of a dental implant.

[33] *Waldman B, Ansquer JC, Sullivan DR et al.* **Effect of fenofibrate on uric acid and gout in type 2 diabetes: a post-hoc analysis of the randomised, controlled FIELD study**. The lancet. Diabetes & endocrinology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29496472
ABSTRACT
BACKGROUND: Gout is a painful disorder and is common in type 2 diabetes. Fenofibrate lowers uric acid and reduces gout attacks in small, short-term studies. Whether fenofibrate produces sustained reductions in uric acid and gout attacks is unknown. METHODS: In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, participants aged 50-75 years with type 2 diabetes were randomly assigned to receive either co-micronised fenofibrate 200 mg once per day or matching placebo for a median of 5 years follow-up. We did a post-hoc analysis of recorded on-study gout attacks and plasma uric acid concentrations according to treatment allocation. The outcomes of this analysis were change in uric acid concentrations and risk of on-study gout attacks. The FIELD study is registered with ISRCTN, number ISRCTN64783481. FINDINGS: Between Feb 23, 1998, and Nov 3, 2000, 9795 patients were randomly assigned to fenofibrate (n=4895) or placebo (n=4900) in the FIELD study. Uric acid concentrations fell by 20.2% (95% CI 19.9-20.5) during the 6-week active fenofibrate run-in period immediately pre-randomisation (a reduction of 0.06 mmol/L or 1 mg/dL) and remained -20.1% (18.5-21.7, p<0.0001) lower in patients taking fenofibrate than in those on placebo in a random subset re-measured at 1 year. With placebo allocation, there were 151 (3%) first gout events over 5 years, compared with 81 (2%) among those allocated fenofibrate (HR with treatment 0.54, 95% CI 0.41-0.70; p<0.0001). In the placebo group, the cumulative proportion of patients with first gout events was 7.7% in patients with baseline uric acid concentration higher than 0.36 mmol/L and 13.9% in those with baseline uric acid concentration higher than 0.42 mmol/L, compared with 3.4% and 5.7%, respectively, in the fenofibrate group. Risk reductions were similar among men and women and those with dyslipidaemia, on diuretics, and with elevated uric acid concentrations. For participants with elevated baseline uric acid concentrations despite taking allopurinol at study entry, there was no heterogeneity of the treatment effect of fenofibrate on gout risk. Taking account of all gout events, fenofibrate treatment halved the risk (HR 0.48, 95% CI 0.37-0.60; p<0.0001) compared with placebo. INTERPRETATION: Fenofibrate lowered uric

acid concentrations by 20%, and almost halved first on-study gout events over 5 years of treatment. Fenofibrate could be a useful adjunct for preventing gout in diabetes. FUNDING: None.

[34] *Lu N, Li X, Yu J et al.* **Curcumin Attenuates Lipopolysaccharide-Induced Hepatic Lipid Metabolism Disorder by Modification of m(6) A RNA Methylation in Piglets**. Lipids 2018; 53:53-63.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29488640
ABSTRACT
N(6) -methyladenosine (m(6) A) regulates gene expression and affects cellular metabolism. In this study, we checked whether the regulation of lipid metabolism by curcumin is associated with m(6) A RNA methylation. We investigated the effects of dietary curcumin supplementation on lipopolysaccharide (LPS)-induced liver injury and lipid metabolism disorder, and on m(6) A RNA methylation in weaned piglets. A total of 24 Duroc x Large White x Landrace piglets were randomly assigned to control, LPS, and CurL (LPS challenge and 200 mg/kg dietary curcumin) groups (n = 8/group). The results showed that curcumin reduced the increase in relative liver weight as well as the concentrations of aspartate aminotransferase and lactate dehydrogenase induced by LPS injection in the plasma and liver of weaning piglets ($p < 0.05$). The amounts of total cholesterol and triacylglycerols were decreased by curcumin compared to that by the LPS injection ($p < 0.05$). Additionally, curcumin reduced the expression of Bcl-2 and Bax mRNA, whereas it increased the p53 mRNA level in the liver ($p < 0.05$). Curcumin inhibited the enhancement of SREBP-1c and SCD-1 mRNA levels induced by LPS in the liver. Notably, dietary curcumin affected the expression of METTL3, METTL14, ALKBH5, FTO, and YTHDF2 mRNA, and increased the abundance of m(6) A in the liver of piglets. In conclusion, the protective effect of curcumin in LPS-induced liver injury and hepatic lipid metabolism disruption might be due to the increase in m(6) A RNA methylation. Our study provides mechanistic insights into the effect of curcumin in protecting against hepatic injury during inflammation and metabolic diseases.

[35] *Yang L, Ma G, Yu T et al.* **A case report of Brugada-like ST-segment elevation probably due to coronary vasospasm**. Medicine (Baltimore) 2018; 97:e9900.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29489690
ABSTRACT
RATIONALE: Vasospastic angina is caused by sudden occlusive vasoconstriction of a segment of an epicardial artery, with transient ST-segment elevation on electrocardiography. Brugada Syndrome is an inherited arrhythmogenic cardiac disorder with a diagnostic electrocardiography characterized by coved-type ST-segment elevation in right precordial leads (V1-V3). Those two diseases usually have no correlation. In this report, we discuss an interesting case of a patient who was diagnosed as vasospastic angina according to his coronary angiography, but his electrocardiography showed a Brugada-like ST-segment elevation. PATIENT CONCERNS: Our patient had a 9-month history of temporary but progressive substernal burning sensation with acid bilges of shoulders and arms, as well as profuse sweating at night. DIAGNOSES: Although he had no abnormal laboratory test result, no dysfunctional recorded echocardiogram or documented arrhythmia after being admitted to the hospital, his electrocardiography showed a Brugada-like ST-segment elevation. The coronary

angiography result confirmed a diagnosis of vasospastic angina. INTERVENTIONS: The patient was prescribed diltiazem, aspirin, isosorbide mononitrate and rosuvastatin and was strongly advised to quit cigarettes and alcohol. OUTCOMES: Follow-up at half a year turned out well. LESSONS: This case links Brugada syndrome to coronary vasospasm. They may share similar mechanisms. Provocation test and gene test needs to be ran to distinguish both. Long-term follow-up is essential for it may bring a warning sign for life threatening ventricular arrhythmias.

[36] *Stivaros S, Garg S, Tziraki M et al.* **Randomised controlled trial of simvastatin treatment for autism in young children with neurofibromatosis type 1 (SANTA)**. Molecular autism 2018; 9:12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29484149
ABSTRACT
Background: Neurofibromatosis 1 (NF1) is a monogenic model for syndromic autism. Statins rescue the social and cognitive phenotype in animal knockout models, but translational trials with subjects > 8 years using cognition/behaviour outcomes have shown mixed results. This trial breaks new ground by studying statin effects for the first time in younger children with NF1 and co-morbid autism and by using multiparametric imaging outcomes. Methods: A single-site triple-blind RCT of simvastatin vs. placebo was done. Assessment (baseline and 12-week endpoint) included peripheral MAPK assay, awake magnetic resonance imaging spectroscopy (MRS; GABA and glutamate+glutamine (Glx)), arterial spin labelling (ASL), apparent diffusion coefficient (ADC), resting state functional MRI, and autism behavioural outcomes (Aberrant Behaviour Checklist and Clinical Global Impression). Results: Thirty subjects had a mean age of 8.1 years (SD 1.8). Simvastatin was well tolerated. The amount of imaging data varied by test. Simvastatin treatment was associated with (i) increased frontal white matter MRS GABA ($t(12) = -2.12$, $p = .055$), GABA/Glx ratio ($t(12) = -2.78$, $p = .016$), and reduced grey nuclei Glx (ANCOVA $p < 0.05$, Mann-Whitney $p < 0.01$); (ii) increased ASL perfusion in ventral diencephalon (Mann-Whitney $p < 0.01$); and (iii) decreased ADC in cingulate gyrus (Mann-Whitney $p < 0.01$). Machine-learning classification of imaging outcomes achieved 79% ($p < .05$) accuracy differentiating groups at endpoint against chance level (64%, $p = 0.25$) at baseline. Three of 12 (25%) simvastatin cases compared to none in placebo met 'clinical responder' criteria for behavioural outcome. Conclusions: We show feasibility of peripheral MAPK assay and autism symptom measurement, but the study was not powered to test effectiveness. Multiparametric imaging suggests possible simvastatin effects in brain areas previously associated with NF1 pathophysiology and the social brain network. Trial registration: EU Clinical Trial Register (EudraCT) 2012-005742-38 (www.clinicaltrialsregister.eu).

[37] *Nhoek P, Chae HS, Masagalli JN et al.* **Discovery of Flavonoids from Scutellaria baicalensis with Inhibitory Activity Against PCSK 9 Expression: Isolation, Synthesis and Their Biological Evaluation**. Molecules (Basel, Switzerland) 2018; 23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29495284
ABSTRACT
Nine flavonoids were isolated and identified from a chloroform-soluble fraction of the roots of Scutellaria baicalensis through a bioactivity-guided fractionation using a proprotein convertase subtilisin/kexin type 9 (PCSK9) monitoring assay in HepG2 cells. All structures were established

by interpreting the corresponding spectroscopic data and comparing measured values from those in the literature. All compounds were assessed for their ability to inhibit PCSK9 mRNA expression; compounds 1 (3,7,2'-trihydroxy-5-methoxy-flavanone) and 4 (skullcapflavone II) were found to suppress PCSK9 mRNA via SREBP-1. Furthermore, compound 1 was found to increase low-density lipoprotein receptor protein expression. Also, synthesis of compound 1 as a racemic mixture form (1a) was completed for the first time. Natural compound 1 and synthetic racemic 1a were evaluated for their inhibitory activities against PCSK9 mRNA expression and the results confirmed the stereochemistry of 1 was important.

[38] *Asad F, Khan M, Rizvi F*. **Atorvastatin as an adjuvant with betamethasone valerate reduces disease severity and cardiovascular risks in Psoriasis**. Pak J Med Sci 2017; 33:1507-1511.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29492087
ABSTRACT
Objectives: To evaluate the effect of Atorvastatin as an adjuvant with betamethasone valerate on disease severity and cardiovascular risks in chronic plaque type psoriatic patients. Methods: It is an interventional study conducted in Pharmacology Department of BMSI, JPMC with the collaboration of Dermatology Department of JPMC, Karachi. The duration of study was from June 2013 to June 2016. Seventy five psoriatic patients were prescribed Tablet Atorvastatin 40-20 mg/day (40mg for first three months twice daily followed by 20mg once daily for the next three month) plus topical Betamethasone Valerate 0.1% once daily for 6 months (three week apply than one week interval). The efficacy and safety profile of drugs was measured by PASI, DLQI, hsCRP, LFTS and Lipid profile. Results: The percentage change of PASI is 86.749+/-0.547, DLQI is 82.697+/-.2.61 and hsCRP is 40.371+/-8.505, which showed highly significant improvement in patient at the end of last follow up. LFTs and CPK for safety profile of therapy showed non-significant results. Conclusion: Atorvastatin used as an adjuvant therapy with currently existing standard therapy (topical betamethasone) in patients having mild to moderate plaque type psoriasis reduces disease severity and cardiovascular risks.

[39] *Oliveira CV, Zorzi VN, Fighera MR et al.* **Subtle improvement of seizure susceptibility by atorvastatin treatment during epileptogenesis**. Pharmacological reports : PR 2017; 70:364-371.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29477945
ABSTRACT
BACKGROUND: The process by which a brain insult elicits epilepsy is termed epileptogenesis and it is characterized by numerous molecular and functional alterations. Statins are first-line drugs for hypercholesterolemia and related diseases, and display neuroprotective properties in clinical and experimental studies. Considering the importance in developing therapeutic strategies to prevent or modify epileptogenesis, we aimed the present study to test the hypothesis that atorvastatin modifies seizure susceptibility of mice after status epilepticus (SE). METHODS: Male and female C57BL/6 mice were submitted to the pilocarpine-induced SE and then treated with atorvastatin (10 or 100mg/kg, once daily by gavage) for 14days. At days 7 and 14 post SE we evaluated the susceptibility of mice to the convulsant effects of a low dose of PTZ (30mg/kg). Cell loss in the hilus of dentate gyrus was evaluated by Giemsa staining. RESULTS: Latencies to myoclonic jerks and to tonic-clonic seizures decreased between baseline (before

SE) and days 7 and 14 after SE, confirming the development of seizure susceptibility. Atorvastatin protected against PTZ-induced tonic-clonic seizures in both sexes at day 14 post-SE. Protective effects were similar in both female and male mice, except that a high dose of atorvastatin was required for females (protection at 100mg/kg versus 10mg/kg in males). Giemsa staining did not reveal neuroprotective effects of atorvastatin. CONCLUSIONS: Atorvastatin treatment during epileptogenesis had slight beneficial effects on seizure susceptibility. These seem not related to neuroprotection. Further studies are needed to determine the disease-modifying potential of atorvastatin in epilepsy.

[40] *Ayerbe L, Forgnone I, Foguet-Boreu Q et al.* **Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis**. Psychological medicine 2018:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29490716
ABSTRACT
BACKGROUND: The high cardiovascular (CV) morbidity and mortality reported for patients with psychiatric disorders may possibly be due to a poorer management of CV risk factors (CVRFs). However, these healthcare disparities remain poorly understood. In this paper, studies comparing the management of smoking, diabetes, hypertension and dyslipidaemia, in patients with and without depression, anxiety, schizophrenia, bipolar or personality disorder, were reviewed. METHODS: Prospective studies comparing rates of screening, diagnosis, treatment and control of CVRFs were searched in PubMed, Embase, PsychInfo, Scopus and Web of Science (inception to January 2017). The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used. Studies were assessed for quality. Wherever possible, meta-analyses were conducted to summarize the findings. RESULTS: Twenty studies, out of the 18 333 references initially identified, were included. Most studies were heterogeneous in design. Two areas permitted meta-analyses: the pooled odds ratio for quitting smoking for those with depression was 0.64 (0.49-0.80) $p < 0.001$; the pooled difference of glycated haemoglobin for patients with type 2 diabetes and depression was 0.18 (0.06-0.31) $p = 0.005$. Individual studies showed associations between: schizophrenia and lower probability of having smoking habit recorded; schizoid personality disorder and higher probability of remaining non-smokers after quitting; anxiety and poorer control of type I diabetes; depression, anxiety or schizophrenia and lower probability of having a diagnosis of hypertension; schizophrenia or bipolar disorder and lower use of antihypertensive and lipid-lowering drugs. CONCLUSIONS: A proactive clinical management, together with further studies, are needed to reduce the CV morbidity and mortality of patients with psychiatric disorders.

[41] *Cicero AFG*. **[Red yeast rice, monacolin K, and pleiotropic effects.]**. Recenti progressi in medicina 2018; 109:154e-157e.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29493648
ABSTRACT
The extracts of red yeast rice represent a nutraceutical with proven cholesterol lowering effect. Its efficacy is proportional to the concentration on monacolin K in the extract that could reach the amount of 10 mg per daily dose. The daily assumption of monacolin K could then reduce LDL-cholesterol plasma levels by 15-25% in 6-8 weeks. The LDL-cholesterol reduction is

associated with a proportional reduction in total cholesterolemia, non-HDL cholesterolemia, plasma apolipoprotein B, high-sensitivity C-reactive protein, and matrix metalloproteinases 2 and 9. Then, the red yeast rice lipid-lowering efficacy is associated with a significant improvement of endothelial function and pulse wave velocity, which are well-known and validated instrumental biomarkers of vascular aging. Beyond the cholesterol lowering efficacy and the statin-like mechanism of action, the risk of the use of monacolin K 10 mg per day are minimal, and mild myalgias could be foreseen only in frail patients previously intolerant to minimal statin dosages. In conclusion, red yeast rice titrated in monacolin K represents a good therapeutic tool for the management of moderate hypercholesterolemias in patients with low added cardiovascular disease risk.

[42] *Dias IHK, Milic I, Lip GYH et al.* **Simvastatin reduces circulating oxysterol levels in men with hypercholesterolaemia**. Redox biology 2018; 16:139-145.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29501047
ABSTRACT
Oxysterols (OHC) are biologically active cholesterol metabolites circulating in plasma that may be formed enzymatically (e.g. 24S-OHC, 25-OHC and 27-OHC) or by autoxidative mechanisms (e.g. 7-ketocholesterol, 7beta-OHC and 25-OHC). Oxysterols are more soluble than cholesterol and are reported to exert inflammatory, cytoprotective and apoptotic effects according to concentration and species. Esterified oxysterols have been analysed in people with dementia and cardiovascular diseases although there is no consistent relationship between oxysterol esters and disease. However, oxysterol esters are held in lipoprotein core and may not relate to the concentration and activity of plasma free oxysterols. Methodological limitations have challenged the analysis of free oxysterols to date. We have developed a fast, sensitive and specific quantitative LC-MS/MS, multiple reaction monitoring (MRM) method to target five oxysterols in human plasma with analyte recoveries between 72% and 82% and sensitivities between 5 and 135pg/ml. A novel method was used to investigate the hypothesis that simvastatin may reduce the concentrations of specific plasma free oxysterols in hypercholesterolaemia. Twenty healthy male volunteers were recruited (aged 41-63 years); ten were asymptomatic with high plasma cholesterol >6.5mM and ten were healthy with normal plasma cholesterol (<6.5mM). Simvastatin (40mg/day) was prescribed to those with hypercholesterolaemia. Plasma samples were taken from both groups at baseline and after three months. Simvastatin reduced plasma cholesterol by ~35% ($p<0.05$) at the end of three months. Oxysterols generated by autoxidation (but not enzymatically) were elevated up to 45 fold in hypercholesterolaemic midlife men. Plasma oxysterols were restored to those of healthy controls after simvastatin intervention suggesting that autoxidation is either prevented by simvastatin directly or that autoxidation is less prevalent when plasma cholesterol concentrations are within the normal range.

[43] *Gabus V, Wuerzner G, Saubade M et al.* **[Strategies for cardiovascular disease prevention]**. Revue medicale suisse 2018; 14:488-492.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29489130
ABSTRACT

Atherosclerosis is a disease which develops very gradually over decades. Under the influence of modifiable cardiovascular risk factors, such as blood pressure, LDL-cholesterol level, smoking or lifestyle, clinical symptoms of atherosclerosis manifest more or less early in life. When cardiovascular risk factors accumulate, the risk of having a cardiovascular event increases and the benefits of prevention measures are greater. This article summarizes existing strategies for controlling modifiable cardiovascular risk factors in primary prevention. The physician can rely on an interprofessional network of cardiovascular prevention. Managing risk factors while respecting the autonomy and priorities of the patient will bring the greatest benefit.

[44] *Gencer B, Nanchen D, Collet TH et al.* **[Current update on PCKS9 inhibitors]**. Revue medicale suisse 2018; 14:482-486.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29489129
ABSTRACT
PCSK9 (proprotein convertase subtilisin kexin 9) monoclonal antibodies (mAb) are new therapeutic agents to lower efficiently LDL-cholesterol levels. New data from large clinical trials suggest that the addition of PCSK9 mAb to statins can reduce the incidence of major adverse cardiovascular events in very high risk patients. Alirocumab and evolocumab are two agents available in Switzerland with specific limitations for reimbursement. PCSK9 mAb should be considered in patients with clinical atherosclerotic cardiovascular disease (ASCVD), as well as in patients with familial hypercholesterolemia without ASCVD who have substantially high LDL-cholesterol levels despite the use of statin at maximally tolerated dose with or without ezetimibe, or intolerance to appropriate doses of several statins.

[45] *Nanchen D, Genest J.* **[Screening for atherosclerosis to prevent cardiovascular risk : a pro-contra debate]**. Revue medicale suisse 2018; 14:477-480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29489128
ABSTRACT
Detecting atherosclerosis using imaging techniques is the subject of intense debate in the scientific community. Among the arguments in favor of screening, a better identification or better stratification of cardiovascular risk is mentioned, compared to cardiovascular risk scores based solely on traditional risk factors, such as blood pressure or cholesterol levels. Imaging techniques are also used to monitor the progression of atherosclerosis among patients using lipid-lowering or antihypertensive drugs in primary prevention. However, several experts in recent years have challenged the clinical utility of these imaging techniques in asymptomatic adults. This article proposes a debate << for or against >> to describe the main arguments for or against the use of imaging for screening for atherosclerosis.

[46] *Carnevale R, Nocella C, Petrozza V et al.* **Localization of lipopolysaccharide from Escherichia Coli into human atherosclerotic plaque**. Scientific reports 2018; 8:3598.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29483584
ABSTRACT
Experimental studies showed that gut-derived lipopolysaccharide (LPS) is pro-atherogenic, however, its relationship with human atherosclerosis is still to be defined. We investigate if gut-derived LPS from Escherichia Coli localizes in human carotid plaque and its potential role as pro-

inflammatory molecule in the atherosclerotic lesion. LPS from Escherichia Coli and Toll-like receptor 4 (TLR4) were studied in specimens from carotid and thyroid arteries of 10 patients undergoing endarterectomy and 15 controls matched for demographic and clinical characteristics. Blood LPS were significantly higher in patients compared to controls. Immunochemistry analysis revealed positivity for antibodies against LPS and TLR4 coincidentally with positivity for CD68 only in the atherosclerotic plaque of carotid arteries but not in thyroid arteries; the positivity for LPS and TLR4 was greater in the area with activated macrophages. LPS concentration similar to that detected in atherosclerotic plaque resulted in a dose-dependent TLR4-mediated Nox2 up-regulation by human monocytes. These data provide the first evidence that LPS from Escherichia Coli localizes in human plaque and may contribute to atherosclerotic damage via TLR4-mediated oxidative stress.

[47] *Ingrand I, Solinas M, Ingrand P et al.* **Lack of effects of simvastatin on smoking cessation in humans: A double-blind, randomized, placebo-controlled clinical study**. Scientific reports 2018; 8:3836.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29497063
ABSTRACT
A recent pre-clinical study has shown that brain-penetrating statins can reduce risks of relapse to cocaine and nicotine addiction in rats. Based on this information, we conducted a randomized, double-blind, placebo-controlled, proof-of-concept trial to assess the efficacy of simvastatin in smoking cessation. After informed consent, 118 participants received behavioral cessation support and were randomly assigned to a 3-month treatment with simvastatin or placebo. The primary outcome was biochemically verified abstinence or smoking reduction at 3-month post-target quit date (TQD). Secondary outcomes were abstinence during weeks 9-12 post-TQD, prolonged abstinence or reduction at months 6 and 12 post-TQD, safety and craving assessed at each visit during the 3-month period of treatment. Simvastatin treatment was not associated with higher 3-month abstinence or smoking reduction compared to placebo. There was no significant difference in any of the secondary outcomes. Simvastatin was well tolerated. Over 3 and 9 months follow-up period, 78% simvastatin and 69% placebo participants were retained in the study. At 6 and 12 months, smoking remained significantly reduced from baseline in both groups. Our results demonstrate that a 3-month simvastatin treatment (40 mg/day), added to individual behavioral cessation support, does not improve significantly smoking cessation compared to placebo in humans.

[48] *Steenman M, Espitia O, Maurel B et al.* **Identification of genomic differences among peripheral arterial beds in atherosclerotic and healthy arteries**. Scientific reports 2018; 8:3940.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29500419
ABSTRACT
Calcification is independently associated with cardiovascular events and morbidity. The calcification burden in atherosclerotic lesions quantitatively and qualitatively differs between arterial beds. Cardiovascular risk factors (CVRF) differentially affect plaque development between arterial beds. The aim of this study was to evaluate the impact of CVRF on atherosclerotic plaque calcification and to further study the molecular arterial heterogeneity that could account for these differences. Histological analysis was performed on atherosclerotic

plaques from 153 carotid, 97 femoral and 28 infrapopliteal arteries. CVRF showed minor associations with plaque calcification: age and hypertension affected only the overall presence of calcification but not the type of the calcification, which significantly differed between arterial beds. Transcriptome analysis revealed distinct gene expression profiles associated with each territory in atherosclerotic and healthy arteries. Canonical pathway analysis showed the preferential involvement of immune system-related processes in both atherosclerotic and healthy carotid arteries. Bone development-related genes were among those mostly enriched in atherosclerotic and healthy femoral arteries, which are more prone to developing endochondral calcification. This study highlights the heterogeneous nature of arteries from different peripheral vascular beds and contributes to a better understanding of atherosclerosis formation and evolution.

[49] *Woodside DG, Tanifum EA, Ghaghada KB et al.* **Magnetic Resonance Imaging of Atherosclerotic Plaque at Clinically Relevant Field Strengths (1T) by Targeting the Integrin alpha4beta1**. Scientific reports 2018; 8:3733.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29487319
ABSTRACT
Inflammation drives the degradation of atherosclerotic plaque, yet there are no non-invasive techniques available for imaging overall inflammation in atherosclerotic plaques, especially in the coronary arteries. To address this, we have developed a clinically relevant system to image overall inflammatory cell burden in plaque. Here, we describe a targeted contrast agent (THI0567-targeted liposomal-Gd) that is suitable for magnetic resonance (MR) imaging and binds with high affinity and selectivity to the integrin alpha4beta1(very late antigen-4, VLA-4), a key integrin involved in recruiting inflammatory cells to atherosclerotic plaques. This liposomal contrast agent has a high T1 relaxivity (~2 x 10(5) mM(-1)s(-1) on a particle basis) resulting in the ability to image liposomes at a clinically relevant MR field strength. We were able to visualize atherosclerotic plaques in various regions of the aorta in atherosclerosis-prone ApoE(-/-) mice on a 1 Tesla small animal MRI scanner. These enhanced signals corresponded to the accumulation of monocyte/macrophages in the subendothelial layer of atherosclerotic plaques in vivo, whereas non-targeted liposomal nanoparticles did not demonstrate comparable signal enhancement. An inflammatory cell-targeted method that has the specificity and sensitivity to measure the inflammatory burden of a plaque could be used to noninvasively identify patients at risk of an acute ischemic event.

[50] *Blaha V, Blaha M, Lanska M et al.* **[The role of PCSK9-inhibitors and of lipoprotein apheresis in the treatment of homozygous and severe heterozygous familial hypercholesterolemia: A rivalry, or are things quite different?]**. Vnitr Lek 2018; 64:43-50.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498875
ABSTRACT
PCSK9-inhibitors belong to the new class of hypolipidemic agents. They enhance catabolism of low density lipoprotein cholesterol (LDL-C) through inhibiting activity of proprotein convertase subtilisin/kexin type 9 (PCSK9). They are monoclonal antibodies (alirocumab, evolocumab etc). Under clinical development are also other types of PCSK9-inhibitors which act at a subcellular level. The treatment with PCSK9-inhibitors can be beneficially combined with lipoprotein

apheresis (LA). If such treatment using PCSK9-inhibitors is possible with regard to an individual patients genotype, the combination of LA and PCSK9-inhibitors leads to slowing the space of LDL-C increase between individual procedures of apheresis and enables attaining of the lowest possible values of LDL-cholesterolemia for the longest possible period of time. Due to high efficiency of PCSK9-inhibitors lowering LDL-C, but also their lower cost as compared to therapeutic LA, PCSK9-inhibitors now take precedence over the use of extracorporeal lipoprotein apheresis which, nonetheless, still remains the final method for hypolipidemic treatment of patients with severe hypercholesterolemia, who are resistant to conventional therapy while not reaching the target lipid values and at high cardiovascular risk. They belong to extracorporeal elimination methodologies which remove low density lipoprotein (LDL) cholesterol from circulating blood. LA in combination with higher doses of statins and ezetimib currently represents the most efficient method of treatment of homozygous and statin-refractory heterozygous familial hypercholesterolemia (FH). Residual cardiovascular risk in these patients still remains high, in particular because, despite the aforementioned treatment, the target values for lipids according to present recommendations cannot be reached. The combination of LA with the new drugs is promising, primarily due to its potential for further lowering of LDL-cholesterolemia between the individual apheresis procedures. Preliminary results of the ongoing studies indicate that the new hypolipidemic drugs in combination with LA, or when used separately, will substantially enrich and improve the treatment of refractory FH.Key words: alirocumab - atherosclerosis - evolocumab - hypercholesterolemia - cardiovascular disease - lipoprotein apheresis.

[51] *Karasek D, Vaverkova H*. **[Diabetic dyslipidemia and microvascular complications of diabetes]**. Vnitr Lek 2018; 64:17-24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498871
ABSTRACT
Diabetic dyslipidemia is one of the main risk factors for atherosclerosis. Although its participation in diabetic microvascular complications is not that dominant, dyslipidemia may play an important role in formation and progression of these complications. Pathophysiological mechanisms by which diabetic dyslipidemia affects the etiopathogenesis of diabetic nephropathy, retinopathy, neuropathy and diabetic foot are presented. The data from clinical studies and treatment possibilities for particular microvascular complications using lipid-lowering therapy are discussed.Key words: diabetes mellitus - diabetic foot - dyslipidemia - nephropathy - neuropathy - retinopathy.

[52] *Lastuvka J, Oreska S, Tomcik M, Vrablik M*. **[Cardiovascular risk in patients with rheumatic disease and its management]**. Vnitr Lek 2018; 64:51-59.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29498876
ABSTRACT
Cardiovascular disease (CVD) risk in patients with rheumatic diseases is increased by 50 % compared to the general population. This is a result of the increased inflammatory activity as well as modification of traditional CVD risk factors by the primary disease. So called lipid paradox, paradoxical decrease of concentrations of atherogenic plasma lipids due to increased inflammatory activity and their rise with successful anti-inflammatory treatment, is of particular

importance. CVD risk in rheumatic diseases is further modified by drugs used for their treatment: while some treatment modalities increase the risk (e.g. glucocorticoids), others may act in an opposite direction (methotrexate, biological therapies). CVD risk stratification in patients with rheumatic diseases is uneasy; so far none of the specific scoring systems has been shown superior to traditional ones designed for the general population. Principles of cardiovascular risk intervention remain the same as for the general population: the management starts with lifestyle measures (healthy diet, increase in physical activity and smoking cessation) complemented with pharmacotherapy when indicated. Blood pressure as well as lipid lowering therapies should be led according to the same principles as in the general population and, also, to the same treatment goals. To improve CVD prevention outcomes in patients with rheumatic diseases it seems feasible to work in interdisciplinary teams led by a rheumatologist cooperating with a specialist in CVD prevention strategies (general practitioner, cardiologist, internist, diabetes specialist). A nutritional therapist and a physiotherapist are important members of the team, too. Interdisciplinary and complex CVD prevention in patients with rheumatic diseases decreases CVD morbidity.Key words: cardiovascular risk - intervention - lipid paradox - rheumatic diseases - risk factors - risk stratification.

[53] *Weber ML*. **[Can Pravastatin influence Pregnancies at High-risk for Preeclampsia?]**. Zeitschrift fur Geburtshilfe und Neonatologie 2018; 222:31-33.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29499584
ABSTRACT
Statins seem to positively influence the inflammatory, anti-angiogenic milieu of pregnancies with underlying placental ischemia by their pleiotropic effects. This might prevent, ameliorate and delay preeclampsia. To confirm the benefits of pravastatin on gestational age at birth as well as clinic and angiogenic markers in pregnancies at high-risk for preeclampsia, the Department of Obstetrics at the University Hospital Leipzig plans a randomized, double-blinded, placebo-controlled feasibility study.

[54] *Huo Y*. **[Intensive lipid-lowering strategy for Chinese population at high risk of cardiovascular disease]**. Zhonghua xin xue guan bing za zhi 2018; 46:83-86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29495227
ABSTRACT

[55] *Zhang HW, Li S, Guo YL et al.* **[Prevalence and clinical characteristics of familial hypercholesterolemia among Chinese patients undergoing coronary angiography due to angina-like chest pain]**. Zhonghua xin xue guan bing za zhi 2018; 46:104-108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29495232
ABSTRACT
Objectives: To investigate the prevalence rate and clinical characteristics of familial hypercholesterolemia (FH) in Chinese patients undergoing coronary angiography due to angina-like chest pain. Methods: From March 2011 to December 2016, a total of 9 908 consecutive patients undergoing coronary angiography in Fuwai Hospital due to angina-like chest pain were enrolled. The age of enrolled patients was (56.6+/-11.1) years old, and 6 782 cases (68.4%) were male. The patients were divided into two groups: FH group (n=271) and non-FH group

(n=9 637) according to the Dutch Lipid Clinic Network diagnostic criteria. A retrospective analyze was performed on the baseline features between the two groups including lipids levels, coronary artery disease (CAD) characteristics, and lipids-lowering treatments. Results: In the total cohort, the prevalence of definite/probable FH was 2.7% (271/9 908). The incidence of premature coronary artery disease (PCAD) (women < 60 years old, or men < 55 years old) was higher in patients with FH than that in patients without FH (70.2%(201/271) vs. 44.5% (4 287/9 637); chi(2)=93.738, P<0.001). Patients with FH had higher level of TC and LDL-C when compared with patients without FH ((6.74+/-2.48) mmol/L vs. (4.15+/-1.10) mmol/L; (4.53+/-2.39) mmol/L vs. (2.52+/-0.97) mmol/L; t=19.403, 22.233, P<0.001, respectively). Additionally, 84.9% (230/271) of FH patients were treated with statin at different intensities, but none of them achieved the LDL-C<2.6 mmol/L. Conclusions: Chinese patients with familial hypercholesterolemia not only showed a high presence of PCAD and higher lipids levels, but also exhibited a low rate of achievement of low-density lipoprotein cholesterol targets despite statin therapy. Our results thus highlight the importance of early diagnosis and intensive treatment of FH patients.