Literature update week 38 (2018)

[1] *Cao YX, Liu HH, Li S, Li JJ*. **A Meta-Analysis of the Effect of PCSK9-Monoclonal Antibodies on Circulating Lipoprotein (a) Levels**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30229525
ABSTRACT
BACKGROUND: Lipoprotein (a) [Lp(a)] is an atherogenic lipoprotein. While no effective therapy for Lp(a) is currently available, recently, several pooled analyses with small sample sizes have suggested that proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9-mAbs) could reduce circulating Lp(a) levels. This meta-analysis was performed to comprehensively investigate the efficacy of PCSK9-mAbs with respect to serum Lp(a) concentrations. METHODS: PubMed, MEDLINE, Embase, ClinicalTrials.gov, Cochrane CENTRAL, Web of Science and recent conferences up to July 2018 were searched. Randomized clinical trials evaluating the effect of PCSK9-mAbs and control treatment on plasma Lp(a) concentrations were included. Mean differences and odds ratios with 95% confidence intervals (CIs) were used. RESULTS: Twenty-seven randomized clinical trials with a total of 11,864 participants were included. PCSK9-mAbs showed a significant efficacy in reducing Lp(a) (- 21.9%, 95% CI - 24.3 to - 19.5), irrespective of PCSK9-mAb types, treatment duration, participant characteristics, treatment methods, differences of control treatment, baseline Lp(a) levels, and test methods. The greatest reduction was achieved with 150 mg alirocumab biweekly (- 24.6%, 95% CI - 28.0 to - 21.2) and 140 mg evolocumab monthly (- 26.8%, 95% CI - 31.6 to - 21.9). Meta-regression analyses found that the more intense low-density lipoprotein cholesterol levels declined during PCSK9-mAb treatment, the greater the reduction in Lp(a) levels. Safety was in accordance with previous reports. CONCLUSIONS: The results of this analysis suggested that PCSK9-mAbs could significantly reduce circulating Lp(a) levels. Long-term studies may be needed to confirm the effect of PCSK9-mAbs on Lp(a) in the future.

[2] *Contreras-Duarte S, Chen P, Andia M et al.* **Attenuation of atherogenic apo B-48-dependent hyperlipidemia and high density lipoprotein remodeling induced by vitamin C and E combination and their beneficial effect on lethal ischemic heart disease in mice**. Biological research 2018; 51:34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30219096
ABSTRACT
BACKGROUND AND AIMS: Atherosclerotic cardiovascular disease is highly prevalent and its underlying pathogenesis involves dyslipidemia including pro-atherogenic high density lipoprotein (HDL) remodeling. Vitamins C and E have been proposed as atheroprotective agents for cardiovascular disease management. However, their effects and benefits on high density lipoprotein function and remodeling are unknown. In this study, we evaluated the role of vitamin C and E on non HDL lipoproteins as well as HDL function and remodeling, along with their effects on inflammation/oxidation biomarkers and atherosclerosis in atherogenic diet-fed SR-B1 KO/ApoER61(h/h) mice. METHODS AND RESULTS: Mice were pre-treated for 5 weeks before and during atherogenic diet feeding with vitamin C and E added to water and diet, respectively. Compared to a control group, combined vitamin C and E administration reduced serum total cholesterol and triglyceride levels by decreasing apo B-48-containing lipoproteins, remodeled HDL particles by reducing phospholipid as well as increasing PON1 and apo D

content, and diminished PLTP activity and levels. Vitamin supplementation improved HDL antioxidant function and lowered serum TNF-alpha levels. Vitamin C and E combination attenuated atherogenesis and increased lifespan in atherogenic diet-fed SR-B1 KO/ApoER61(h/h) mice. CONCLUSIONS: Vitamin C and E administration showed significant lipid metabolism regulating effects, including HDL remodeling and decreased levels of apoB-containing lipoproteins, in mice. In addition, this vitamin supplementation generated a cardioprotective effect in a murine model of severe and lethal atherosclerotic ischemic heart disease.

[3] *Wang C, Zheng Q, Zhang M, Lu H*. **Lack of ethnic differences in the pharmacokinetics and pharmacodynamics of evolocumab between Caucasian and Asian populations**. British journal of clinical pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30225890
ABSTRACT
AIM: To evaluate the potential ethnic differences in the pharmacokinetics (PK) and pharmacodynamics (PD) of evolocumab in Caucasian and Asian populations using population PK/PD modelling analysis. METHODS: Data from different ethnic groups in 5 Phase I clinical trials, including two American studies, one Japanese study and two Chinese studies, were chosen for model building and evaluation. A target-mediated drug disposition (TMDD) model together with an indirect response model best captured evolocumab binding and the removal of unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) as well as a reduction in circulating low-density lipoprotein cholesterol (LDL-C). Ethnicity and other related factors (body weight, target expression level, etc.) were analysed as potential covariates. RESULTS: The estimated linear clearance and volume of evolocumab were 0.24 L/day and 2.75 L, respectively, which was consistent with the previous modelling results from the American trials. Detailed parameters are shown in Table 2. The time course of the LDL-C reduction was described by an indirect response model with the elimination rate of LDL-C being modulated by unbound PCSK9. The concentration of unbound PCSK9 associated with the half-maximal inhibition (IC50) of LDL-C elimination was 1.28 nM. Both the PK and PD characteristics were consistent between the Caucasian and Asian populations. CONCLUSION: The TMDD model successfully described the PK and PD characteristics of evolocumab, and this analysis found no significant differences in the PK/PD relationship for its LDL-C lowering effects between Caucasians and Asians.

[4] *Yao D, Jing T, Niu L et al.* **Amyloidogenesis Induced by Diet Cholesterol and Copper in a Model Mouse for Alzheimer's Disease and Protection Effects of Zinc and Fluvastatin**. Brain research bulletin 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30227236
ABSTRACT
Alzheimer's disease (AD) is one of the severe chronic diseases characterized with amyloid beta (Abeta) aggregation and formation of senile-plaque (SP) like structures. Numerous risk factors including trace metals and cholesterol in diet have been identified as potential players for the onset of Abeta aggregation. To further illustrate the effects of copper and cholesterol in AD pathology, we employed an AD model mouse strain (Tg2567) and examined the histological and biochemical changes in the mouse brains and blood. When supplied with 0.1 mg/L copper in

drinking water and 2% cholesterol in the food, the mice showed significant deposit of amyloid beta (Abeta) and SP plaque formation in hippocampus and temporal cortex regions in their brains. These mice also showed elevated superoxide dismutase (SOD) activity and increased ceruloplasmin (CP) concentration, and reduced glutathione peroxidase (Gpx) activity in the blood. The physiological function tests indicated these mice were significantly impeded on learning and memory. We further examined the counteracting effects of 0.1 mg/L zinc and 1.0 mg/L fluvastatin (Cholesterol-lowering drug). The combination of zinc and fluvastatin effectively reversed the copper/cholesterol caused memory loss, anatomic amyloid deposits and the biochemical changes in the blood. This work provides more evidence of high-level cholesterol and copper as risk factors to trigger amyloid aggregation and mental dementia; zinc and reduction of food cholesterol levels can protect the animals from amyloid accumulation and learning impairment. The beneficial outcomes of zinc and fluvastatin could hint some potential usages in preventive measures for high-risk AD individuals, but further rigorous test are needed.

[5] *Mickiewicz A, Borowiec-Wolna J, Bachorski W et al.* **Long-term lipoprotein apheresis in the treatment of severe familial hypercholesterolemia refractory to high intensity statin therapy: Three year experience at a lipoprotein apheresis centre**. Cardiology journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30234904

ABSTRACT

BACKGROUND: Severe familial hypercholesterolemia (FH) individuals, refractory to conventional lipid-lowering medications are at exceptionally high risk of cardiovascular events. The established therapeutic option of last choice is lipoprotein apheresis (LA). Herein, it was sought to investigate the clinical usefulness of LA in a highly selected group of severe heterozygous FH (HeFH), as recently described by the International Atherosclerosis Society (IAS), for their efficacy in lipid reduction and safety. METHODS: Efficacy and safety of LA were investigated in 318 sessions of seven severe HeFH females with cardiovascular disease, over a mean period of 26.9 +/- 6.5 months. Relative reduction of low density lipoprotein cholesterol (LDL-C) >/= 60%, clinical complications and vascular access problems were evaluated and compared between the direct adsorption of lipoproteins (DALI) and lipoprotein filtration (Membrane Filtration Optimized Novel Extracorporeal Treatment [MONET]). Additionally, lipoprotein (a) [Lp(a)], total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fibrinogen concentrations were investigated. RESULTS: The relative reduction of LDL-C, TC, TG and Lp(a) were 69.4 +/- 12.9%, 59.7 +/- 9.1, 51.5 +/- 14.2% and 71.3 +/- 14.4%, respectively. A similar efficacy was found in both systems in LDL-C removal. DALI system led to larger depletions of Lp(a) (80.0 [76-83]% vs. 73.0 [64.7-78.8]%; $p < 0.001$). The frequency of clinical side effects and vascular access problems were low (8.5%). CONCLUSIONS: Long-term LA in severe HeFH individuals is safe and efficiently reduces LDL-C and Lp(a). Higher efficacy of the DALI system than MONET in Lp(a) removal may indicate the need for individualized application of the LA system in severe HeFH individuals.

[6] *Genena K, Ali M, Christmas D, Siu H*. **Coronary Artery Ectasia Presenting as a Non-ST Elevation Myocardial Infarction in a Young Adult: Case Presentation and Literature Review**. Case reports in cardiology 2018; 2018:9817812.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30225148

ABSTRACT

While acute coronary syndromes most commonly occur secondary to unstable atherosclerotic plaque, coronary aneurysms, also known as coronary artery ectasia (CAE), represent a less common etiology. Whereas coronary atherosclerosis accounts for about 50% of CAE, the remaining 50% are either congenital or secondary to a host of inflammatory and connective tissue disorders, with Kawasaki disease being a well-known association. Patients with CAE have worse outcomes than the general population regardless of the presence of associated atherosclerotic coronary artery disease. We report the case of a young male presenting with chest pain, a right bundle branch block on electrocardiography, an elevated troponin level, and a regional wall motion abnormality on echocardiography who is found to have diffuse coronary artery ectasia on coronary angiography and is managed medically with dual antiplatelet therapy.

[7] *Xia Y, Zhu L, Yuan X, Wang Y*. **Synthesis and evaluation of 2-azetidinone and 1H-pyrrole-2,5-dione derivatives as cholesterol absorption inhibitors for reducing inflammation response and oxidative stress**. Chemistry & biodiversity 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30230227

ABSTRACT

Excess lipid accumulation can initiate the development and progression of atherosclerotic lesions, thus eventually leading to cardiovascular disease. Lipid-lowering medication therapy is one of the cornerstones of cardiovascular disease therapy. On the basis of the cholesterol absorption inhibitor ezetimibe, we successfully synthesized seven 2-azetidinone derivatives and eighteen 1H-pyrrole-2,5-dione derivatives. Most of the new compounds significantly inhibited cholesterol uptake in vitro. In addition, one of the most active inhibitors, compound 14q, showed no cytotoxicity in L02 and HEK293T cell lines. Further evaluation indicated 14q considerably inhibited the amount of TNF-alpha, ROS, MDA, and LDH in vitro. Therefore, 14q might be a novel cholesterol absorption inhibitor.

[8] *Saedi A, Rostamizadeh K, Parsa M et al.* **Preparation and Characterization of Nanostructured Lipid Carriers as Drug Delivery System: Influence of Liquid Lipid Types on Loading and Cytotoxicity**. Chemistry and physics of lipids 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30219661

ABSTRACT

In this study, we aimed to investigate the influence of liquid lipid types on different features of NLC. Four variations of liquid lipids such as coconut oil, fish oil, black seed oil and linseed oil were used, while for all variations, cetyl palmitate was used as the solid lipid. Different NLC were characterized and compared in terms of particle size, zeta potential, polydispersity index (PDI), drug entrapment percentage and drug loading capacity. The results indicated that NLC containing black seed oil has the smallest size. Other features like PDI, zeta potential and entrapment efficiency were the same for all the liquid lipids. By close margins, the NLC containing black seed oil had the highest percent of drug release and antioxidant activity compared to the rest. Diffusion was the major mechanism of the drug release according to the drug release kinetic fitted by Higuchi's model. Differential scanning calorimetry (DSC) and

fourier transform infrared spectroscopy (FT-IR) confirmed no strong interaction between NLC constituents. The particles showed spherical shape morphology under atomic force microscopy (AFM). According to the cell viability assay on MCF-7 cell line, the curcumin loaded NLC composed of linseed oil showed better cytotoxic activity compared to the free curcumin.

[9] *Ajith TA, Jayakumar TG*. **Omega-3 fatty acids in coronary heart disease: Recent updates and future perspectives**. Clinical and experimental pharmacology & physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30230571
ABSTRACT
Incidence of coronary heart disease (CHD) increases worldwide with varying etiological factors. In addition to the control of risk factors, dietary modification has been recommended to reduce the prevalence. Omega-3 (omega-3) fatty acids (FAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), of fish oil are beneficial for the prevention of CHD. The effect can be ascribed to anti-inflammatory, vasodilating, antiarrhythmic, antihypertensive activities and lowering of triacyl glycerol level. The American Heart Association advises two fish meals per week in subjects without CHD or supplementation of 1 g of EPA plus DHA per day in subjects with CHD. Despite the beneficial effects of EPA/DHA reported in some of the clinical trials, results of many others were inconsistent that can be ascribed to short duration of studies, low doses of omega-3 FAs, variations in the EPA:DHA ratio, selection of patients with different risk factors or interaction of omega-3 FAs with drugs used in the therapy. Therefore, well designed clinical trials in various populations are warranted. This article discusses the current update and future prospective of omega-3 FAs in CHD.

[10] *Nowak KL, Wang W, Farmer-Bailey H et al.* **Vascular Dysfunction, Oxidative Stress, and Inflammation in Autosomal Dominant Polycystic Kidney Disease**. Clinical journal of the American Society of Nephrology : CJASN 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30228110
ABSTRACT
BACKGROUND AND OBJECTIVES: Both increased arterial stiffness and vascular endothelial dysfunction are evident in patients with autosomal dominant polycystic kidney disease, even early in the course of the disease when kidney function in preserved. Vascular dysfunction in autosomal dominant polycystic kidney disease is thought to be related to vascular oxidative stress and inflammation, but direct evidence is lacking. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: We assessed carotid-femoral pulse-wave velocity (arterial stiffness) and brachial artery flow-mediated dilation (vascular endothelial function) in participants with early-stage autosomal dominant polycystic kidney disease (eGFR>/=60 ml/min per 1.73 m(2)) and a history of controlled hypertension and in healthy controls. Brachial artery flow-mediated dilation was also assessed after infusion of ascorbic acid to inhibit vascular oxidative stress compared with saline. Vascular endothelial cells were collected from a peripheral vein to measure expression of proteins, and circulating markers were also assessed by ELISA or liquid chromatography-tandem mass spectrometry. RESULTS: In total, 61 participants with autosomal dominant polycystic kidney disease (34+/-9 years old [mean+/-SD]) and 19 healthy controls (30+/-5 years old) were studied. Carotid-femoral pulse-wave velocity was higher in participants

with autosomal dominant polycystic kidney disease compared with healthy controls (650+/-131 versus 562+/-81 cm/s; P=0.007). Brachial artery flow-mediated dilation was 8.2%+/-5.8% in participants with autosomal dominant polycystic kidney disease and 10.8%+/-4.7% in controls (P=0.08). Among participants with autosomal dominant polycystic kidney disease, flow-mediated dilation increased from 7.7%+/-4.5% to 9.4%+/-5.2% with ascorbic acid, a difference of 1.72 (95% confidence interval, 0.80 to 2.63), whereas in control participants, flow-mediated dilation decreased nonsignificantly from 10.8%+/-4.7% to 10.6%+/-5.4%, a difference of -0.20 (95% confidence interval, -1.24 to 0.84; P interaction =0.02). Endothelial cell protein expression of NF-kappaB was greater in participants with autosomal dominant polycystic kidney disease (0.48+/-0.12 versus 0.41+/-0.10 [intensity versus human umbilical vein endothelial cell control]; P=0.03). However, circulating oxidative stress markers and bioactive lipid mediators did not significantly differ according to the autosomal dominant polycystic kidney disease diagnosis. CONCLUSIONS: These results provide support for the hypothesis that vascular oxidative stress and inflammation develop with autosomal dominant polycystic kidney disease. PODCAST: This article contains a podcast at https://www.asn-online.org/media/podcast/CJASN/2018_09_18_CJASNPodcast_18_10_.mp3 .

[11] *Barbour LA, Hernandez TL*. **Maternal Lipids and Fetal Overgrowth: Making Fat from Fat**. Clinical therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30236792
ABSTRACT
There is increasing recognition that maternal glucose concentrations lower than those previously used for diagnosis of gestational diabetes mellitus (GDM) and targeted for treatment can result in excess fetal growth. Yet, mothers with GDM who appear to have optimal glycemic control and mothers with obesity and normal glucose tolerance still have a significantly increased risk for delivering infants who are large for gestational age, or even more importantly, who have increased adiposity at birth. What is less appreciated is that in addition to glucose, maternal lipids are also substrates for fetal fat accretion and that placental lipases can hydrolyze maternal triglycerides (TGs) to free fatty acids for fetal-placental availability. Maternal TG levels are 40% to 50% higher on average in mothers with obesity and GDM compared to those in normal-weight mothers early in pregnancy and are sustained at higher levels throughout gestation. Increasing evidence supports that maternal TG, both fasting and postprandial, are also predictors of newborn adiposity (newborn %fat), a risk factor for childhood obesity, and that early exposure is at least as strong of a risk factor as later exposure in mothers with obesity. In the setting of maternal nutrient excess and maternal insulin resistance, which lead to fetal hyperinsulinemia, excess free fatty acid exposure in the fetus may result in lipid storage and fetal fat development in subcutaneous and possibly other depots. In this commentary, we provide further evidence to make a case for targeting maternal fasting and postprandial TG in mothers with obesity who have elevated TG in early pregnancy to determine whether a TG-lowering interventional approach might limit fetal overgrowth and potentially mitigate the intrauterine contribution to childhood obesity and metabolic disease.

[12] *Khan R, Rheaume E, Tardif JC*. **Examining the Role of and Treatment Directed at IL-1beta in Atherosclerosis**. Current atherosclerosis reports 2018; 20:53.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30219977

ABSTRACT

PURPOSE: The purpose of this review was to examine the role of IL-1beta in the inflammatory process central to the development of atherosclerosis and to discuss current clinical evidence for treatments targeting IL-1beta in coronary artery disease. RECENT FINDINGS: IL-1beta has been shown to modulate atherosclerotic plaque progression by upregulating the synthesis of adhesion molecules on endothelial cells, as well increasing activation and proliferation of vascular smooth muscle cells. Animal studies have further suggested that alterations in the balance between agonists and antagonists of IL-1beta are important in promoting atherosclerosis. In humans, preliminary assessment of therapy targeting IL-1beta noted early reductions in serum inflammatory biomarkers among those with systemic inflammatory or coronary artery disease. The CANTOS trial, a large randomized double-blind study found that canakinumab, a monoclonal antibody targeting IL-1beta, reduced ischemic events in patients being treated for secondary prevention. Cellular, animal, and now clinical studies have suggested a role for therapies aimed at IL-1beta for treatment of CAD. However, given potential side effects and costs of these medications, further study is required to determine which patients may be most suited for treatment above current standard of care.

[13] *Nichols GA, Philip S, Reynolds K et al.* **Increased Residual Cardiovascular Risk in Patients with Diabetes and High vs. Normal Triglycerides Despite Statin-Controlled LDL Cholesterol**. Diabetes Obes Metab 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30225881

ABSTRACT

AIMS: To determine whether high triglycerides (TG) in the presence of statin-controlled LDL-C influence cardiovascular disease (CVD) risk among patients with diabetes in real-world clinical practice. MATERIALS AND METHODS: We identified adults with diabetes from the Southern California and Northwest regions of Kaiser Permanente. We included patients on statin therapy with LDL-C from 40-100 mg/dL who were not on other lipid-lowering therapies and had a prior diagnosis of atherosclerotic CVD or at least one other CVD risk factor. We grouped patients into high (200-499 mg/dL, n=5,542) or normal (<150 mg/dL, n=22,411) TGs from 2010 through December 2016 to compare incidence rates and rate ratios of first non-fatal MI, non-fatal stroke, unstable angina, coronary revascularization. We adjusted the multivariable analyses for age, sex, race/ethnicity, smoking status, blood pressure, HbA1c, serum creatinine, presence of ischemic heart disease, and study site. RESULTS: The adjusted rate ratios for the four outcomes were all statistically significantly different. The incidence rate for non-fatal MI was 30% higher in the high TG group (rate ratio 1.30, 95% CI 1.08-1.58, p=0.006). The rate was 23% higher for non-fatal stroke (1.23, 1.01-1.49, p=0.037), d 21% higher for coronary revascularization (1.21, 1.02-1.43, p=0.027), and nonsignificantly 33% higher for unstable angina (1.33, 0.87-2.03, p=0.185). CONCLUSIONS: Despite statin-controlled LDL-C levels, CV events were greater among patients with diabetes and high TG levels. Because we controlled for cardiometabolic risk factors, it is likely that the difference in TG levels contributed to the excess risk observed in patients with high TGs.

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[14] *Chikowore T, Cockeran M, Conradie KR, van Zyl T*. **C679X loss-of-function PCSK9 variant lowers fasting glucose levels in a black South African population: A longitudinal study**. Diabetes Res Clin Pract 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30227170
ABSTRACT
AIMS: To determine the longitudinal association of the loss-of-function (LOF) PCSK9 variants (C679X and A443T), proxies of PCSK9 inhibitor drugs, with LDL-C, fasting glucose and glycated hemoglobin. METHODS: We conducted a five year, longitudinal study, nested within the Prospective Urban and Rural Epidemiology study, among 737 apparently healthy, male and female black South Africans of the North West province. Genotyping of the C679X and A443T PCSK9 variants was achieved using Taqman assays from Applied Biosystems. Generalized estimating equations were used to determine longitudinal association of the A443T and C679X PCSK9 variants with LDL-C, fasting glucose and glycated hemoglobin. RESULTS: C679X and A443T variant carriers were associated with significant reductions in LDL-C of -0.98(-1.29, -0.67) mmol/L; p < 0.001) and -0.39(-0.57, -0.20) mmol/L; p < 0.001) respectively, compared to the non-carriers. Only C679X variant was independently associated with reductions in fasting glucose of -0.37 (-0.61, -0.13) mmol/L; p = 0.002) compared to non-carriers. However, the association of the selected variants with glycated hemoglobin were not significant.C679X and A443T carriers were associated with -0.07 (-0.23, 0.09) %; p = 0.400), 0.05 (-0.13, 0.22) %; p = 0.599) of glycated haemoglobin respectively. CONCLUSION: Our results indicated that carriers of A443T and C679X variants exhibit sustained low LDL-C levels over 5 years and have varied effects on T2D biomarkers compared to non-carriers.

[15] *Rashid I, Maghzal GJ, Chen YC et al.* **Myeloperoxidase is a potential molecular imaging and therapeutic target for the identification and stabilization of high-risk atherosclerotic plaque**. European heart journal 2018; 39:3301-3310.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30219874
ABSTRACT
Aims: As the inflammatory enzyme myeloperoxidase (MPO) is abundant in ruptured human atherosclerotic plaques, we aimed to investigate the role of MPO as a potential diagnostic and therapeutic target for high-risk plaque. Methods and results: We employed the tandem stenosis model of atherosclerotic plaque instability in apolipoprotein E gene knockout (Apoe-/-) mice. To test the role of MPO, we used Mpo-/-Apoe-/- mice and the 2-thioxanthine MPO inhibitor AZM198. In vivo MPO activity was assessed by liquid chromatography-tandem mass spectrometry detection of 2-chloroethidium generation from hydroethidine and by bis-5HT-DTPA-Gd (MPO-Gd) molecular magnetic resonance imaging (MRI), while plaque phenotype was verified histologically. Myeloperoxidase activity was two-fold greater in plaque with unstable compared with stable phenotype. Genetic deletion of MPO significantly increased fibrous cap thickness, and decreased plaque fibrin and haemosiderin content in plaque with unstable phenotype. AZM198 inhibited MPO activity and it also increased fibrous cap thickness and decreased fibrin and haemosiderin in plaque with unstable phenotype, without affecting lesion monocytes and red blood cell markers or circulating leukocytes and lipids. MPO-Gd MRI demonstrated sustained enhancement of plaque with unstable phenotype on T1-weighted imaging that was two-fold greater than stable plaque and was significantly attenuated by both

AZM198 treatment and deletion of the Mpo gene. Conclusion: Our data implicate MPO in atherosclerotic plaque instability and suggest that non-invasive imaging and pharmacological inhibition of plaque MPO activity hold promise for clinical translation in the management of high-risk coronary artery disease.

[16] *Deng X, Ma J, Song M et al.* **Effects of products designed to modulate the gut microbiota on hyperlipidaemia**. European journal of nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30238315
ABSTRACT
PURPOSE: Fatalities due to heart and cerebrovascular diseases caused by uncontrolled hyperlipidaemia increase every year; on the other hand, lipid-lowering drugs are known to cause side effects. The gut microbiota has been thoroughly investigated by researchers and consumers, because they have unique functional properties and littler side effects. However, the effects of the gut microbiota remain controversial. We conducted a meta-analysis to assess the effects of products designed to modulate the gut microbiota on various hyperlipidaemias. METHODS: We systematically searched PubMed, Embase, Cochrane Library (Central), and Web of Science for randomized controlled trials (published before June 2017, and those only in English) to compare treatment (products designed to modulate the gut microbiota) versus placebo. Our main endpoints were total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) in serum. We assessed pooled data using a fixed effects model. RESULTS: Of 1337 identified studies, 21 were eligible and included in our analysis (n = 1436 participants). The combined estimate of effect size for the impact of products designed to modulate the gut microbiota on serum TC (WMD - 11.07 mg/dL, 95% CI - 13.72 to - 8.43, $p < 0.001$), LDL-C (WMD - 10.96 mg/dL, 95% CI - 13.37 to - 8.56, $p < 0.001$), and HDL-C (WMD 0.72 mg/dL, 95% CI 0.06-1.38, $p = 0.032$) were statistically significant, while no significant effect was found on TG concentrations (WMD - 0.56 mg/dL, 95% CI - 5.59 to 4.47, $p = 0.828$). Subgroup analysis showed parallel trials, probiotics, and long-term intervention had better effects on lowering blood lipid levels. CONCLUSION: Products designed to modulate the gut microbiota results in changes of the plasma lipid concentrations and these changes may protect against cardiovascular disease.

[17] *Wang H, Li J, Fu X et al.* **Effect of simvastatin on expression of VEGF and TGF-beta1 in atherosclerotic animal model of type 2 diabetes mellitus**. Experimental and therapeutic medicine 2018; 16:2889-2894.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30233664
ABSTRACT
Expression of vascular endothelial growth factor (VEGF) and transforming growth factor-beta1 (TGF-beta1) in atherosclerosis animal model of type 2 diabetes mellitus treated with simvastatin was investigated. Clean grade mature Sprague Dawley (SD) rats were divided into three groups: Normal control (n=10), model (n=13) and treatment group (n=13); low-dose simvastatin was administered. The changes of VEGF and TGF-beta1 levels were analyzed by tail vein blood sampling. The relationship between levels of VEGF, TGF-beta1 and treatment time was analyzed. The expression level of VEGF in the treatment group after 4 and 8 weeks of intervention was lower compared with the model group ($P<0.05$). The expression level of TGF-

beta1 in the treatment group after 8 weeks of intervention was higher than that in the model group (P<0.05). The expression level of VEGF in the treatment group after 8 weeks of intervention was lower than that after 1 week of intervention (P<0.05). The expression level of TGF-beta1 was increased in the model group after 8 weeks of intervention compared with 1 week before and after the intervention (P<0.05). The expression level of TGF-beta1 in the treatment group at 2, 4 and 8 weeks after intervention were significantly higher than that before intervention (P<0.05). The expression of TGF-beta1 increased after 4 and 8 weeks after intervention compared with 1 week after intervention (P<0.05). The expression of VEGF was negatively correlated with TGF-beta1 expression in the treatment group; negative correlation was found between VEGF and treatment time. There was a positive correlation between TGF-beta1 and treatment time. VEGF and TGF-beta1 may be involved in the development of type 2 diabetes (T2MD) atherosclerosis (AS). Simvastatin may play a therapeutic role in T2MD AS by downregulating VEGF and upregulating the expression of TGF-beta1.

[18] *Wang C, Xu W, Liang M et al.* **CTRP13 inhibits atherosclerosis via autophagy-lysosome-dependent degradation of CD36**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201801267RR.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30222079
ABSTRACT
C1q/tumor necrosis factor-related protein 13 (CTRP13) is a secreted adipokine that can ameliorate abnormal glucose and lipid metabolism. However, the functional role of CTRP13 in the development of atherosclerotic plaques has yet to be described. In this study, we collected blood samples from patients of coronary artery diseases and apolipoprotein E (ApoE)(-/-) mice that were fed a Western diet for 12 wk to induce atherosclerosis and found that serum CTRP13 level was decreased. En face staining of aortas and aortic sinus in ApoE(-/-) mice showed that ectopic CTRP13 infusion in vivo dramatically decreased lesion areas, as well as reduced inflammatory responses with less macrophage content. In primary peritoneal macrophages in vitro, CTRP13 supplement reduced oxidized LDL uptake, foam-cell formation, and trapping, together with the suppressed cluster of differentiation 36 (CD36) protein levels. Reduced CD36 protein level was attributed to the autophagy-lysosome-dependent degradation of CD36 at the post-transcriptional level. The blocking of autophagy-lysosome induction could increase CD36 protein level, foam-cell formation, and migration, thus abolishing the protective effects of CTRP13 on atherosclerosis. In summary, these findings define CTRP13 as a novel approach for preventing atherosclerotic plaque formation via modulation of lipid uptake and foam-cell migration.-Wang, C., Xu, W., Liang, M., Huang, D., Huang, K. CTRP13 inhibits atherosclerosis via autophagy-lysosome-dependent degradation of CD36.

[19] *Duntas LH, Brenta G*. **A Renewed Focus on the Association Between Thyroid Hormones and Lipid Metabolism**. Frontiers in endocrinology 2018; 9:511.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30233497
ABSTRACT
Thyroid dysfunction, manifesting as either overt or subclinical hypothyroidism, negatively affects lipid metabolism: this leads to hypercholesterolemia which progressively increases the risk for cardiovascular disease and, potentially, mortality. Hypercholesterolemia in

hypothyroidism is mainly due to a reduction in low-density lipoprotein (LDL) receptor activity, this accompanied by concomitant diminishing control by triiodothyronine (T3) of sterol regulatory element-binding protein 2 (SREBP-2), which modulates cholesterol biosynthesis by regulating rate-limit degrading enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) activity. Recently, 3,5-diiodothyronine (T2), a natural thyroid hormone derivative, was found to repress the transcription factor carbohydrate-response element-binding protein (ChREBP) and also to be involved in lipid catabolism and lipogenesis, though via a different pathway than that of T3. While thyroid hormone could therapeutically reverse the dyslipidemic profile commonly occurring in hypothyroidism, it should be borne in mind that the potency of the effects may be age-and sex-dependent. Thyroid hormone administration possibly also sustains and enhances the efficacy of hypolipidemic drugs, such as statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9), in patients with dyslipidemia and hypothyroidism.

[20] *Dornellas APS, Boldarine VT, Pedroso AP et al.* **High-Fat Feeding Improves Anxiety-Type Behavior Induced by Ovariectomy in Rats**. Frontiers in neuroscience 2018; 12:557.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30233288

ABSTRACT

Menopause-induced changes may include increased incidence of both depression/anxiety and obesity. We hypothesized that behavioral changes that may develop after ovarian failure could be related to neurochemical and metabolic aspects affected by this condition and that high-fat intake may influence these associations. The present study investigated in rats the effects of ovariectomy, either alone or combined with high-fat diets enriched with either lard or fish-oil, on metabolic, behavioral and monoaminergic statuses, and on gene expression of neuropeptides and receptors involved in energy balance and mood regulation. Female rats had their ovaries removed and received either standard chow (OvxC) or high-fat diets enriched with either lard (OvxL) or fish-oil (OvxF) for 8 weeks. The Sham group received only chow diet. Ovariectomy increased feed efficiency and body weight gain and impaired glucose homeostasis and serotonin-induced hypophagia, effects either maintained or even accentuated by the lard diet but counteracted by the fish diet. The OvxL group developed obesity and hyperleptinemia. Regarding components of hypothalamic serotonergic system, both ovariectomy alone or combined with the fish diet increased 5-HT2C expression while the lard diet reduced 5-HT1B mRNA. Ovariectomy increased the anxiety index, as derived from the elevated plus maze test, while both high-fat groups showed normalization of this index. In the forced swimming test, ovariectomy allied to high-lard diet, but not to fish-oil diet, reduced the latency to immobility, indicating vulnerability to a depressive-like state. Linear regression analysis showed hippocampal AgRP to be negatively associated with the anxiety index and hypothalamic AgRP to be positively associated with the latency to immobility. These AgRp gene expression associations are indicative of a beneficial involvement of this neuropeptide on both depression and anxiety measures. The present findings demonstrate metabolic, neurochemical and behavioral alterations after ovaries removal and highlight a positive effect of high-fat feeding on the anxiety-like behavior shown by ovariectomized animals. Since the polyunsaturated omega-3 intake (fish diet), unlike the saturated fat intake (lard diet), failed to induce

deleterious metabolic or neurochemical consequences, further studies are needed focusing on the potential of this dietary component as an adjuvant anxiolytic agent after menopause.

[21] *Cicero AFG, Fogacci F, Bove M et al.* **Optimizing Lipid Pattern by Adding a Combined Nutraceutical or Pravastatin to Fenofibrate Treatment in Hypertriglyceridemic Subjects: Single Site, Randomized, Open-Label, Post-Market Clinical Investigation**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30229462
ABSTRACT
INTRODUCTION: Fenofibrate is an effective and safe treatment for hypertriglyceridemia. However, after TG reduction a residual dyslipidemia could appear and require further treatment. AIM: To comparatively evaluate the short-term tolerability and efficacy of a combined lipid-lowering nutraceutical and pravastatin 40 mg in fenofibrate treated patients. METHOD: We prospectively enrolled 40 patients well-tolerating treatment with micronized fenofibrate 145 mg/day and with residual dyslipidemia (LDL-C > 115 mg/dL and TG > 150 mg/dL). Exclusion criteria have been type 2 diabetes, Familial Hypercholesterolemia, previous cardiovascular diseases and severe chronic kidney disease. Then, we have randomly assigned the patients to treatment with pravastatin 40 mg or a combined lipid-lowering nutraceutical (Armolipid Plus((R)), containing monacolin 3 mg and berberine 500 mg). RESULTS: After 8 weeks of treatment, 80% of pravastatin treated patients (N. 16/20) and 75% of those treated with Armolipid Plus((R)) (N. 15/20) reached the desired LDL-C target, while 50% of pravastatin treated patients (N. 10/20) and 80% of the Armolipid Plus((R)) treated ones reached the desired TG target (N. 16/20). No one adverse event has been registered during Armolipid Plus((R)), while 1 patient claimed myalgia and 1 reported significant increase of CPK (> 3 ULN) during pravastatin treatment. Both patients were then treated with Armolipid Plus((R)) with resolution of symptoms and CPK increase, respectively. CONCLUSION: In hypertriglyceridemic patients treated with fenofibrate, the association with a combined lipid lowering nutraceutical seem to be more effective in optimizing residual hypertriglyceridemia than pravastatin 40 mg, while being more tolerable and having similar effect on LDL-C plasma level.

[22] *Katsiki N, Mikhailidis DP*. **Lipids: a personal view of the past decade**. Hormones (Athens, Greece) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30229482
ABSTRACT
The past decade has witnessed considerable progress in the field of lipids. New drugs have been "rapidly" developed and some of these drugs have already been evaluated in event-based large trials. This evidence has led to the guidelines recommending new, more aggressive treatment goals for low-density lipoprotein cholesterol (LDL-C) levels. Although LDL-C remains the principal goal for cardiovascular disease (CVD) risk reduction, there has also been considerable interest in other lipid variables, such as high-density lipoprotein cholesterol, triglycerides, and lipoprotein(a). Statin intolerance is now considered a very important topic in daily clinical practice. This has resulted in more attention focusing on non-statin drugs [e.g., ezetimibe and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors] and statin-related side effects. The latter mainly involve muscles, but there is also a need to consider other

adverse effects associated with statin use (e.g., new onset diabetes). New specific areas of statin use have attracted interest. For example, statin-loading before procedures (e.g., coronary stenting), the prevention of stroke, and the treatment of non-alcoholic fatty liver disease (NAFLD). Statins will remain the most widely used drugs to treat dyslipidaemia and decrease CVD risk. However, we also need to briefly consider some other lipid-lowering drugs, including those that may become available in the future.

[23] *Grazioso G, Bollati C, Sgrignani J et al.* **The First Food-Derived Peptide Inhibitor of the Protein-Protein Interaction between Gain-of-Function PCSK9D374Yand the LDL Receptor**. Journal of agricultural and food chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30226051
ABSTRACT
Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) is involved in cholesterol homeostasis, because it induces the low density lipoprotein receptor (LDLR) degradation. This protein may carry some positive or negative mutations: PCSK9D374Y is one of the most dangerous gain-of-function mutations. This paper reports the identification of the first food-derived peptide able to inhibit the protein-protein interaction (PPI) between PCSK9D374Y and LDLR. In fact, T9 (GQEQSHQDEGVIVR), an absorbable peptide deriving from lupin ss-conglutin, is able to impair the PPI between PCSK9D374Y and the LDLR, with an IC50 value equal to 285.6+/-2.46 muM. The consequence of this inhibition is an increase of the protein level of the LDLR located on hepatic cell membranes up to 74.3+/-4.4% and the restoration of the functional capability of HepG2 cells to uptake extracellular LDL up to 83.1+/-1.6%. Finally, the putative binding mode of T9 to the LDLR binding site located on PCSK9D374Y was postulated by in silico tools.

[24] *Wight TN*. **A Role for Extracellular Matrix in Atherosclerotic Plaque Erosion**. Journal of the American College of Cardiology 2018; 72:1504-1505.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30236313
ABSTRACT

[25] *Leite GAA, de Barros JWF, Martins ADC, Jr. et al.* **Ascorbic acid supplementation ameliorates testicular hormonal signaling, sperm production and oxidative stress in male rats exposed to rosuvastatin during pre-puberty**. Journal of applied toxicology : JAT 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30240002
ABSTRACT
Dyslipidemias are occurring earlier in the population due to the augmentation of obesity. Rosuvastatin reduces cholesterol and triglycerides; however, previous studies have shown that it may affect male reproduction. Ascorbic acid (AA), an antioxidant compound, plays a protective role in the male reproductive system. This study aimed to evaluate whether pre-pubertal exposure to rosuvastatin may impair testicular structure and antioxidant status in male rats and if supplementation with AA may alleviate these damages. Male rats were randomly divided into six experimental groups (n = 10) on postnatal day (PND) 23 and received the different treatments by gavage from PND 23 to 53. The experimental groups received vehicle (saline solution 0.9%), 3 or 10 mg/kg/day of rosuvastatin diluted in saline solution 0.9%, supplementation with 150 mg/day of AA, 3 mg/kg/day of rosuvastatin in association with 150

mg/day of AA or 10 mg/kg/day of rosuvastatin associated with 150 mg/day of AA. Testicular parameters were assessed on PND 53 and 110. There were diminished androgen receptors staining in the Sertoli cells and increased germ cell death in rosuvastatin-exposed groups, in both periods. Spermatids showed lower estrogen alpha-receptors staining in the group exposed to 10 mg of statin at adulthood. There were androgen depletion and increased lipid peroxidation and catalase activity in statin-exposed groups. Rosuvastatin exposure during pre-puberty impaired testicular structure, steroid receptor distribution and increased oxidative stress; however, AA was able to ameliorate the impairment provoked by statin exposure.

[26] *Oh TK, Park HY, Shin HJ et al.* **The Role of Perioperative Statin Use in the Prevention of Delirium After Total Knee Replacement Under Spinal Anesthesia**. The Journal of arthroplasty 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30236494
ABSTRACT
BACKGROUND: The relationship between statin use and incidence of postoperative delirium (POD) is controversial. We investigated the association between perioperative statin use and occurrence of delirium after total knee arthroplasty (TKA) under spinal anesthesia. METHODS: We retrospectively reviewed the electronic medical records of patients who underwent TKA under spinal anesthesia at a single tertiary care hospital between January 2005 and October 2017. POD incidence was recorded for patients who received statins continuously from 1 month before surgery until discharge and for patients who did not receive any statins. Univariable and multivariable logistic regression analyses were conducted to investigate an association between occurrence of POD and perioperative statin use. RESULTS: In total, 6020 procedures were included, and 992 (16.4%) were associated with perioperative statin use. POD was confirmed for 304 (5.0%) procedures. The statin group showed a 1.7% significant lower incidence (P = .017) of POD (35/992, 3.5%) than the no statin group (1420/5,028, 5.4%). In multivariable logistic regression analysis, the POD incidence in the statin group was 34% lower than that in the no statin group (odds ratio [OR] 0.66, 95% confidence interval [CI] 0.45-0.97, P = .036]. Moreover, the POD incidence was decreased by 37% (OR 0.63, 95% CI 0.40-0.99, P = .047) and 79% (OR 0.21, 95% CI 0.05-0.88, P = .033) respectively, when atorvastatin and simvastatin were administered. CONCLUSION: Continuous perioperative statin use may be associated with a significantly lower risk of delirium after TKA under spinal anesthesia; simvastatin was the most effective statin for POD prevention.

[27] *Liu Q, Wang Y, Cheng X*. **The functional effect of atorvastatin dose-dependent via inflammation factors on acute ST segment elevation myocardial infarction after emergency percutaneous coronary intervention**. Journal of cardiovascular medicine (Hagerstown, Md.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30222665
ABSTRACT
OBJECTIVE: To investigate the effect of different doses of atorvastatin on patients with acute ST segment elevation myocardial infarction (MI) after emergency percutaneous coronary intervention (PCI). METHODS: A total of 265 patients with acute ST segment elevation MI who underwent emergency PCI were enrolled, 133 in high-dose atorvastatin administration (40

mg/day) and 132 in moderate-dose atorvastatin administration (20 mg/day). All the patients continued treatment for 1 year. The incidences of major adverse cardiovascular events (MACE) were recorded, including cardiovascular death, spontaneous MI, and unplanned revascularization. The association between clinical incidences and different doses of atorvastatin treatment was studied. RESULTS: Through tracking 1 year's treatment, the level of low-density lipoprotein cholesterol was lower in high-dose atorvastatin administration than in moderate treatment (1.6 +/- 0.6 vs. 1.8 +/- 0.6, P = 0.041). MACE significantly decreased in high-dose atorvastatin administration than in moderate treatment (9.8 vs. 18.2%, P = 0.03). Spontaneous MI was significantly more attenuated in high-dose treatment than in moderate treatment (6.8 vs. 12.8%, P = 0.03). Unplanned revascularization robustly decreased in patients with high-dose administration than those with moderate-dose treatment (5.2 vs. 8.3%, P = 0.03). There was no difference in the rate of adverse events between the two groups. CONCLUSION: For patients with acute ST segment elevation MI who underwent emergency PCI, high-dose atorvastatin could provide better performance than moderate-dose in our long-term tracking.

[28] *Braun LR, Feldpausch MN, Czerwonka N et al.* **Effects of Pitavastatin on Insulin Sensitivity and Liver Fat: A Randomized Clinical Trial**. The Journal of clinical endocrinology and metabolism 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30239757
ABSTRACT
Context: HMG-CoA reductase inhibitors (statins) are widely prescribed. Statins may have important metabolic effects on insulin sensitivity and liver fat, but limited studies have assessed these effects using euglycemic hyperinsulinemic clamp, stable isotopes, and 1H magnetic resonance spectroscopy (MRS) for liver fat quantification. Objective: To study the effects of pitavastatin on hepatic fat and insulin sensitivity. Design: Six month, double-blind, randomized, placebo-controlled trial. Setting: Academic clinical research center in Boston, MA. Participants: Overweight, insulin-resistant, men aged 40-65 years who had not received statin therapy for >/= 1 year. Interventions: Pitavastatin 4mg or placebo daily. Outcome: The primary endpoints were changes in insulin sensitivity measured by euglycemic hyperinsulinemic clamp and liver fat measured by 1H-MRS. Results: Pitavastatin showed no effect on endogenous glucose production (DeltaRa glucose 0.07+/-0.07 vs. 0.04+/-0.07 mg/kg/min, pitavastatin vs. placebo, P=0.76) or insulin stimulated glucose uptake during "low dose" (DeltaM 0.1+/-0.1 vs. -0.3+/-0.2 mg/kg/min, P=0.11) and "high dose" (DeltaM -0.5+/-0.3 vs. -0.7+/-0.4 mg/kg/min, P=0.70) euglycemic hyperinsulinemic clamps. There was also no effect of pitavastatin on fasting glucose, hemoglobin A1c, and 2-hour glucose following 75g glucose challenge. There was also no change in liver fat fraction (-1+/-1 vs. -0+/-1%, P=0.56). Conclusion: Compared to placebo, pitavastatin did not affect hepatic or whole-body insulin sensitivity, and it did not reduce liver fat.

[29] *Tada H, Kawashiri MA, Nomura A et al.* **Oligogenic familial hypercholesterolemia, LDL cholesterol, and coronary artery disease**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30241732
ABSTRACT

BACKGROUND: The genetic background of severe familial hypercholesterolemia (FH) has yet to be determined. OBJECTIVE: We tested if genetic variants associated with low-density lipoprotein (LDL)-altering autosomal recessive diseases influenced LDL cholesterol levels and the odds for coronary artery disease in patients with high LDL cholesterol. METHODS: We recruited 500 individuals with elevated LDL cholesterol levels (>/=180 mg/dL or >/=140 mg/dL for subjects <15 years). We sequenced the exons of 3 FH genes (LDLR, apolipoprotein B, and proprotein convertase subtilisin/kexin type 9) and 4 LDL-altering accessory genes (ABCG5, ABCG8, APOE, and LDL receptor adaptor protein 1). In addition, 4 single nucleotide polymorphisms associated with polygenic FH in East Asian subjects were genotyped. Oligogenic FH patients were defined as those who harbored damaging variants of both conventional FH genes and LDL-altering accessory genes. RESULTS: We identified damaging variants of conventional FH genes in 248 participants (50%). We also detected damaging variants in accessory genes in 57 patients (11%) and identified oligogenic FH in 27 of these patients (5%). Polygenic score in the subjects without any FH mutations was significantly higher than those in any other groups. Compared with monogenic FH, oligogenic FH exhibited significantly higher LDL cholesterol (265 mg/dL, 95% confidence interval [CI] 216-312, and 210 mg/dL, 95% CI 189-243; P = .04). Oligogenic FH exhibited higher odds for coronary artery disease when compared with monogenic FH, although it did not reach statistical significance (odds ratio 1.41, 95% CI 0.68-2.21, P = .24). CONCLUSIONS: Among patients with elevated LDL cholesterol, those with oligogenic FH had higher LDL cholesterol than monogenic FH.

[30] *Jin L, Zhou J, Shi W et al.* **Effects of six types of aspirin combination medications for treatment of acute cerebral infarction in China: A network meta-analysis**. Journal of clinical pharmacy and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30225937

ABSTRACT

WHAT IS KNOWN AND OBJECTIVE: Previous studies have shown that various aspirin combinations might be beneficial for the treatment of acute cerebral infarction (ACI). The aim of this study was to evaluate the efficacy of six aspirin combinations in the treatment of ACI using network meta-analysis (NMA). The performance of these combinations is then ranked according to results of this analysis. METHODS: Multiple databases were consulted to find randomized controlled trials (RCT) of six different aspirin combinations for the treatment of ACI. NMA was conducted on the data using stata (13.0) software. The odds ratio (OR) was calculated. The studies included in this paper were divided into a control group (aspirin alone) and an observation group (one of six aspirin combinations). RESULTS: A total of 103 eligible RCTs were identified. A total of 13 317 cases were included in the study, and the results showed that the six types of aspirin combinations (aspirin with atorvastatin, ozagrel sodium, low molecular weight heparin [LMWH], clopidogrel, cilostazol and ginkgo damo) were all significantly superior (P < 0.05) to aspirin alone. The combination of aspirin with LMWH had the highest probability of being the most clinically efficacious intervention, with a surface under the cumulative ranking (SUCRA) curve of 79.1. The combination of aspirin with ozagrel sodium was the worst, with a SUCRA value of 29.7. WHAT IS NEW AND CONCLUSION: A combination of aspirin with LMWH is the best option among the six aspirin combinations considered for the treatment of ACI. The combination of aspirin with ozagrel sodium was ranked the last.

[31] *Branco JC, Alexandrino G, Alves A, Reis J*. **An exceptional cause of drug-induced colitis: cholestyramine**. Journal of gastrointestinal and liver diseases : JGLD 2018; 27:218.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30240461
ABSTRACT

[32] *Yang S, Ye ZM, Chen S et al.* **MicroRNA-23a-5p promotes atherosclerotic plaque progression and vulnerability by repressing ATP-binding cassette transporter A1/G1 in macrophages**. Journal of molecular and cellular cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30227118
ABSTRACT
Disruption of carotid vulnerable atherosclerotic plaque is responsible for acute ischemic stroke (AIS) and the early detection and intervention approach are greatly limited. Undertaking a microarray of microRNAs (miRNAs) in the plasma of AIS patients with carotid vulnerable plaques, miR-23a-5p was markedly elevated and was positively correlated with the plaque progression and vulnerability. Correspondingly, we found that miR-23a-5p expression was significantly increased in both plasma and macrophages from atherosclerosis mice. Bioinformatics analysis and in vitro knockdown experiments identified that ATP-binding cassette transporter A1/G1 as a novel target of miR-23a-5p. Luciferase reporter assays showed that miR-23a-5p repressed the 3' untranslated regions (UTR) activity of ABCA1/G1. Moreover, functional analyses demonstrated that transfection of miR-23a-5p inhibitor enhanced cholesterol efflux and decreased foam cell formation through upregulating ABCA1/G1 expression levels. Furthermore, long term in vivo systemically delivered miR-23a-5p antagomir significantly increased ABCA1/G1 expression in the aorta of ApoE(-/-) mice. Importantly, the miR-23a-5p antagomir therapy significantly reduced atherosclerosis progression and promoted plaque stability. Our observations indicate that miR-23a-5p promotes macrophage-derived foam cell formation and might be a key regulator contributing to atherosclerotic plaque progression and vulnerability.

[33] *Joseph M, Das Gupta R, Shetty S et al.* **How Adequate are Macro- and Micronutrient Intake in Pregnant Women with Diabetes Mellitus? A Study from South India**. Journal of obstetrics and gynaecology of India 2018; 68:400-407.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30224846
ABSTRACT
Background: Diabetes is the most common condition in pregnancy with a worldwide prevalence of 16.9%. Aim: To determine the adequacy of the nutrient intake of pregnant women with diabetes mellitus. Methods: This is a cross-sectional study of 85 pregnant women who met the diagnostic inclusion criteria for diabetes mellitus (gestational and pre-gestational diabetes mellitus) and who were being managed at the outpatient clinic of a tertiary care teaching hospital. Their demography, clinical characteristics (from updated medical records), anthropometric measures (using standard procedures), nutrient intake and meal pattern (obtained using 24 h recall, food frequency and their log diaries) were collected. Results: The mean age of the group was 29.9 + 4.5 years, 54% were in the second trimester of pregnancy with a mean glycosylated haemoglobin level of 6.3 + 1.4%. The mean BMI indicated that 47% of

them were in the obese grade 1 category. Insulin was used in one-third of the population. The overall macronutrient and micronutrient intakes of the population were below the recommended daily allowances for Indians (60-70% of RDA). There was a deficit in the intake of calories, fibre, proteins, iron, calcium, carotene, folic acid, thiamine, riboflavin and niacin. Between the two groups, the pre-GDM women had a significantly better nutrient intake and this could be attributed to a greater exposure to nutrition counselling that they have received during the earlier part of their diabetes care. Conclusion: The gestational period should be viewed as a window of opportunity to modify dietary patterns and introduce healthy lifestyle practices for the woman and her family.

[34] *Davidson ER, Snider MJ, Bartsch K et al.* **Tolerance of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors in Patients With Self-Reported Statin Intolerance**. Journal of pharmacy practice 2018:897190018799218.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30222031
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to lower atherogenic lipid markers in patients with statin intolerance; however, external validity of these findings is unclear in patients with self-reported statin intolerance. OBJECTIVE: The objective of this study was to describe the tolerability of evolocumab and alirocumab in patients with self-reported statin intolerance. Secondary objectives were to describe their efficacy and obtainability. METHODS: A retrospective chart review was completed and included adult patients with self-reported statin intolerance who were prescribed a PCSK9 inhibitor. Patient-reported side effects, laboratory values, and insurance information were collected for assessment of study objectives. RESULTS: During the study period, 55 patients were prescribed PCSK9 inhibitor, 42 started therapy, and 34 had at least 1 follow-up visit. While myalgias occurred in 14.7% (n = 5) of patients, flu-like symptoms in 11.8% (n = 4), and fatigue in 2.9% (n = 1), only 5.9% (n = 2) of prescriptions for PCSK9 inhibitors were discontinued. Low-density lipoprotein cholesterol (LDL-C) was reduced 48.7% (95% confidence interval [CI]: -1.7%-99.1%), and 20 (58.8%) patients achieved a >/=50% reduction in LDL-C. Regarding obtainability, of the 57 prescriptions written, 77.2% (n = 44) required prior authorization and 5.3% (n = 3) were denied by insurance. CONCLUSION: PCSK9 inhibitors were well tolerated in patients with self-reported statin intolerance.

[35] *Amini M, Bahmani F, Foroozanfard F et al.* **The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial**. Journal of psychosomatic obstetrics and gynaecology 2018:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30230402
ABSTRACT
OBJECTIVE: This study was conducted to evaluate the effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of women with polycystic ovary syndrome (PCOS). METHODS: This randomized double-blind, placebo-controlled trial was conducted on 60 women with PCOS, aged 18-40 years old. Participants were randomly assigned into two groups to receive either 2 x 1000 mg/day fish oil omega-3 fatty acid (n = 30) or placebo

(n = 30) after lunch for 12 weeks. Metabolic profiles were quantified at baseline and after the 12-week intervention. RESULTS: Compared with the placebo, omega-3 fatty acid intake led to a significant improvement in Beck Depression Inventory [beta (difference in the mean outcomes measures between treatment groups after intervention) -1.05; 95% CI: -1.84, -0.26; p = .01], general health questionnaire (beta -1.68; 95% CI: -3.12, -0.24; p = .02) and depression anxiety and stress scale (beta -2.03; 95% CI: -3.60, -0.46; p = .01). Omega-3 fatty acid supplementation significantly decreased serum insulin levels (beta -2.09 microIU/mL; 95% CI: -3.77, -0.41; p = .01), homeostasis model of assessment-insulin resistance (beta -0.74; 95% CI: -1.13, -0.34; p < .001), total testosterone (beta -0.23 ng/mL; 95% CI: -0.39, -0.06; p = .03) and hirsutism (beta -0.75; 95% CI: -1.17, -0.33; p = .001), and significantly increased the quantitative insulin sensitivity check index (beta 0.01; 95% CI: 0.003, 0.02; p = .008) compared with the placebo. Additionally, omega-3 fatty acid intake resulted in a significant decrease in high sensitivity C-reactive protein (beta -1.46 mg/L; 95% CI: -2.16, -0.75; p < .001) and malondialdehyde (beta -0.28 micromol/L; 95% CI: -0.52, -0.05; p = .03); also significant rises in plasma total glutathione (beta 59.09 micromol/L; 95% CI: 7.07, 111.11; p = .02) was observed compared with the placebo. Omega-3 fatty acid supplementation did not change other metabolic parameters. CONCLUSION: Overall, omega-3 fatty acid supplementation for 12 weeks to patients with PCOS had beneficial effects on mental health parameters, insulin metabolism, total testosterone, hirsutism and few inflammatory markers and oxidative stress.

[36] *Aburuz S, Al-Bekairy A, Alqahtani AA et al.* **Comparison of the application of treatment Panel III and American College of Cardiology/American heart Association guidelines for blood cholesterol treatment in Saudi Arabia**. Journal of the Saudi Heart Association 2018; 30:349-355.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30228788
ABSTRACT
Background: One of the major risk factors for cardiovascular diseases is hyperlipidemia. The primary aim of this study was to estimate the proportion of individuals between 40-75 years old that would be eligible for statin therapy based on ACC/AHA guideline as compared to ATP-III guideline in a population of patients in Saudi Arabia. We also intended to extrapolate the results to the entire Saudi population, and estimate the cost implications of the ACC/AHA treatment guideline. Methods: This study was a retrospective, observational study involving adult patients aged between 40-75 years old. The study was conducted at the primary health care clinics at King Abdul-Aziz Medical/Riyadh. The eligibility for statins use was assessed and compared for each patient based on both the recent 2013 ACC-AHA guideline and the 2002 ATP-III guideline. The cost implication of applying the ACC/AHA treatment guideline was estimated based on the average cost for 40 mg Atorvastatin in the Saudi Market. Results: A total of 1005 patients were included in the study. Using the ATP-III guideline, there were 139 male (43.7%) and 279 female (40.6%) eligible to receive statin therapy. Based on the 2013 ACC/AHA guideline, treatment is recommended in 315 males (99.1%) and 564 females (82.1%). On the other hand, high-intensity statin was recommended in 302 male (95%) and 400 female (58.2%). Only 74 (10.5%) patients were prescribed high-intensity statin of the 702 eligible patients. Extrapolating the results to the entire Saudi population, 2.369 million additional patients would be eligible for statin therapy when applying the ACC/AHA guideline. Applying

the new guideline would result in a cost increase of at least 4.318 billion SR per year. Conclusions: The eligibility for statin therapy was much higher when applying the ACC/AHA guideline as compared to ATP-III guideline. Applying the recent ACC/AHA dyslipidemia guideline increased the number of patients eligible for statin therapy to approximately two folds. This would be associated with a substantial increase in cost and possibly side effects. The concerns surrounding the ACC/AHA guideline should be addressed at the national level.

[37] *Iqubal A, Sharma S, Sharma K et al.* **Intranasally administered pitavastatin ameliorates pentylenetetrazol-induced neuroinflammation, oxidative stress and cognitive dysfunction**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30227132
ABSTRACT
AIM: The present study aimed to evaluate the neuroprotective potential of intranasally administered pitavastatin in the PTZ-induced kindling model. MATERIALS AND METHODS: Subconvulsant dose of PTZ (35mg/kg, i.p) was administered on an alternate day until the development of kindling. Behavioural test, biochemical tests and inflammatory cytokines were estimated. Comparative molecular docking study of sodium valproate (VPA) and pitavastatin was performed to predict the binding affinity with GABAA and GABA transaminase. Intranasally administered pitavastatin (0.5mg/kg and 1mg/kg) and VPA (200mg/kg) were used to investigate its protective effect. KEY FINDINGS: Comparative in-silico study showed docking score of -4.56 and -2.86 against GABAA receptor whereas -5.56 and -1.86, against GABA transaminase. Root mean square deviation (RMSD) of 0.39A and 0.55A was found for pitavastatin and VPA, respectively. The present study showed the dose-dependent protective effect of intranasally administered pitavastatin and oral VPA against PTZ-induced seizure, cognitive impairment, oxidative stress, and neuroinflammation. SIGNIFICANCE: Our findings suggest that the intranasally administered pitavastatin is potential therapeutic approach to managing PTZ-induced kindling and associated comorbid conditions via its antioxidant, anti-inflammatory, and anticonvulsant potential. Further, pitavastatin can modulate GABAA receptor and GABA transaminase enzyme to ameliorate seizure. Meanwhile, more extensive studies are required to establish the molecular mechanism underlying the neuroprotective effect of pitavastatin.

[38] *Mazidi M, Katsiki N, Kengne AP et al.* **Adiposity mediates the association between whole grain consumption, glucose homeostasis and insulin resistance: findings from the US NHANES**. Lipids in health and disease 2018; 17:219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30223829
ABSTRACT
BACKGROUND: Growing evidence suggests an inverse association between whole grain (WG) consumption and insulin resistance (IR) or inflammation. However, it is still unclear whether adiposity plays a role in this relationship. We investigated whether the associations between WG intake with IR, glucose homeostasis and inflammation are mediated by adiposity in US adults. METHODS: The 2005-2010 National Health and Nutrition Examination Surveys participants were included. WG intake was assessed and markers of IR and glucose homeostasis, inflammation, general and central adiposity. Analysis of co-variance and mediation analysis were applied, while accounting for survey design. RESULTS: Overall 16,621

participants were included in this analysis (mean age = 47.1 years, 48.3% men). After adjustment for age, gender, and race, mean C-reactive protein (CRP), apolipoprotein B (apo-B), fasting blood glucose (FBG), insulin, homeostatic model assessment of IR (HOMA-IR) and beta cell function (HOMA-beta), hemoglobin A1c (HbA1c), and 2 h glucose after an oral glucose tolerance test decreased with increasing quarters of WG (all $p < 0.001$). Body mass index (BMI) had significant mediation effects on the associations between WG intake and CRP, apo-B, fasting glucose, insulin, HOMA-IR, HOMA-B, HbA1c, triglyceride to high density lipoprotein-cholesterol (TG:HDL-C) ratio and triglyceride-glucose (TyG) index (all $p < 0.05$) after adjustment for age, gender, race/ethnicity, educational status, smoking and level of physical activity. Both waist circumference (WC) and anthropometrically predicted visceral adipose tissue (apVAT) mediated the association between WG intakes with CRP, FBG, HbA1c, TG:HDL-C ratio and TyG index, i.e. WC and apVAT had indirect effect (all $p < 0.05$). CONCLUSION: Our findings provide insights into the favourable impact of WG consumption on IR and inflammation, which may be affected by both central and visceral adiposity, i.e. the link between WG with IR and inflammation is more mediated in overweight/obese compared with lean individuals.

[39] *Yingchun H, Yahong M, Jiangping W et al.* **Increased inflammation, endoplasmic reticulum stress and oxidative stress in endothelial and macrophage cells exacerbate atherosclerosis in ApoCIII transgenic mice**. Lipids in health and disease 2018; 17:220.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30223835
ABSTRACT
BACKGROUND: Overexpression of apolipoprotein CIII (ApoCIII) leads to hypertriglyceridemia (HTG) which promotes atherosclerosis development. However, it remains unclear whether ApoCIII affects the atherosclerosis alone by promoting the inflammation and endoplasmic reticulum (ER) stress, or in combination with HTG. METHODS: Transgenic (ApoCIIItg) mouse models were used to investigate the atherogenic role of ApoCIII. Since endothelial cells and macrophages play crucial roles in atherosclerosis, we examined whether triglyceride-rich lipoproteins (TRLs), the major lipoproteins, in plasma of ApoCIIItg mice affect inflammation and ER stress levels in these cells. To further investigate the role of ApoCIII and triglyceride, we incubated HUVECs cells and peritoneal macrophages with TRLs with or without ApoCIII. RESULTS: Increased inflammation and ER stress were found in the aorta of ApoCIIItg mice. TRLs increased ER stress and oxidative stress in HUVECs and macrophages in a dose dependent. Moreover, TRLs together with ApoCIII could induce a higher inflammation level than TRLs alone in these cells. CONCLUSIONS: Both TRLs and ApoCIII contribute to the progression of atherosclerosis, and the modulation of TRLs and ApoCIII may represent a novel therapeutic approach against HTG induced atherosclerosis.

[40] *DiNicolantonio JJ, O'Keefe JH*. **Good Fats versus Bad Fats: A Comparison of Fatty Acids in the Promotion of Insulin Resistance, Inflammation, and Obesity**. Missouri medicine 2017; 114:303-307.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30228616
ABSTRACT
Recently, debate has erupted in both the scientific community and throughout the lay public around whether a low-fat or low-carbohydrate diet is better for weight loss. In other words, is it

better to cut fat or cut carbohydrate for weight loss. However, going beyond this debate (fat versus carbohydrate), are questions around whether certain fatty acids are worse for promoting insulin resistance, inflammation, and obesity. The overall evidence in the literature suggests that medium-chain saturated fats (such as lauric acid, found in coconut oil) and monounsaturated fat (oleic acid, found in olive oil) are less likely to promote insulin resistance, inflammation, and fat storage compared to long-chain saturated fatty acids (such as stearic acid found in large quantities in butter, but particularly palmitic acid found in palm oil) especially when consumed on top of a diet moderate in refined carbohydrates. Compared to long-chain saturated fats, lauric acid and oleic acid have an increased fatty acid oxidation rate, are more likely to be burned for energy and less likely to be stored in adipose tissue, and thus promote increased energy expenditure. Omega-6 polyunsaturated fatty acids (PUFAs), such as linoleic acid, as found in vegetable oils may contribute to obesity, whereas omega-3 PUFA may be protective. Importantly, both olive oil as part of a Mediterranean diet, and omega-3 from fish and fish oil have been proven to reduce risk of cardiovascular (CV) events.

[41] *Malur P, Menezes A, DiNicolantonio JJ et al.* **The Microvascular and Macrovascular Benefits of Fibrates in Diabetes and the Metabolic Syndrome: A review**. Missouri medicine 2017; 114:464-471.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30228666
ABSTRACT
Background: The purpose of this article is to discuss the evidence regarding potential macrovascular and microvascular benefits of fibrate therapy in general and fenofibrate specifically. Methods: We performed a literature review summarizing the results of studies testing fibrates on relevant. Results: Although statins are the first line therapy with an unparalleled amount of evidence for reducing the risk of cardiovascular disease (CVD) in patients with dyslipidemia and the metabolic syndrome (MetS), there are several landmark studies that have focused on the potential benefits of fibrate therapy for reducing CVD risk. Fibrates confer benefits mostly for patients with diabetes mellitus (DM), MetS, and atherogenic dyslipidemia. Recently, many studies have shown that fibrates confer benefits on the vascular system as well as the liver and kidneys. Fibrates also have demonstrable benefits in cohorts of patients with DM and renal disease. Conclusions: Fibrates appear to provide significant microvascular and macrovascular benefits particularly in patients with DM, MetS, or renal disease.

[42] *Li L, Shen C, Huang YX et al.* **A New Strategy for Rapidly Screening Natural Inhibitors Targeting the PCSK9/LDLR Interaction In Vitro**. Molecules (Basel, Switzerland) 2018; 23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30235833
ABSTRACT
The interaction between proprotein convertase subtilisin/kexin type 9 (PCSK9) and the low-density lipoprotein receptor (LDLR) is a promising target for the treatment of hypercholesterolemia. In this study, a new method based on competitive affinity and tag detection was developed, which aimed to evaluate potent natural inhibitors preventing the interaction of PCSK9/LDLR directly. Herein, natural compounds with efficacy in the treatment of hypercholesterolemia were chosen to investigate their inhibitory activities on the PCSK9/LDLR

interaction. Two of them, polydatin (1) and tetrahydroxydiphenylethylene-2-O-glucoside (2), were identified as potential inhibitors for the PCSK9/LDLR interaction and were proven to prevent PCSK9-mediated LDLR degradation in HepG2 cells. The results suggested that this strategy could be applied for evaluating potential bioactive compounds inhibiting the interaction of PCSK9/LDLR and this strategy could accelerate the discovery of new drug candidates for the treatment of PCSK9-mediated hypercholesterolemia.

[43] *Stacey D, Fauman EB, Ziemek D et al.* **ProGeM: a framework for the prioritization of candidate causal genes at molecular quantitative trait loci**. Nucleic acids research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30239796
ABSTRACT
Quantitative trait locus (QTL) mapping of molecular phenotypes such as metabolites, lipids and proteins through genome-wide association studies represents a powerful means of highlighting molecular mechanisms relevant to human diseases. However, a major challenge of this approach is to identify the causal gene(s) at the observed QTLs. Here, we present a framework for the 'Prioritization of candidate causal Genes at Molecular QTLs' (ProGeM), which incorporates biological domain-specific annotation data alongside genome annotation data from multiple repositories. We assessed the performance of ProGeM using a reference set of 227 previously reported and extensively curated metabolite QTLs. For 98% of these loci, the expert-curated gene was one of the candidate causal genes prioritized by ProGeM. Benchmarking analyses revealed that 69% of the causal candidates were nearest to the sentinel variant at the investigated molecular QTLs, indicating that genomic proximity is the most reliable indicator of 'true positive' causal genes. In contrast, cis-gene expression QTL data led to three false positive candidate causal gene assignments for every one true positive assignment. We provide evidence that these conclusions also apply to other molecular phenotypes, suggesting that ProGeM is a powerful and versatile tool for annotating molecular QTLs. ProGeM is freely available via GitHub.

[44] *Crimarco A, Turner-McGrievy GM, Wirth MD et al.* **Baseline markers of inflammation, lipids, glucose, and Dietary Inflammatory Index scores do not differ between adults willing to participate in an intensive inflammation reduction intervention and those who do not**. Nutrition and health 2018:260106018800645.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30229691
ABSTRACT
BACKGROUND: Chronic inflammation is associated with numerous chronic diseases and can be managed with diet. AIM: The purpose of this study was to examine differences in baseline characteristics and plasma inflammation levels between two groups of participants that participated in an intensive, lifestyle intervention or a remotely delivered intervention. This work also assessed the association between Dietary Inflammatory Index (DII)((R)) scores and participants' inflammatory and metabolic biomarkers at baseline. METHOD: Ninety-five participants (61 intervention, 34 control) chose to enroll in either a 12-month intervention consisting of a face-to-face nutrition, physical activity, and stress management intervention or a remotely-delivered intervention (control group) focusing on general cancer prevention. The intervention group met at the University of South Carolina for classes and the control group had

materials emailed to them. A quantile regression was used to compare participants' high-sensitivity C-reactive protein and interleukin-6 levels. Multiple linear regression was used to determine the association between DII scores and biomarkers. RESULTS: There were significant differences in age, body mass index, body fat percentage, and blood pressure between groups, but there were no differences in levels of inflammatory biomarkers. Values of interleukin-6 at the 90th percentile of its distribution were 8.31 pg/ml higher among those in DII quartile 4 compared with quartile 1 (p = 0.02). All other outcomes were not significant. CONCLUSION: Given similar levels of inflammatory biomarkers, participants opting for the control group would also have benefited from a more intensive lifestyle intervention focusing on reducing inflammation.

[45] *Rantanen JM, Riahi S, Johansen MB et al.* **Effects of Marine n-3 Polyunsaturated Fatty Acids on Heart Rate Variability and Heart Rate in Patients on Chronic Dialysis: A Randomized Controlled Trial**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30227610
ABSTRACT
Marine n-3 polyunsaturated fatty acids (PUFA) may improve autonomic dysfunction, as indicated by an increase in heart rate variability (HRV) and reduce the risk of sudden cardiac death. Hence, the aim of this study was to investigate the effects of marine n-3 PUFA on 24-h HRV in patients on chronic dialysis, who have a high risk of sudden cardiac death. Between June 2014 and March 2016, 112 patients on chronic dialysis from Denmark were allocated to a daily supplement of 2 g marine n-3 PUFA or control for three months in a randomized, double-blinded, controlled trial. A 48-h Holter monitoring was performed and mean 24-h HRV indices for the two days were available in 85 patients. The mean age was 62.3 years (SD: 14.3) and median dialysis vintage was 1.7 years (IQR: 0.5, 6.4). Within-group and between-group changes in outcome were evaluated by a paired and two sample t-test, respectively. Marine n-3 PUFA did not change the primary endpoint SDNN (SD of all RR-intervals) reflecting overall HRV, but other HRV indices increased and the mean RR-interval increased significantly, corresponding to a decrease in heart rate by 2.5 beats per minute (p = 0.04). In conclusion, marine n-3 PUFA did not change SDNN, but the mean heart rate was significantly reduced and changes in other HRV-indices were also observed, indicating an increase in vagal modulation that might be protective against malignant ventricular arrhythmias.

[46] *Entezarjou A, Mohammad MA, Andell P, Koul S*. **Culprit vessel: impact on short-term and long-term prognosis in patients with ST-elevation myocardial infarction**. Open heart 2018; 5:e000852.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30228908
ABSTRACT
Background: ST-elevation myocardial infarction (STEMI) occurs as a result of rupture of an atherosclerotic plaque in the coronary arteries. Limited data exist regarding the impact of culprit coronary vessel on hard clinical event rates. This study investigated the impact of culprit vessel on outcomes after primary percutaneous coronary intervention (PCI) of STEMI. Methods: A total of 29 832 previously cardiac healthy patients who underwent primary PCI between 2003 and 2014 were prospectively included from the Swedish Coronary Angiography and Angioplasty

Registry and the Registry of Information and Knowledge about Swedish Heart Intensive care Admissions. Patients were stratified into three groups based on culprit vessel (right coronary artery (RCA), left anterior descending artery (LAD) and left circumflex artery (LCx)). The primary outcome was 1-year mortality. The secondary outcomes included 30-day and 5-year mortality, as well as heart failure, stroke, bleeding and myocardial reinfarction at 30 days, 1 year and 5 years. Univariable and multivariable analyses were done using Cox regression models. Results: One-year analyses revealed that LAD infarctions had the highest increased risk of death, heart failure and stroke compared with RCA infarctions, which had the lowest risk. Sensitivity analyses revealed that reduced left ventricular ejection fraction on discharge partially explained this increased relative risk in mortality. Furthermore, landmark analyses revealed that culprit vessel had no significant influence on 1-year mortality if a patient survived 30 days after myocardial infarction. Subgroup analyses revealed female sex and multivessel disease (MVD) as significant high-risk groups with respect to 1-year mortality. Conclusions: LAD and LCx infarctions had a relatively higher adjusted mortality rate compared with RCA infarctions, with LAD infarctions in particular being associated with an increased risk of heart failure, stroke and death. Culprit vessel had limited influence on mortality after 1 month. High-risk patient groups include LAD infarctions in women or with concomitant MVD.

[47] *Woodcock J, Khan MA*. **FDA Analysis of Atorvastatin Products Refutes Report of Methyl Ester Impurities**. Therapeutic innovation & regulatory science 2014; 48:554-556.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30231449
ABSTRACT

[48] *Wu H, Wu G*. **Improving Good Practice: A Survey of Unlicensed and Off-Label Drug Use in a General Hospital in China**. Therapeutic innovation & regulatory science 2013; 47:397-404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30235519
ABSTRACT
BACKGROUND: Off-label and unlicensed drug use is common in Europe and the US; however, information about this issue in China is limited. OBJECTIVE: To determine the scope and scale of off-label and unlicensed drug use in general hospitals in Shanghai, China, and to evaluate the varying levels of supporting evidence. METHODS: A total of 493 cases of discharge history were randomly sampled. Off-label uses were defined according to package inserts, the China Pharmacopeia Clinical Medication Notice (2010), and New Pharmacology (16th edition). All drugs administered were assessed to determine whether their use was unlicensed and off-label. RESULTS: There were 459 cases (93.10%) of off-label drug use, and 47.64% of total therapeutic drugs prescribed were off-label. Of these cases, 8.72% of patients received 1 off-label drug, and 9.94% of patients received 2 off-label drugs. Use of multiple off-label medications per patient was also common, and the percentage of patients receiving 3, 4, 5, 6, 7, 8, 9, and >/=10 medications was 9.74%, 9.74%, 8.72%, 7.91%, 12.58%, 7.10%, 5.88%, and 12.78%, respectively. Categories of off-label drugs used most frequently were vitamins, cardiovascular drugs, and gastroenteric drugs. The most common off-label use was that the indication for which a drug was prescribed was not approved (83.49%); other off-label uses involved disregard for contraindications and drug incompatibility (6.37%), dose exceeding approved amount (4.76%), unapproved route of administration (4.65%), and unapproved

dosing intervals (0.73%). Vitamins and nutritional supplements are the drugs most frequently prescribed off-label, while off-label use of vasodilators, lipid-lowering drugs, and adjuvant therapy medications for cardiovascular and cerebrovascular conditions is also common. CONCLUSION: Unlicensed and off-label prescribing of drugs may be common in China.

[49] *Fang C, Luo T, Chen X, Lin L*. **[Elevated level of serum PCSK9 in patients with systemic lupus erythematosus]**. Xi bao yu fen zi mian yi xue za zhi = Chinese journal of cellular and molecular immunology 2018; 34:541-545.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30236208
ABSTRACT
Objective To detect the level of serum proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with systemic lupus erythematosus (SLE) and investigate the correlation between PCSK9 level and disease parameters. Methods Forty-seven SLE patients and 30 age, sex-matched healthy controls (HCs) were included in our research. Traditional cardiovascular disease (CVD) risk factors were compared between the two groups. The level of serum PCSK9 was examined by ELISA. Carotid intima-media thickness (cIMT) was measured by carotid ultrasound. According to the measured value of cIMT, SLE patients were divided into SLE-AS (cIMT>/=1.0 mm) and SLE-NonAS (cIMT<1.0 mm) subgroups. Atherogenic factors and PCSK9 levels were compared between the two subgroups. Univariate correlational analysis of PCSK9 levels and disease parameters was conducted in the SLE patients. Results No difference was found in the total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), ApoA1, ApoB, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood-glucose (FBG), body mass index (BMI) or uric acid (UA) between the SLE patients and HCs. However, the higher ratio of cIMT thickening and the elevation of serum PCSK9 levels were observed in the SLE patients as compared with the HCs. No significant difference in the traditional risk factors for CVD was found, but significant difference in the level of C-reactive protein (CRP) existed between the SLE-AS subgroup and SLE-NonAS subgroup. The level of serum PCSK9 in the SLE-AS subgroup was significantly higher than that in the SLE-NonAS subgroup. PCSK9 concentrations were positively correlated with CRP levels, but not correlated obviously with the age, SLEDAI, lipids parameters (TC, LDL-C, ApoA1, ApoB, TG, HDL-C), BMI or UA levels. This tendency seemed to be more significant in the female patients. Conclusion Elevated level of serum PCSK9 can be observed in SLE patients, especially in those with thickening of cIMT. PCSK9 may be associated with atherogenic inflammation in SLE.