Literature update week 50 (2018)

[1] *Pauk M, Bordukalo-Niksic T, Brkljacic J et al.* **A novel role of bone morphogenetic protein 6 (BMP6) in glucose homeostasis**. Acta diabetologica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30539233
ABSTRACT
AIMS: Bone morphogenetic proteins (BMPs) are involved in the development and homeostasis of multiple organs and tissues. There has been a significant focus on understanding the role of BMPs in pancreatic beta-cell dysfunction associated with type 2 diabetes (T2D). Our objective was to investigate the relationship between BMP6 and glucose homeostasis. METHODS: Ob/ob mice were treated with BMP6 for 6 days and analyzed for insulin release, body weight, lipid parameters and glucose tolerance. Quantitative real-time PCR, chromatin immunoprecipitation and glucose output assays were used to assess BMP6 effect on gluconeogenesis in rat hepatoma H4IIE cells. Specificity of BMP6 receptors was characterized by the utilization of various receptor Fc fusion proteins in luciferase reporter gene and glucose output assays in INS1 and H4IIE cells. RESULTS: Treatment of ob/ob mice with BMP6 for 6 days resulted in a reduction of circulating glucose and lipid levels, followed by a significantly elevated plasma insulin level in a dose-dependent manner. In addition, BMP6 improved the glucose excursion during an oral glucose tolerance test, lowering the total glycemic response by 21%. In rat H4IIE hepatoma cells, BMP6 inhibited gluconeogenesis and glucose output via downregulation the PepCK expression. Moreover, BMP6 inhibited glucose production regardless of the presence of cAMP, antagonizing its glycogenolytic effect. BMP6 acted on pancreatic and liver cells utilizing Alk3, Alk6 and ActRIIA serine/threonine kinase receptors. CONCLUSIONS: Collectively, we demonstrate that BMP6 improves glycaemia in T2D mice and regulates glucose metabolism in hepatocytes representing an exciting prospect for future treatments of diabetes.

[2] *Dekkers CC, Westerink J, Hoepelman AIM, Arends JE*. **Overcoming Obstacles in Lipid-lowering Therapy in Patients with HIV - A Systematic Review of Current Evidence**. AIDS reviews 2018; 20:205-219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30548018
ABSTRACT
Cardiovascular risk management in human immunodeficiency virus (HIV)-infected individuals is gaining increased attention due to the rising incidence and prevalence of cardiovascular disease in this population. Despite the availability of efficacious treatment strategies, implementation of guideline advocated preventive therapy, such as lipid-lowering therapy with statins, is hampered by perceived, expected, and real side effects as well as by expected interactions with combination antiretroviral therapy. These obstacles to optimal treatment have resulted in a large gap between the number of patients in whom lipid-lowering therapy is indicated and those actually taking lipid-lowering medication. In the past few years, research has shown that the majority of patient-reported side effects is not causally related to statin therapy but is attributable to the nocebo effect. Furthermore, excessive caution due to expected drug interactions between statins and antiretroviral therapy is often unnecessary, especially with novel classes of antiretroviral therapy. The main aim of this review is to discuss the causes and consequences of this lipid-lowering treatment gap in HIV-infected patients together with a practical guide on how to overcome these obstacles. In addition, new treatment options on the

optimal cardiovascular management focusing primarily on novel classes of antiretroviral therapy and lipid-lowering medication will be discussed.

[3] *Medvedev RB, Tanashyan MM, Skrylev SI et al.* **[Relation between ultrasonographic and morphological characteristics of atherosclerotic plaques of carotid sinus]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2018; 24:43-48.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30531768
ABSTRACT
The authors revealed relation between the structure of an atherosclerotic plaque (ASP) and intensity of the ultrasound signal reflected form the ASP. Our prospective pilot study included a total of 90 patients (71 men and 19 women aged from 47 to 79 years, with the median age 62 years) presenting with atherosclerotic stenosis of the carotid sinus (CS) and undergoing treatment at the Research Centre of Neurology (Moscow) from April 2015 to March 2016. All patients underwent ultrasonographic examination followed by morphological study of the structure of the plaques removed during carotid endarterectomy (CEA). It was revealed that intensity of the ultrasound signal from an ASP depended on the morphological structure of the ASP components: the foci of atheromatosis were associated with an ultrasound range of 1.1-5.6 dB, those of fibrosis - with the range 23.1-30.5 dB, and those of calcinosis - with the range 42.3-44.7 dB (presented are the values from the 15th to 85th percentiles). It was determined that an increase of intensity of the ultrasound signal reflected from the foci of atheromatosis and fibrosis in the ASP was associated with the presence of small calcificates therein, and a decrease of intensity of the ultrasound signal from the portions of fibrosis in the ASP - with large accumulation of lipophages or newly formed vessels in these portions.

[4] *Lee SH, Choi JH*. **Involvement of inflammatory responses in the early development of calcific aortic valve disease: lessons from statin therapy**. Animal cells and systems 2018; 22:390-399.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30533261
ABSTRACT
Calcific aortic valve disease (CAVD) is the most common degenerative heart valve disease. Among the many risk factors for this disease are age, hypercholesterolemia, hypertension, smoking, type-2 diabetes, rheumatic fever, and chronic kidney disease. Since many of these overlap with risk factors for atherosclerosis, the molecular and cellular mechanisms of CAVD development have been presumed to be similar to those for atherogenesis. Thus, attempts have been made to evaluate the therapeutic efficacy of statins, representative anti-atherosclerosis drugs with lipid-lowering and anti-inflammatory effects, against CAVD. Unfortunately, statins have shown little or no effect on CAVD development. But some reports suggest that statins may prevent or reduce the development of early stage CAVD in which having calcification is absent or minimal. These results suggest that therapeutic approaches should differ according to the stage of disease, and that a precise understanding of the mechanism of aortic valve calcification is required to identify novel therapeutic targets for advanced CAVD. Given the involvement of inflammatory processes in the development and progression of CAVD, current therapeutic approaches for chronic inflammatory cardiovascular disease like atherosclerosis may help to prevent or minimize the early development of CAVD. In

this review, we focus on several inflammatory cellular and molecular components involved in CAVD that might be considered drug targets for preventing CAVD.

[5] *Rallidis LS, Kiouri E, Rallidi M, Kosmas N*. **Reply to: "Bridging the treatment gap in patients at 'extreme' cardiovascular risk: Evidence from a lipid clinic"**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30551893
ABSTRACT

[6] *Kim WH, Lee CH, Han JH et al.* **C/EBP homologous protein deficiency inhibits statin-induced myotoxicity**. Biochem Biophys Res Commun 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30528737
ABSTRACT
It has been well established that HMG-CoA reductase inhibitors (statins) cause adverse side effects in skeletal muscle ranging from mild to fatal myotoxicity upon dose, drug interaction, and exercise. However, the underlying mechanisms by which statins induce myotoxicity have not been fully addressed. Recent reports showed that statins induce endoplasmic reticulum (ER) stress and cell death in immune cells and myoblasts in vitro. Therefore, the goal of study is to investigate the molecular mechanism by which statins induce skeletal muscle cell death and myopathy via the regulation of ER stress. Biochemical data showed that TUDCA, an ER stress inhibitor, inhibited atorvastatin- and simvastatin-induced protein cleavages of PARP-1 and caspase-3, respectively. Actually, statin treatment activated marker proteins of unfolded protein responses (UPR) including ATF6, CHOP, and spliced XBP1 and these responses were inhibited by TUDCA. In addition, statin treatment induced mRNA levels of UPR marker genes, suggesting that statins activate ER stress in a transcriptional regulation. The physiological relevance of ER stress in statin-induced myopathy was demonstrated in a mouse model of myopathy, in which instillation of simvastatin and atorvastatin led to myopathy. Notably, the reduction of muscular endurance in response to statin instillation was significantly improved in TUDCA treating group compared to vehicle control group. Moreover, CHOP deficiency mice showed restoration of statin-induced reduction of muscular endurance, suggesting that statin induces myopathy via ER stress and in a CHOP-dependent manner. Taken together, these findings indicate that statins specifically induce myopathy in an ER stress-dependent manner, suggesting the therapeutic potential of ER stress regulation in preventing adverse effects of statin.

[7] *Amput P, McSweeney C, Palee S et al.* **The effects of proprotein convertase subtilisin/kexin type 9 inhibitors on lipid metabolism and cardiovascular function**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019; 109:1171-1180.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30551367
ABSTRACT
Low density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease. Although there are several developed lipid lowering drugs such as statins and fenofibrates, many patients do not achieve an adequate response. Recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been developed as a new therapeutic strategy for cholesterol regulation. PCSK9 binds to low density lipoprotein receptors (LDLR) and

initiates LDLR degradation, elevating LDL-C. Therefore, PCSK9 inhibition could exert beneficial effects on cardiovascular disease outcomes. This review comprehensively summarizes and discusses the effects of PCSK9 inhibitors on lipid metabolism and cardiovascular function comparatively with current lipid lowering drugs. This review also details essential information regarding the cardiovascular benefits of PCSK9 inhibition which could encourage further clinical studies.

[8] *El-Seweidy MM, Sarhan Amin R, Husseini Atteia H et al.* **Dyslipidemia induced inflammatory status, platelet activation and endothelial dysfunction in rabbits: Protective role of 10-Dehydrogingerdione**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 110:456-464.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30530048
ABSTRACT
10-Dehydrogingerdione is a novel cholesteryl ester transfer protein (CETP) inhibitor of natural origin. Some synthetic CETP inhibitors have recently been reported to suppress proprotein convertase subtilisin/kexin type 9 (PCSK9). Therefore, the present study aimed mainly to clarify the effect of 10-Dehydrogingerdione on cellular adhesion inflammatory molecules, platelet activation and endothelial dysfunction markers in addition to PCSK9 as compared to atorvastatin in dyslipidemic rabbits. Dyslipidemia was induced in 30 male rabbits, distributed in 3 equal groups through feeding dietary cholesterol (0.5% w/w) for 3 months. Two dyslipidemic groups were concurrently treated with either atorvastatin or 10-Dehydrogingerdione (10 mg/kg/ day, p.o) and dietary cholesterol. One additional group including 10 normal rabbits fed normal diet served as normal control (NC) group. Both 10-Dehydrogingerdione and atorvastatin significantly reduced serum CETP level and activity as well as PCSK9 and low density lipoprotein cholesterol (LDL-C) levels but increased high density lipoprotein cholesterol (HDL-C) levels as compared to dyslipidemic control (DC) rabbits ($p < 0.001$). Both treatments also induced a marked decrease in the interferon-gamma (IFN-gamma), soluble CD40 ligand (sCD40L) and soluble P-selectin (sP-selectin) levels, inflammatory cell infiltration, as well as atherogenic and coronary risk indexes in addition to aortic atheromatous changes and intima/media ratio, respectively as compared to the DC group ($p < 0.001$). The reduction in these markers showed a significant correlation with PCSK9 suppression and CETP inhibitory effect. Interestingly, 10-Dehydrogingerdione exerted a greater ameliorative potential regarding these biomarkers than atorvastatin. Our findings suggest that 10-Dehydrogingerdione is a promising PCSK9 inhibitor with a significant protective value against many atherosclerotic risk factors.

[9] *Guo X, Wang L, Xia X et al.* **Effects of atorvastatin and/or probucol on recovery of atherosclerosis in high-fat-diet-fed apolipoprotein E-deficient mice**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019; 109:1445-1453.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30551396
ABSTRACT
INTRODUCTION: We have investigated the possible effects and mechanism of atorvastatin, a statin, and/or probucol, a powerful antioxidant used to lower cholesterol before 1995, on the atherosclerosis development. METHODS: Apolipoprotein-E-deficient (ApoE(-/-)) mice fed with the high fat diet were randomly divided into 3 groups (n = 10/each group): Placebo,

Atorvastatin (10 mg/ kg/d), and atorvastatin (10 mg/kg/d) plus probucol (10 mg/kg/d) groups. C57BL/6 J mice were fed with normal diet as the control group (n = 10). Animals were sacrificed 10 weeks after the intervention. To evaluate the experimental atherosclerosis, blood tests were used for measuring serum lipoprotein profile, Western blots for endoplasmic reticulum (ER) stress protein expression, H&E staining for plaque lesions, immunohistology for macrophages, inflammatory cytokines, innate immune receptor TLR-4, transcription factor NF-kappaB, and atherosclerosis plaques. RESULTS: Compared with the control group, ApoE(-/-) mice in the placebo group showed with the significantly ($p < 0.05$) higher levels of serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL) and oxidized low density lipoprotein (ox-LDL), PERK, GRP78, CHOP, IL-1beta, TNF-alpha and NF-kappaB, but with the lower levels of high-density lipoprotein cholesterol (HDL) and TLR-4, and also the increase in macrophages and the aortic media collagen, and the decrease in the elastic fibers ($p < 0.01$). Treatment with atorvastatin recovered all these features ($p < 0.05$ or $p < 0.01$) near to the levels in the control group. In addition, the combination of atorvastatin and probucol has shown the slightly stronger effect than the use of atorvastatin alone without statistical significances when comparing most bio-markers of atherosclerosis, but with significant differences in the reduction of the plaque lesion areas and macrophages ($p < 0.05$). CONCLUSIONS: Atorvastatin and/or probucol suppresses ER stress and increase the level of TLR-4, which lowers NF-kappaB, resulting in the recovery of atherosclerosis in the ApoE(-/-) mouse model.

[10] *Haybar H, Goudarzi M, Mehrzadi S et al.* **Effect of gemfibrozil on cardiotoxicity induced by doxorubicin in male experimental rats**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019; 109:530-535.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30551518
ABSTRACT
Cardiotoxicity is an adverse effect of the anticancer drug doxorubicin (DOX). Gemfibrozil (GEM) is a lipid-lowering drug with a number of biological properties such as anti-inflammatory and antioxidant activities. Therefore, we decided to investigate the effect of GEM on DOX-induced cardiotoxicity in rats. Twenty-eight adult male Wistar rats were divided into four experimental groups as follows: Group I received normal saline (2 ml/kg) orally for 14 days, group II received DOX (2.5 mg/kg; in six injections; accumulative dose: 15 mg/kg) intraperitonially for 14 days, group III received DOX + GEM (100 mg/kg) orally for 14 days concomitantly with DOX administration, and group IV received GEM orally for 14 days. Lipid panel, various biochemical biomarkers, and histological observations were evaluated in serum and heart samples. According to our results, DOX significantly increased the levels of lipid panel (triglycerides, total cholesterol, and low-density lipoproteins cholesterol) as well as markers of cardiac dysfunction (Aspartate aminotransferase, Creatine kinase-muscle/brain, Lactate dehydrogenase and Cardiac Troponin I). Moreover, DOX significantly increased malondialdehyde and nitric oxide levels in cardiac tissue. Furthermore, administration of DOX reduced the level of glutathione as well as the superoxide dismutase, catalase, and Glutathione peroxidase activities. DOX-treated rats showed significantly higher tumor necrosis factor-alpha and interleukin-1beta. GEM administration significantly attenuated the lipid panel and biochemical biomarkers in DOX-treated rats. Our results were confirmed by histopathological evaluations of the heart. Based

on our findings, GEM is a promising cardioprotective agent in patients treated with DOX through mitigative effects on biochemical markers and oxidative stress indices.

[11] *Palko-Labuz A, Sroda-Pomianek K, Wesolowska O et al.* **MDR reversal and pro-apoptotic effects of statins and statins combined with flavonoids in colon cancer cells**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019; 109:1511-1522.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30551403
ABSTRACT
The resistance of cancer cells to a variety of structurally non-related cytotoxic drugs is known as multidrug resistance phenomenon (MDR). In cellular membranes an activity of MDR transporters such as P-glycoprotein (ABCB1) is affected by their lipid environment. Many various compounds have been examined for their ability to restore drug-sensitivity of resistant cancer cells. Statins, inhibitors of the key enzyme of mevalonate pathway HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase are drugs commonly prescribed in order to reduce serum level of cholesterol and to diminish the risk of cardiovascular disease. Statins as drugs that influence lipid composition of cell membrane and in that way they also exert influence on lipid bilayer properties appear to be good candidates as MDR modulators. In this work it was shown that statins - mevastatin and simvastatin exert antiproliferative, pro-apoptotic and reversing drug resistance effect in human colon adenocarcinoma cell line LoVo and its drug-resistant subline LoVo/Dx. A hypothesis was also checked whether flavones, which as it is well known are able to influence the biosynthesis of cholesterol, may change the anticancer activity of statins. Our investigations have revealed that combined use of statins and studied flavonoids results in enhanced cell growth inhibition and apoptosis and lower cancer cell proliferation as compared to the application only statins alone. Moreover, in drug resistant LoVo/Dx cells a stronger decrease of resistance to doxorubicine was observed in the presence of statins in combination with flavones as compared to the effect observed for statins only.

[12] *Fhoula I, Rehaiem A, Najjari A et al.* **Functional Probiotic Assessment and In Vivo Cholesterol-Lowering Efficacy of Weissella sp. Associated with Arid Lands Living-Hosts**. BioMed research international 2018; 2018:1654151.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30539003
ABSTRACT
The research and the selection of novel probiotic strains from novel niches are receiving increased attention on their proclaimed health benefits to both humans and animals. This study aimed to evaluate the functional properties of Weissella strains from arid land living-hosts and to select strains with cholesterol-lowering property in vitro and in vivo, for use as probiotics. They were assessed for acid and bile tolerance, antibiotic susceptibility, membrane properties, antibacterial activity, antiadhesive effect against pathogens to host cell lines, and cholesterol assimilation in vitro. Our results showed that the majority of strains revealed resistance to gastrointestinal conditions. All the strains were nonhemolytic and sensitive to most of the tested antibiotics. They also exhibited high rates of autoaggregation and some of them showed high coaggregation with selected pathogens and high adhesion ability to two different cell lines (Caco-2 and MIM/PPk). Particularly, W. halotolerans F99, from camel feces, presented a broad antibacterial spectrum against pathogens, reduced Enterococcus faecalis and Escherichia coli

adhesion to Caco-2 cells, and was found to reduce, in vitro, the cholesterol level by 49 %. Moreover, W. halotolerans F99 was evaluated for the carbohydrate utilization as well as the serum lipid metabolism effect in Wistar rats fed a high-cholesterol diet. W. halotolerans F99 showed an interesting growth on different plant-derivative oligosaccharides as sole carbon sources. Compared with rats fed a high-fat (HF) diet without Weissella administration, total serum cholesterol, low-density lipoprotein cholesterol, and triglycerides levels were significantly ($p<0.001$) reduced in W. halotolerans F99-treated HF rats, with no significant change in high-density lipoprotein cholesterol HDL-C levels. On the basis of these results, this is the first study to report that W. halotolerans F99, from camel feces, can be developed as cholesterol-reducing probiotic strain. Further studies may reveal their potential and possible biotechnological and probiotic applications.

[13] *Murray M, Dordevic AL, Cox KHM et al.* **Study protocol for a double-blind randomised controlled trial investigating the impact of 12 weeks supplementation with a Fucus vesiculosus extract on cholesterol levels in adults with elevated fasting LDL cholesterol who are overweight or have obesity**. BMJ open 2018; 8:e022195.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30552248

ABSTRACT

INTRODUCTION: Hyperlipidaemia, hyperglycaemia and chronic inflammation are risk factors for chronic diseases cardiovascular disease and type 2 diabetes. Polyphenols are bioactive compounds found in marine algae with potential antihyperlipidaemic, antihyperglycaemic and anti-inflammatory effects. The modulation of these risk factors using bioactive polyphenols may represent a useful strategy for disease prevention and management; research in humans, however, remains limited. This trial aims to determine the impact of a polyphenol-rich brown seaweed extract on fasting hyperlipidaemia, hyperglycaemia and inflammation. Effects on mood and cognition will also be evaluated. METHODS AND ANALYSIS: Fifty-eight hypercholesterolaemic participants who are overweight or have obesity will be randomised to receive either a polyphenol-rich brown seaweed extract (2000 mg dose containing 600 mg polyphenols) or placebo (2000 mg rice flour) daily for 12 weeks. Fasting venous blood samples will be taken at baseline, week 6 and week 12 of the intervention to assess serum cholesterol (total, low-density lipoprotein and high-density lipoprotein) and triglyceride concentrations, plasma glucose and insulin concentrations and markers of inflammation. Mood and cognitive function will be evaluated as exploratory outcomes. Independent t-tests or equivalent will be used to determine differences between the two groups in changes from baseline to week 12. Analysis of variance will be used to assess differences between the groups across the three time points (baseline, week 6 and week 12). ETHICS AND DISSEMINATION: Ethics approval has been granted by the Monash University Human Research Ethics Committee (2017-8689-10379). Results from this trial will be disseminated through publication in peer-reviewed journals, national and international presentations, and a PhD thesis. These results are essential to inform the use of polyphenol-rich brown seaweeds as a functional food or nutritional supplement ingredients for health promotion and disease prevention and management in humans. TRIAL REGISTRATION NUMBER: ACTRN12617001039370; Pre-results.

[14] *Brunham LR, Ruel I, Aljenedil S et al.* **Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018**. The Canadian journal of cardiology 2018; 34:1553-1563.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527143
ABSTRACT
Familial hypercholesterolemia (FH) is the most common monogenic disorder causing premature atherosclerotic cardiovascular disease. It affects 1 in 250 individuals worldwide, and of the approximately 145,000 Canadians estimated to have FH, most are undiagnosed. Herein, we provide an update of the 2014 Canadian Cardiovascular Society position statement on FH addressing the need for case identification, prompt recognition, and treatment with statins and ezetimibe, and cascade family screening. We provide a new Canadian definition for FH and tools for clinicians to make a diagnosis. The risk of atherosclerotic cardiovascular disease in patients with "definite" FH is 10- to 20-fold that of a normolipidemic individual and initiating treatment in youth or young adulthood can normalize life expectancy. Target levels for low-density lipoprotein cholesterol are proposed and are aligned with the Canadian Cardiovascular Society guidelines on dyslipidemia. Recommendation for the use of inhibitors of proprotein convertase kexin/subtilisin type 9 are made in patients who cannot achieve therapeutic low-density lipoprotein cholesterol targets on maximally tolerated statins and ezetimibe. The writing committee used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology in the preparation of the present document, which offers guidance for practical evaluation and management of patients with FH. This position statement also aims to raise awareness of FH nationally, and to mobilize patient support, promote knowledge translation, and availability of treatment and health care resources for this under-recognized, but important medical condition.

[15] *Turgeon RD, Tsuyuki RT, Gyenes GT, Pearson GJ*. **Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial**. The Canadian journal of cardiology 2018; 34:1600-1605.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527147
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are efficacious lipid-lowering agents, but more precise estimates of their effects on major adverse cardiovascular events (MACE), mortality, and safety are needed. We systematically reviewed and meta-analyzed randomized controlled trials with durations >/= 6 months comparing MACE, mortality, and safety with PCSK9 inhibitors vs control. We searched CENTRAL, Embase, MedLine and the grey literature to November 7, 2018. From 2048 articles, we included 23 trials (n = 60,723). PCSK9 inhibitors reduced MACE (relative risk, 0.83; 95% confidence interval, 0.78-0.88), but did not clearly reduce mortality (relative risk, 0.93; 95% confidence interval, 0.85-1.02) or increase adverse events. In conclusion, PCSK9 inhibitors reduce nonfatal MACE, are well tolerated, but effects on mortality remain unclear.

[16] *Gupta KK, Ali S, Sanghera RS*. **Pharmacological Options in Atherosclerosis: A Review of the Existing Evidence**. Cardiology and therapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30543029

ABSTRACT
Coronary heart disease (CHD) is the leading cause of mortality worldwide and high low-density lipoprotein (LDL) cholesterol levels have been shown to be key in the pathogenesis of this condition. Lipid control has therefore been the subject of decades of research and has led to many large and robust randomized controlled trials, as well as the highest grossing drug of all time-Lipitor (atorvastatin). Statin therapy has long been indicated for secondary and more recently primary prevention. However, despite the large-scale use of statins, CHD prevalence remains high, and some patients do not respond to statin therapy. There has been a large push to find and test alternative lipid-lowering agents, these include fibrates, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors. It is the aim of this review to assess the literature surrounding each of these groups of drugs.

[17] *Spartalis M, Spartalis E, Tzatzaki E et al.* **The beneficial therapy with colchicine for atherosclerosis via anti-inflammation and decrease in hypertriglyceridemia**. Cardiovascular & hematological agents in medicinal chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30526472
ABSTRACT
BACKGROUND: Lipid-lowering therapy and control of cardiovascular risk factors are the current recommendations of atherosclerotic disease management. Despite optimal treatment though the rate of acute coronary syndrome events remains high. Inflammation plays an essential role in the pathophysiology of atherosclerotic plaque formation, progression and rupture, which conclusively causes acute clinical episodes. OBJECTIVE: This review aims to give a conceptual description of the potential therapeutic benefits and effects of colchicine in inflammation-mediated atherosclerotic disease and hypertriglyceridemia. METHOD: A complete literature survey was performed using the PubMed database search to collect available information regarding colchicine, atherosclerosis, and hypertriglyceridemia. RESULTS: A total of 42 studies met the selection criteria for inclusion in the review. Inflammation is a well-known key mediator of atherogenesis in coronary artery disease. Colchicine has direct anti-inflammatory effects by inhibiting critical inflammatory signaling networks as the inflammasome, pro-inflammatory cytokines, and expression of adhesion molecules, preventing both local chemoattraction of inflammatory cells such as neutrophils and systemic inflammation including the decrease of the release of IL-1beta by the neutrophils. CONCLUSION: Colchicine reduces the levels of inflammatory markers, stabilizes the coronary plaque, leads to more favorable cardiac healing after damage, and reduces the acute coronary syndromes event recurrence. Colchicine reduces the myocardial infarct size, myocardial fibrosis, and improves the hemodynamic parameters. Several studies report the potential attenuating role of colchicine on triglyceride levels. Current evidence though regarding the pathophysiological mechanism of colchicine's triglyceride-lowering effect remains scarce.

[18] *Hakansson KEJ, Goossens EAC, Trompet S et al.* **Genetic associations and regulation of expression indicate an independent role for 14q32 snoRNAs in Human Cardiovascular Disease**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30544252
ABSTRACT

Aims: We have shown that 14q32 microRNAs are highly involved in vascular remodeling and cardiovascular disease. However, the 14q32 locus also encodes 41 'orphan' small nucleolar RNAs (snoRNAs). We aimed to gather evidence for an independent role for 14q32 snoRNAs in human cardiovascular disease. Methods & Results: We performed a look-up of the 14q32 region within the dataset of a Genome Wide Association Scan (GWAS) in 5244 participants of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Single Nucleotide Polymorphisms (SNPs) in the snoRNA-cluster were significantly associated with heart failure. These snoRNA-cluster SNPs were not linked to SNPs in the microRNA-cluster or in MEG3, indicating that snoRNAs modify the risk of cardiovascular disease independently. We looked at expression of 14q32 snoRNAs throughout the human cardio-vasculature. Expression profiles of the 14q32 snoRNAs appeared highly vessel-specific. When we compared expression levels of 14q32 snoRNAs in human venae saphenae magnae (VSM) with those in failed VSM-coronary bypasses, we found that 14q32 snoRNAs were upregulated. SNORD113.2, which showed a 17-fold upregulation in failed bypasses, was also upregulated twofold in plasma samples drawn from patients with ST-Elevation Myocardial Infarction (STEMI) directly after hospitalization compared to 30 days after start of treatment. Fitting with the genomic associations however, 14q32 snoRNA expression was highest in failing human hearts. In vitro studies show that the 14q32 snoRNAs bind predominantly to methyl-transferase Fibrillarin, indicating that they act through canonical mechanisms, but on non-canonical RNA targets. The canonical C/D-box snoRNA seed sequences were highly conserved between humans and mice. Conclusions: 14q32 snoRNAs appear to play an independent role in cardiovascular pathology. 14q32 snoRNAs are specifically regulated throughout the human vasculature and their expression is upregulated during cardiovascular disease. Our data demonstrate that snoRNAs merit increased effort and attention in future basic and clinical cardiovascular research.

[19] *Tunon J, Badimon L, Bochaton-Piallat ML et al.* **Identifying the anti-inflammatory response to lipid lowering therapy. A Position Paper from the Working Group on Atherosclerosis and Vascular Biology of the European Society of Cardiology**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30534957

ABSTRACT

Dysregulated lipid metabolism induces an inflammatory and immune response leading to atherosclerosis. Conversely, inflammation may alter lipid metabolism. Recent treatment strategies in secondary prevention of atherosclerosis support beneficial effects of both anti-inflammatory and lipid-lowering therapies beyond current targets. There is a controversy about the possibility that anti-inflammatory effects of lipid-lowering therapy may be either independent or not of a decrease in low-density lipoprotein cholesterol. In this Position Paper, we critically interpret and integrate the results obtained in both experimental and clinical studies on anti-inflammatory actions of lipid-lowering therapy and the mechanisms involved.We highlight that: (1)Besides decreasing cholesterol through different mechanisms, most lipid-lowering therapies share anti-inflammatory and immunomodulatory properties, and the anti-inflammatory response to lipid-lowering may be relevant to predict the effect of treatment, (2)Using surrogates for both lipid metabolism and inflammation as biomarkers or vascular inflammation imaging in future studies may contribute to a better understanding of the relative importance of different mechanisms of action, and (3)Comparative studies of

further lipid lowering, anti-inflammation and a combination of both are crucial to identify effects that are specific or shared for each treatment strategy.

[20] *Shrestha P, van de Sluis B, Dullaart RPF, van den Born J*. **Novel aspects of PCSK9 and lipoprotein receptors in renal disease-related dyslipidemia**. Cellular signalling 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30550765

ABSTRACT
Chronic kidney disease (CKD) is a global health problem with a profound impact on quality of life. Cardiovascular disease is established as a major cause of morbidity and mortality in patients with CKD. Dyslipidemia is frequently observed in CKD patients, suggesting a causal relation between dyslipidemia and cardiovascular disease in CKD patients. Currently, lipid-lowering drugs such as statins, are the primary choice for lipid lowering therapy in high-risk populations. Despite many studies showing CVD risk reduction with statins, CVD still remains the leading cause of the death in CKD.This underscores the need for new therapeutic approaches to reduce cardiovascular risk in CKD patients. Reduced lipoprotein lipase activity, increased very low-density lipoprotein production, increased proprotein convertase subtilisin kexin type 9 (PCSK9) expression and loss of hepatic heparan sulfate proteoglycans (HSPG) syndecan-1 have been associated with CKD-related dyslipidemia. Low-density lipoprotein receptor (LDLR), low-density lipoprotein receptor-related protein 1 (LRP-1) and syndecan-1, are the most important hepatic receptors for lipoprotein clearance. However, their contributions to the pathogenesis of dyslipidemia and cardiovascular disease in CKD remain unclear. Interestingly, in CKD, increased plasma lipid levels are associated with elevated levels of PCSK9. This promotes the proteolysis of LDLR, suggesting a role for PCSK9 in CKD-associated dyslipidemia. Fully humanized monoclonal antibodies targeting PCSK9 have been approved by the US Food and Drug Administration and the European Medicines Agency as lipid lowering treatment for patients with hypercholesterolemia. In CKD sub-group analysis, ODYSSEY COMBO I and ODYSSEY COMBO II studies demonstrated strong reduction in LDL-C by alirocumab compared to placebo and ezetimibe and when added to statins. However, their efficacy in reducing plasma TG is controversial. Therefore, further research work is need for a detailed analysis on efficacy and safety of PCSK9 antibodies in CKD groups. Interestingly, novel findings on PCSK9 interaction with HSPG might shed new insight on altered lipid metabolism in CKD. In this review, we discuss various aspects of lipoprotein metabolism and hepatic lipoprotein receptor signaling pathways along with the concept of renal disease-related dyslipidemia. Furthermore, this review highlights the drawbacks of current lipid-lowering therapies and proposes novel approaches for lipid management in CKD.

[21] *Sliz E, Kettunen J, Holmes MV et al.* **Metabolomic Consequences of Genetic Inhibition of PCSK9 Compared With Statin Treatment**. Circulation 2018; 138:2499-2512.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30525347

ABSTRACT
BACKGROUND: Both statins and proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors lower blood low-density lipoprotein cholesterol levels to reduce risk of cardiovascular events. To assess potential differences between metabolic effects of these 2 lipid-lowering therapies, we performed detailed lipid and metabolite profiling of a large randomized statin

trial and compared the results with the effects of genetic inhibition of PCSK9, acting as a naturally occurring trial. METHODS: Two hundred twenty-eight circulating metabolic measures were quantified by nuclear magnetic resonance spectroscopy, including lipoprotein subclass concentrations and their lipid composition, fatty acids, and amino acids, for 5359 individuals (2659 on treatment) in the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial at 6 months postrandomization. The corresponding metabolic measures were analyzed in 8 population cohorts (N=72 185) using PCSK9 rs11591147 as an unconfounded proxy to mimic the therapeutic effects of PCSK9 inhibitors. RESULTS: Scaled to an equivalent lowering of low-density lipoprotein cholesterol, the effects of genetic inhibition of PCSK9 on 228 metabolic markers were generally consistent with those of statin therapy (R2=0.88). Alterations in lipoprotein lipid composition and fatty acid distribution were similar. However, discrepancies were observed for very-low-density lipoprotein lipid measures. For instance, genetic inhibition of PCSK9 had weaker effects on lowering of very-low-density lipoprotein cholesterol compared with statin therapy (54% versus 77% reduction, relative to the lowering effect on low-density lipoprotein cholesterol; P=2x10-7 for heterogeneity). Genetic inhibition of PCSK9 showed no significant effects on amino acids, ketones, or a marker of inflammation (GlycA), whereas statin treatment weakly lowered GlycA levels. CONCLUSIONS: Genetic inhibition of PCSK9 had similar metabolic effects to statin therapy on detailed lipid and metabolite profiles. However, PCSK9 inhibitors are predicted to have weaker effects on very-low-density lipoprotein lipids compared with statins for an equivalent lowering of low-density lipoprotein cholesterol, which potentially translate into smaller reductions in cardiovascular disease risk.

[22] *Oh M, Lee CW, Ahn JM et al.* **Comparison of Fimasartan and Amlodipine Therapy on Carotid Atherosclerotic Plaque Inflammation**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30537083
ABSTRACT
BACKGROUND: The renin-angiotensin system plays an important role in promoting atherosclerotic plaque inflammation, which may be inhibited by angiotension-II receptor blockers. HYPOTHESIS: We investigated the effects of fimasartan and amlodipine therapy on carotid atherosclerotic plaque inflammation using (18) F-fluorodeoxyglucose ((18) FDG) positron emission tomography (PET) imaging. METHODS: Fifty patients with acute coronary syndrome and at least one lesion with (18) FDG uptake in the carotid artery (target to background ratio (TBR) >/= 1.6) were randomly assigned to receive either fimasartan (60mg once a day) or amlodipine (5mg once a day). (18) FDG PET examinations were performed in all patients at baseline and 6 months. The primary endpoint was the percent change in the index vessel TBR for the most diseased segment (MDS TBR). RESULTS: The two groups had similar baseline characteristics. At the 6 month follow-up, index vessel and aorta MDS TBR significantly decreased in both groups. However, the percent change in index vessel MDS TBR was similar between the two groups (-9.33+/-14.2% vs. -7.73+/-19.1%, respectively, p = 0.9). No significant difference was found for the percent change in the whole vessel TBR for the index vessel between the two groups, with similar findings for changes in MDS TBR or whole vessel TBR for the aorta. Total cholesterol, LDL cholesterol levels, and blood pressure improved to a similar degree in both groups. CONCLUSIONS: Fimasartan and amlodipine reduce carotid

atherosclerotic plaque inflammation similarly in patients with acute coronary syndrome, offering the same level of effectiveness.

[23] *Mues KE, Bogdanov AN, Monda KL et al.* **How well can familial hypercholesterolemia be identified in an electronic health record database?** Clinical epidemiology 2018; 10:1667-1677.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532597
ABSTRACT
Background: Familial hypercholesterolemia (FH) is a condition characterized by high cholesterol levels and increased risk for coronary heart disease (CHD) that often goes undiagnosed. The Dutch Lipid Network Criteria (DLNC) are used to identify FH in clinical settings via physical examination, personal and family history of CHD, in addition to the presence of deleterious mutations of the LDLR, ApoB, and PCSK9 genes. Agreement between clinical and genetic diagnosis of FH varies. While an ICD diagnosis code was not available for coding FH until 2016, Systematized Nomenclature of Medicine (SNOMED) clinical concept codes, including genetic diagnoses, for FH have been utilized in electronic health records (EHRs). Objective: To evaluate the concordance of identifying FH via SNOMED and ICD-10 CM codes vs the DLNC in an EHR database. Methods: Using the Practice Fusion EHR database, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated comparing an FH cohort identified via SNOMED and ICD-10 CM codes to one identified via the DLNC. Results: Among 907,616 patients with hypercholesterolemia, 2,180 were identified as FH via SNOMED code (zero were identified via ICD-10 CM), 259 had a DLNC score 6-8 (probable FH), and 45 had a DLNC score >8 (definite FH). Compared to DLNC score >8, the sensitivity, specificity, and PPV of the FH SNOMED code were 84.4%, 99.4%, and 6.4%, respectively. Compared to DLNC score >/=6, the sensitivity was 36.8% and the specificity was 99.5% with a PPV of 18.7%. Conclusion: Compared to the clinical criteria for FH, identification of FH patients via SNOMED diagnosis codes had high sensitivity and specificity, but low PPV. The discordance of these two techniques in identifying FH patients speaks to the challenges in identifying FH patients in large electronic databases such as administrative claims and EHR.

[24] *Wagner JB, Abdel-Rahman S, Gaedigk R et al.* **Impact of genetic variation on pravastatin systemic exposure in pediatric hypercholesterolemia**. Clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30549267
ABSTRACT
This study investigated the impact of SLCO1B1 genotype on pravastatin systemic exposure in hypercholesterolemic children and adolescents. Participants (8-20 years) with at least one allelic variant of SLCO1B1 c.521T>C (521TC, n=15; 521CC, n=2) and wild type controls (521TT, n=15) completed a single oral dose pharmacokinetic study. Inter-individual variability of pravastatin acid (PVA) exposure within SLCO1B1 genotype groups exceeded the ~2-fold difference in mean PVA exposure observed between SLCO1B1 genotype groups (p>0.05, q>0.10). 3'alpha-iso-pravastatin acid (3alpha-PVA) and lactone isomer formation in the acidic environment of the stomach prior to absorption also was variable and affected PVA exposure in all genotype groups. The SLCO1B1 c.521 gene variant contributing to variability in systemic exposure to PVA in our pediatric cohort was comparable with previous studies in adults.

However, other demographic and physicochemical factors appear to also contribute to inter-individual variability in the dose-exposure relationship.

[25] *Downs TN*. **Statins: The Burglar of Memory?** The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists 2018; 33:706-710.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30545434
ABSTRACT
Alzheimer's disease is becoming more predominant in our aging population. Statin medications have been reported to contribute to cognitive impairment. Updated cholesterol treatment guidelines significantly increase the proportion of people eligible for treatment with statins. Therefore, uncommon adverse effects related to this medication class have the potential to impact health care by increasing cognitive impairment and/or contributing to statin treatment avoidance. CASE: An 83-year-old Caucasian male was seen in a cognitive evaluation clinic for noticeable memory decline. Memory impairment was confirmed using validated cognitive assessments. Atorvastatin was identified as a possible cause of memory impairment. Shared-decision making between the patient and interdisciplinary team was utilized to discontinue atorvastatin to determine causation. Over a period of 18 months, the patient's cognitive scores initially improved after statin medication was discontinued. However, over time, cognitive scores returned to baseline for memory decline without restart or retrial of any statin within the class. DISCUSSION: This case report is consistent with many previous studies that fail to find an association between statins and cognitive impairment. The course of this case is unique in that the likelihood of association of cognitive impairment decreases with time, highlighting the importance of extended follow-up care. It also highlights the importance of evaluating the evidence supporting the Food and Drug Administration's drugsafety communications to ameliorate any concerns regarding medication therapy, in this case statin therapy. CONCLUSION: This case report is consistent with recent literature that fails to demonstrate an association between statins and cognitive impairment. It also provides support for the practitioner to prescribe and continue statins without fear of precipitating or worsening cognitive impairment.

[26] *Chen S, Redfors B, Liu Y et al.* **Outcomes of patients with and without baseline lipid-lowering therapy undergoing revascularization for left main coronary artery disease: analysis from the EXCEL trial**. Coronary artery disease 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30531253
ABSTRACT
OBJECTIVES: There is a paucity of data on the effect of baseline lipid-lowering therapy (LLT) in patients undergoing revascularization for left main (LM) coronary artery disease (CAD). We compared outcomes for patients with LMCAD randomized to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) according to the presence of baseline LLT in the EXCEL trial. PATIENTS AND METHODS: The EXCEL trial randomized 1905 patients with LMCAD and SYNTAX scores up to 32 to PCI with everolimus-eluting stents versus CABG. Patients were categorized according to whether they were medically treated with LLT at baseline, and their outcomes were examined using multivariable Cox proportional hazards

regression. The primary endpoint was a composite of death, stroke, or myocardial infarction at 3 years. RESULTS: Among 1901 patients with known baseline LLT status, 1331 (70.0%) were medically treated with LLT at baseline. There were no significant differences between the PCI and CABG groups in the 3-year rates of the primary endpoint in patients with versus without baseline LLT (Pinteraction=0.62). Among patients with baseline LLT, the 3-year rate of ischemia-driven revascularization was higher after PCI compared with CABG (13.7 vs. 5.3%; adjusted hazard ratio=2.97; 95% confidence interval: 1.95-4.55; P<0.0001), in contrast to patients without baseline LLT (9.8 vs. 12.1%; adjusted hazard ratio=0.79; 95% confidence interval: 0.47-1.33; P=0.39) (Pinteraction=0.0003). CONCLUSION: In the EXCEL trial, 3-year major adverse event rates after PCI versus CABG for LMCAD were similar and consistent in patients with and without LLT at baseline; however, revascularization during follow-up was more common after PCI compared with CABG in patients with baseline LLT, but not in those without baseline LLT.

[27] *Farmaki P, Damaskos C, Garmpis N et al.* **PCSK9 inhibitors and cardiovascular disease: impact on cardiovascular outcomes**. Curr Drug Discov Technol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30526464
ABSTRACT
Cardiovascular disease (CAD) remains the leading cause of morbidity and mortality in the western world. Hypolipidemic drugs have long been used for the primary and secondary prevention of heart disease. However, the high frequency of recurrent events in patients despite on hypolipidemic therapy has increased the need for new more targeted therapeutic approaches. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are monoclonal antibodies to the PCSK9 gene and represent a new class of drugs that have been shown to further decrease LDL-C when administered as a monotherapy or in combination with statins. In addition to LDL reduction, PCSK9 inhibitors are shown to decrease apolipoprotein B and lipoprotein(a) levels without major adverse effects. Whether or not PCSK9 inhibitors can actually reduce the incidence of cardiovascular events and ameliorate CAD prognosis is yet to be clarified. This review summarizes recent literature on the safety and efficacy of PCSK9 inhibitors on CAD outcome and its potential role in the management of patients with high-risk cardiovascular disease.

[28] *Mori D, Kashihara Y, Yoshikado T et al.* **Effect of OATP1B1 genotypes on plasma concentrations of endogenous OATP1B1 substrates and drugs, and their association in healthy volunteers**. Drug metabolism and pharmacokinetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30528195
ABSTRACT
This study aimed to elucidate the impact of OATP1B1 genotype (*1b/*1b, *1b/*15, and *15/*15) on plasma concentrations of endogenous OATP1B1 substrates. Healthy volunteers with OATP1B1 *1b/*1b (n = 10), *1b/*15 (n = 7), or *15/*15 (n = 2) received oral administration of a cocktail of statins (atorvastatin, pitavastatin, rosuvastatin, and fluvastatin). Mean area under the plasma concentration of atorvastatin, pitavastatin, and rosuvastatin in OATP1B1 *15/*15 were 2.2, 1.7 and 1.58-times greater than the corresponding values in OATP1B1 *1b/*1b, respectively, whereas that of fluvastatin was identical to those in other OATP1B1 genotypes. OATP1B1 *15/*15 also showed higher mean plasma concentrations of

OATP1B1 endogenous substrates compared with the other OATP1B1 genotypes, such as coproporphyrin I, glycochenodeoxycholate sulfate (GCDCA-S), lithocholate sulfate (LCA-S), glycolithocholate sulfate (GLCA-S) and taurolithocholate sulfate (TLCA-S), but not total or direct bilirubin, chenodeoxycholate-24-glucuronide, or omega-dicarboxylic long-chain fatty acids. Area under the plasma concentration-time curves of plasma coproporphyrin I and GLCA-S discriminated OATP1B1 genotype *15/*15 from the other genotypes. In combination with previously published clinical studies, these results support the notion that coproporphyrin I, and GLCA-S and GCDCA-S could be a surrogate probe for assessing human in vivo OATP1B1 activities.

[29] *Garcia Diaz E, Ramirez Medina D, Morera Porras OM, Cabrera Mateos JL*. **Determinants of inertia with lipid-lowering treatment in patients with type 2 diabetes mellitus**. Endocrinologia, diabetes y nutricion 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30541682
ABSTRACT
OBJECTIVE: To assess the control of cLDL in diabetic patients, to measure the impact on such control of inertia with lipid-lowering agents and to explore factors that allow for predicting this inertia. METHODS: Study of historical cohorts of diabetic patients. The proportion of patients who achieved the target cLDL levels was estimated. Therapeutic inertia was considered when the dose of the lipid-lowering agents was not adjusted, or a lipid-lowering agent was not changed or added in patients with initial cLDL outside the target. Change in cLDL from the first to the last visit and inertia with lipid-lowering drugs were analyzed according to comorbidities, cardiovascular risk factors and treatments used. RESULTS: The study simple consisted of 639 patients (mean follow-up time 11.1+/-11.2 months), of whom 27.5% achieved target cLDL levels. Inertia occurred in 43,6% of patients with initial cLDL outside the target. Independent predictors of inertia were the initial cLDL (P<0.001), polyneuropathy (P=0.014), adjustment of antihypertensive agents (P=0.002), adequacy of lipid-lowering agents (P<0.001), use of ezetimibe (P=0.001) and adherence to lipid-lowering drugs (P=0.015). CONCLUSIONS: Inertia with lipid-lowering agents in a diabetic patient is less frequent in the presence of higher cLDL values, in cases of polyneuropathy, when antihypertensive agents are adjusted or changed, and when non-adherence is detected. The adequate initial prescription of statins and the association with ezetimibe decrease the likelihood of committing inertia.

[30] *Franck G, Even G, Gautier A et al.* **Haemodynamic stress-induced breaches of the arterial intima trigger inflammation and drive atherogenesis**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30541066
ABSTRACT
Aims: Inflammatory mediators, including blood cells and their products, contribute critically to atherogenesis, but the igniting triggers of inflammation remain elusive. Atherosclerosis develops at sites of flow perturbation, where the enhanced haemodynamic stress could initiate the atherogenic inflammatory process due to the occurrence of mechanic injury. We investigated the role of haemodynamic stress-induced breaches, allowing the entry of blood cells in the arterial intima, in triggering inflammation-driven atherogenesis. Methods and results: Human coronary samples isolated from explanted hearts, (n = 47) displayed signs of

blood entry (detected by the presence of iron, ferritin, and glycophorin A) in the subintimal space (54%) as assessed by histology, immunofluorescence, high resolution episcopic microscopy, and scanning electron microscopy. Computational flow dynamic analysis showed that intimal haemorrhagic events occurred at sites of flow disturbance. Experimental carotid arteries from Apoe deficient mice showed discrete endothelial breaches and intimal haemorrhagic events specifically occurring at the site of flow perturbation, within 3 days after the exacerbation of the local haemodynamic stress. Endothelial tearing was associated with increased VCAM-1 expression and, within 7 days, substantial Ly6G+ leucocytes accumulated at the sites of erythrocyte-derived iron and lipids droplets accumulation, pathological intimal thickening and positive oil red O staining. The formation of fatty streaks at the sites of intimal breaches was prevented by the depletion of Ly6G+ leucocytes, suggesting that the local injury driven by haemodynamic stress-induced breaches triggers atherogenic inflammation. Conclusion: Haemodynamic-driven breaches of the arterial intima drive atherogenic inflammation by triggering the recruitment of leucocyte at sites of disturbed arterial flow.

[31] *Pais P, Jung H, Dans A et al.* **Impact of blood pressure lowering, cholesterol lowering and their combination in Asians and non-Asians in those without cardiovascular disease: an analysis of the HOPE 3 study**. European journal of preventive cardiology 2018:2047487318819019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30537846

ABSTRACT

BACKGROUND AND DESIGN: There are limited data on the effects of blood pressure and cholesterol lowering in Asians at intermediate risk and no cardiovascular disease. We report an analysis of the effects of blood pressure and cholesterol lowering in Asians enrolled in the Heart Outcomes Prevention Evaluation 3 (HOPE 3) trial. METHODS: We randomly assigned 6241 Asians and 6464 non-Asians at intermediate risk without cardiovascular disease to candesartan 16 mg/hydrochlorothiazide 12.5 mg or placebo and rosuvastatin 10 mg or placebo. The first co-primary outcome was a composite of cardiovascular disease death, myocardial infarction and stroke. The second co-primary outcome additionally included heart failure, cardiac arrest and revascularisation. Median follow-up was 5.6 years. RESULTS: Reduction in systolic blood pressure was less among Asians (4.3 vs. 7.7 mmHg for non-Asians, $P < 0.0001$) mainly due to a lesser effect in Chinese (2.1 mmHg) than in other Asians (7.3 mmHg), reduction in the latter being similar to non-Asians. The effect on the composite outcomes was similar, with no significant benefits from blood pressure lowering for either Asians (Chinese or non-Chinese) or non-Asians. Rosuvastatin reduced low-density lipoprotein cholesterol to a lesser degree in Asians (0.49 mmol/L (-19.1 mg/dL) compared with non-Asians 0.95 mmol/L (-36.7 mg/dL), Pinteraction < 0.0004). Yet both groups had similar reductions in the two co-primary outcomes. There was no increase in permanent medication discontinuation due to muscle-related symptoms in either group. There was an excess in new diabetes in non-Asians (4.70% rosuvastatin, 3.52% placebo, $P = 0.025$) but not in Asians (3.02% rosuvastatin, 4.04% placebo, $P = 0.0342$), Pinteraction = 0021. CONCLUSIONS: Candesartan/hydrochlorothiazide had fewer effects in reducing blood pressure in Chinese and rosuvastatin reduced low-density lipoprotein cholesterol to a lesser extent in Asians compared with non-Asians. There was no overall reduction in clinical events with lowering blood pressure in either Asians or non-Asians,

whereas there were clear and consistent benefits with lipid lowering in both. Despite extensive analyses, we have no obvious explanation for the observed findings. Future studies need to include larger numbers of individuals from different regions of the world to ensure that the results of trials are applicable globally.

[32] *Chen L, Yang Q, Ding R et al.* **Carotid thickness and atherosclerotic plaque stability, serum inflammation, serum MMP-2 and MMP-9 were associated with acute cerebral infarction**. Experimental and therapeutic medicine 2018; 16:5253-5257.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30542482

ABSTRACT

Correlations of carotid intima-media thickness (IMT), atherosclerotic plaque stability, serum inflammatory factors and serum matrix metalloproteinase (MMP)-2 and MMP-9 levels with the condition of disease in patients with acute cerebral infarction were analyzed to explore the predictive value of these risk factors. A total of 56 patients diagnosed with acute cerebral infarction in Jingmen First People's Hospital from February 2016 to January 2017 were selected and divided into the plaque stability group (n=25) and plaque instability group (n=31). Our results showed that the level of total cholesterol (TC) in the plaque instability group was significantly higher than that in the plaque stability group (P<0.05). IMT and National Institutes of Health Stroke Scale (NIHSS) score in the plaque instability group were significantly higher than those in the plaque stability group, but eccentricity index (EI) and Barthel index were significantly lower than those in the plaque stability group (P<0.05). The serum C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) levels in the plaque instability group were significantly higher than those in the plaque stability group (P<0.05). The levels of serum MMP-2 and MMP-9 in the plaque instability group were significantly higher than those in the plaque stability group (P<0.05). Barthel index was correlated with IMT (r=-0.693, P<0.01), MMP-2 (r=-0.605, P<0.01), CRP (r=-0.765, P<0.01) and EI (r=0.811, P<0.01), respectively. Hemoglobin A1c (HbA1c), TC, systolic blood pressure, coronary heart disease, diabetes mellitus, IMT, EI, CRP, TNF-alpha, IL-6, MMP-2 and MMP-9 had independent predictive values for acute cerebral infarction (P<0.05). Carotid IMT, stability of the atherosclerotic plaque, serum inflammation, serum MMP-2 and MMP-9 levels have close correlations with acute cerebral infarction. The larger the carotid IMT is, the more unstable the plaque is and the higher the levels of serum inflammatory factors, MMP-2 and MMP-9 are, the greater the risk of acute cerebral infarction will be.

[33] *Chen Y, Hu K, Bu H et al.* **Probucol protects circulating endothelial progenitor cells from ambient PM2.5 damage via inhibition of reactive oxygen species and inflammatory cytokine production in vivo**. Experimental and therapeutic medicine 2018; 16:4322-4328.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30542381

ABSTRACT

Bone marrow-derived circulating endothelial progenitor cells (EPCs) contribute to angiogenesis and vascular repair. The number and function of EPCs are significantly decreased following exposure to ambient fine particulate matter of </=2.5 microm in diameter (PM2.5) through reactive oxygen species (ROS) generation and inflammatory cytokine secretion. The anti-oxidant drug probucol reduces ROS and inflammatory cytokine production. The present study

was designed to determine the protective effects of probucol on EPCs from PM2.5-associated impairment in vivo and to explore the potential underlying mechanisms. Male C57BL/6 mice were exposed to ambient air containing PM2.5 for one month with or without probucol treatment. Mice that breathed filtered air were used as a control group. Serum and blood cells were collected for analysis. The results indicated that PM2.5 exposure induced increases in blood intracellular ROS, serum inflammatory cytokine levels and the blood cell apoptotic rate, while it decreased the number and proliferation rate of circulating EPCs in the mice with PM2.5 exposure. These effects were significantly reduced/abrogated by probucol treatment. The present in vivo study suggested that probucol protects EPCs from damage through PM2.5 exposure by inhibiting ROS generation and inflammatory cytokine production.

[34] *Dang H, Song B, Dong R, Zhang H*. **Atorvastatin reverses the dysfunction of human umbilical vein endothelial cells induced by angiotensin II**. Experimental and therapeutic medicine 2018; 16:5286-5297.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30542486
ABSTRACT
Statins exert pleiotropic effects on endothelial cells, in addition to lowering cholesterol. This study evaluated angiotensin II (Ang II)-induced dysfunction in human umbilical vein endothelial cells (HUVECs), and the effects of atorvastatin (Ator) on induced HUVECs in vitro. The cytotoxicity of Ang II and Ator was determined by the MTT assay. A series of cellular responses were screened, including oxidative stress, cellular apoptosis, inflammatory response, autophagy, expression of endothelial nitric oxide synthase and the angiogenic function of HUVECs. Ator returned these cellular responses to a normal level. The present study also examined cellular organelle dysfunction. In HUVECs, Ang II triggered mitochondrial damage, as demonstrated by a decreased mitochondrial membrane potential, while Ator attenuated this Ang II-induced damage. The observed cellular dysfunction may cause endothelial senescence due to excessive cell injury. The current study examined several aging markers, which revealed that these disorders of cellular functions triggered endothelial senescence, which was delayed by Ator. Ator also suppressed Ang II-induced angiogenesis damage. The data presented in this study strongly suggested that Ang II induced a series of processes that lead to cellular dysfunction in HUVECs, including oxidative stress, inflammation, and mitochondrial damage, leading to apoptosis and endothelial senescence. However, Ator significantly reversed these effects and modulated intracellular stability. The present study indicated that Ator serves an antagonistic role against HUVEC dysfunction and may potentially prevent several diseases, including coronary disease and atherosclerosis, by maintaining cellular homeostasis.

[35] *Wei B, Liu Y*. **Clinical significance and efficacy analysis of atorvastatin in the treatment of patients with cerebral infarction and aspiration pneumonia**. Experimental and therapeutic medicine 2018; 16:5144-5148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30542469
ABSTRACT
Therapeutic efficacy of the use of oral atorvastatin in the treatment of patients with aspiration pneumonia complicated with cerebral infarction was investigated. Three hundred and fourteen cerebral infarction patients complicated with aspiration pneumonia who were admitted to the

emergency department of Beijing Chaoyang Hospital Jingxi Branch from May 2015 to July 2017 were retrospectively analyzed. Among them, 160 patients who took atorvastatin were treated as observation group, and the remaining 154 patients were the control group. Patients were given basic treatment after diagnosis, and atorvastatin was also used for patients in the observation group. Venous blood was extracted to detect blood lipids and inflammatory cytokines. Patients were followed up for a period of six months, and the mortality was recorded. After treatment, blood lipid function and inflammatory factors in both groups were significantly improved (P<0.05). Hospital stay in the observation group (86.88%) was significantly shorter than that in the control group (76.33%) (P<0.01). After treatment, levels of TC, LDL, TG and CRP in the observation group (86.25%) were significantly lower than those in the control group (76.32%) (P=0.01). However, after treatment, level of HDL-C in the observation group (11.88%) was significantly higher than that in the control group (23.38%) (P=0.01). After treatment, levels of IL-6, IL-8 and TNF-alpha in the observation group were significantly lower than those in the control group (P<0.01). Total effective rate in the observation group was significantly higher than that of the control group (P=0.01). Total death rate in the observation group was significantly lower than that in the control group (P=0.02). In conclusion, atorvastatin is effective in the treatment of cerebral infarction patients complicated with aspiration pneumonia.

[36] *Parham JS, Goldberg AC*. **Mipomersen and its use in familial hypercholesterolemia**. Expert opinion on pharmacotherapy 2018:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30526168
ABSTRACT
INTRODUCTION: Familial Hypercholesterolemia (FH) is an inherited disorder characterized by a defect in the binding and internalization of low-density lipoprotein (LDL) particles, resulting in markedly elevated LDL levels and premature atherosclerosis. It is one of the most common inherited disorders of lipid metabolism. Many FH patients, especially those with homozygous FH do not reach LDL goals with traditional LDL therapies and may require additional, less often used, therapies. Areas covered: Mipomersen is an anti-sense oligonucleotide that prevents production of apolipoprotein B leading to decreased levels of very low-density lipoprotein (VLDL) and LDL. In this review the authors discuss the pharmacokinetics of the drug, the clinical trials evaluating its efficacy and safety, and risks and challenges associated with its clinical implementation. Its use as therapy for the treatment of FH is also discussed. Expert opinion: Mipomersen is approved for use only in homozygous FH. It has frequent adverse effects, such as injection site reactions, flu-like symptoms, and hepatoxicity. It is useful only in patients who have failed other therapies, and it faces competition from other medications that have more tolerable side effect profiles.

[37] *Cervadoro A, Palomba R, Vergaro G et al.* **Targeting Inflammation With Nanosized Drug Delivery Platforms in Cardiovascular Diseases: Immune Cell Modulation in Atherosclerosis**. Frontiers in bioengineering and biotechnology 2018; 6:177.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30542650
ABSTRACT

Atherosclerosis (AS) is a disorder of large and medium-sized arteries; it consists in the formation of lipid-rich plaques in the intima and inner media, whose pathophysiology is mostly driven by inflammation. Currently available interventions and therapies for treating atherosclerosis are not always completely effective; side effects associated with treatments, mainly caused by immunodepression for anti-inflammatory molecules, limit the systemic administration of these and other drugs. Given the high degree of freedom in the design of nanoconstructs, in the last decades researchers have put high effort in the development of nanoparticles (NPs) formulations specifically designed for either drug delivery, visualization of atherosclerotic plaques, or possibly the combination of both these and other functionalities. Here we will present the state of the art of these subjects, the knowledge of which is necessary to rationally address the use of NPs for prevention, diagnosis, and/or treatment of AS. We will analyse the work that has been done on: (a) understanding the role of the immune system and inflammation in cardiovascular diseases, (b) the pathological and biochemical principles in atherosclerotic plaque formation, (c) the latest advances in the use of NPs for the recognition and treatment of cardiovascular diseases, (d) the cellular and animal models useful to study the interactions of NPs with the immune system cells.

[38] *Tintut Y, Hsu JJ, Demer LL*. **Lipoproteins in Cardiovascular Calcification: Potential Targets and Challenges**. Frontiers in cardiovascular medicine 2018; 5:172.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30533416
ABSTRACT
Previously considered a degenerative process, cardiovascular calcification is now established as an active process that is regulated in several ways by lipids, phospholipids, and lipoproteins. These compounds serve many of the same functions in vascular and valvular calcification as they do in skeletal bone calcification. Hyperlipidemia leads to accumulation of lipoproteins in the subendothelial space of cardiovascular tissues, which leads to formation of mildly oxidized phospholipids, which are known bioactive factors in vascular cell calcification. One lipoprotein of particular interest is Lp(a), which showed genome-wide significance for the presence of aortic valve calcification and stenosis. It carries an important enzyme, autotaxin, which produces lysophosphatidic acid (LPA), and thus has a key role in inflammation among other functions. Matrix vesicles, extruded from the plasma membrane of cells, are the sites of initiation of mineral formation. Phosphatidylserine, a phospholipid in the membranes of matrix vesicles, is believed to complex with calcium and phosphate ions, creating a nidus for hydroxyapatite crystal formation in cardiovascular as well as in skeletal bone mineralization. This review focuses on the contributions of lipids, phospholipids, lipoproteins, and autotaxin in cardiovascular calcification, and discusses possible therapeutic targets.

[39] *Amiri Siavashani M, Zadeh Modarres S, Mirhosseini N et al.* **The Effects of Chromium Supplementation on Gene Expression of Insulin, Lipid, and Inflammatory Markers in Infertile Women With Polycystic Ovary Syndrome Candidate for in vitro Fertilization: A Randomized, Double-Blinded, Placebo-Controlled Trial**. Frontiers in endocrinology 2018; 9:726.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30546347
ABSTRACT

Purpose: This study was performed to determine the effects of chromium supplementation on the gene expression of insulin, lipid, and inflammatory markers in infertile women with polycystic ovary syndrome (PCOS) who were candidate for in vitro fertilization (IVF). Methods: Forty women, aged 18-40 years, who had been selected for IVF were recruited in this randomized double-blinded, placebo-controlled trial. They (n = 20/group) were randomly assigned into intervention groups to take either 200 mug/day of chromium or placebo for 8 weeks. Inflammatory markers were measured at baseline and end of the trial. Genes related to insulin, lipid, and inflammation were expressed in peripheral blood mononuclear cells (PBMCs), using RT-PCR method. Results: Chromium supplementation led to a significant reduction in serum high sensitivity C-reactive protein (hs-CRP) (-1.4 +/- 1.5 vs. + 0.2 +/- 2.2 mg/L, p = 0.01) compared with the placebo. RT-PCR findings indicated that chromium supplementation upregulated gene expression of peroxisome proliferator-activated receptor gamma (PPAR-gamma) (p = 0.01), glucose transporter 1 (GLUT-1) (p = 0.001) and low-density lipoprotein receptor (LDLR) (p = 0.01), as well as downregulated gene expression of interleukin-1 (IL-1) (p = 0.004) in PBMCs of patients with PCOS compared with the placebo. Chromium supplementation had no significant effect on gene expression of IL-8, tumor necrosis factor alpha (TNF-alpha), transforming growth factor beta (TGF-beta) and vascular endothelial growth factor (VEGF). Conclusion: Overall, our findings demonstrated that infertile women with PCOS, who were candidate for IVF benefited from chromium supplementation for 8 weeks in terms of lowering hs-CRP and improving gene expression of PPAR-gamma, GLUT-1, LDLR, and IL-1, though chromium had no effect on the gene expression of IL-8, TNF-alpha, TGF-beta, and VEGF. Clinical Trial Registration Number: http://www.irct.ir:IRCT20170513033941N32.

[40] *Zhang H, Cui Y, Zhao Y et al.* **Effects of sartans and low-dose statins on cerebral white matter hyperintensities and cognitive function in older patients with hypertension: a randomized, double-blind and placebo-controlled clinical trial**. Hypertension research : official journal of the Japanese Society of Hypertension 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30552406
ABSTRACT
Cerebral white matter hyperintensities (WMHs) and cognitive impairment are common in elderly hypertensive patients, and more needs to be learned about their prevention and treatment. Our aim was to investigate the effect of low-dose statins on WMH and cognitive function in elderly patients undergoing antihypertensive treatment. A total of 732 elderly hypertensive patients taking hydrochlorothiazide as their baseline medication were randomized using a 2 x 2 factorial design with antihypertensive (telmisartan vs. placebo) and lipid-modulating (low-dose rosuvastatin vs. placebo) arms. Brain magnetic resonance imaging (MRI) and cognitive function data were obtained. After a mean follow-up time of 59.8 (range 12-65) months, there were no differences in WMH progression and cognitive function decline over time between the groups in the antihypertensive arm. The risks of new-incident WMH Fazekas scale scores >/= 2 and the incidence of cognitive impairment did not differ between the telmisartan and placebo groups. Rosuvastatin use was associated with lower risks of new-incident Fazekas scale scores >/=2 (hazard ratio = 0.500; 95% confidence interval: 0.34-0.74) and cognitive impairment (hazard ratio = 0.54; 95% confidence interval: 0.36-0.80). Telmisartan interacted with rosuvastatin on reducing WMH progression and cognitive function decline.

Findings suggest that low-dose rosuvastatin could reduce WMH progression and cognitive function decline in antihypertensive patients, as demonstrated by the interaction between telmisartan and low-dose rosuvastatin to this effect.

[41] *Murakami M, Yamamoto K, Taketomi Y*. **Phospholipase A2 in skin biology: new insights from gene-manipulated mice and lipidomics**. Inflammation and regeneration 2018; 38:31.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30546811
ABSTRACT
The skin represents one of the tissues that are most profoundly influenced by alterations in the quality of lipids (lipoquality). Lipids not only constitute cellular membranes, but also serve as bioactive lipid mediators and essential components of the skin barrier. Phospholipase A2 (PLA2) enzymes supply fatty acids and lysophospholipids from membrane phospholipids, thereby variably affecting cutaneous homeostasis. Accordingly, perturbation of particular PLA2-driven lipid pathways can be linked to various forms of skin disease. In this review article, we highlight the roles of several PLA2 subtypes in cutaneous pathophysiology, as revealed by transgenic/knockout studies in combination with comprehensive lipidomics. We focus mainly on secreted PLA2 group IIF (sPLA2-IIF), which is associated with epidermal hyperplasia through mobilization of a unique lipid metabolite. We also address the distinct roles of sPLA2-IIE in hair follicles and sPLA2-IID in lymphoid immune cells that secondarily affect cutaneous inflammation, and provide some insights into species differences in sPLA2s. Additionally, we briefly overview the patatin-like phospholipase PNPLA1, which belongs to the Ca(2+)-independent PLA2 (iPLA2) family, as a key regulator of skin barrier function through catalysis of a unique non-PLA2 reaction. These knowledges on lipid metabolism driven by various PLA2 subtypes will open novel opportunities for translated studies toward diagnosis and therapy of human skin diseases.

[42] *Acharya P, Talahalli RR*. **Aging and Hyperglycemia Intensify Dyslipidemia-Induced Oxidative Stress and Inflammation in Rats: Assessment of Restorative Potentials of ALA and EPA + DHA**. Inflammation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30535619
ABSTRACT
Effect of aging and hyperglycemia on oxidative stress (OS) and inflammation in dyslipidemic conditions has not been elucidated. Hence, in this study, we assessed the implications of aging, hyperglycemia, and also the dietary effect of n-3 fatty acids (alpha-linolenic acid (ALA) and eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)) on OS and inflammation in dyslipidemic rats. Dyslipidemia was induced in young and aged rats by feeding high-fat lard (HFL) diet. Diabetes was induced in young dyslipidemic rats by administering streptozotocin 30 days after the induction of dyslipidemia. Experimental groups received diets containing canola oil (HF + CNO) and fish oil (HF + FO) as a source of ALA and EPA + DHA respectively. After 60 days of feeding rats with their respective diets, OS and inflammatory markers in serum were assessed. Dyslipidemia caused significant ($p < 0.05$) increase in OS (lipid peroxidation, nitric oxide, and protein carbonyl), pro-inflammatory cytokine (CRP, IL-1beta, MCP-1, and TNF-alpha), and eicosanoid (PGE2, LTB4, and LTC4) level in serum of both young and aged rats. Aged dyslipidemic rats presented significantly ($p < 0.05$) higher level of these markers compared to

young dyslipidemic rats. Hyperglycemia onset further augmented OS and inflammatory markers in young dyslipidemic rats significantly ($p < 0.05$). Administration of n-3 fatty acids downregulated the serum markers of OS and inflammation in all the three experimental models. Thus, aging and hyperglycemia onset intensified dyslipidemia-induced OS and inflammation. Dietary preformed EPA + DHA presented larger restorative potentials than precursor ALA in countering OS and inflammation in all the three experimental models.

[43] *Yang CN, Kok SH, Wang HW et al.* **Simvastatin alleviates bone resorption in apical periodontitis possibly by inhibition of mitophagy-related osteoblast apoptosis**. International endodontic journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30537112
ABSTRACT
AIM: To assess the connection between mitophagy and hypoxia-induced apoptosis in osteoblasts and whether simvastatin alleviates bone resorption in apical periodontitis through modulation of mitophagy-related apoptosis. METHODOLOGY: Hypoxia-induced generation of reactive oxygen species in mitochondria and changes in mitochondrial membrane potential were evaluated respectively by MitoSOX and JC-1 fluorescence dye signaling. Accumulation of mitophagy markers PTEN-induced putative kinase 1 (PINK1) and Parkin in mitochondria was examined by Western blotting and immunofluorescence microscopy. Osteoblast apoptosis was assessed by Western analysis of cleaved-poly (adenosine diphosphate ribose) polymerase (PARP). In a rat model of induced apical periodontitis, the therapeutic effect of simvastatin and its action on osteoblast mitophagy and apoptosis were examined. ANOVA, Fisher's and Student's t test were used to for data analysis. RESULTS: Hypoxia induced mitochondrial dysfunction and stimulated mitophagy in osteoblasts. Hypoxia also provoked apoptosis in osteoblasts and inhibition of mitophagy decreased hypoxia-augmented apoptotic activity. Simvastatin alleviated hypoxia-induced mitochondrial dysfunction, mitophagy and apoptosis. The protective action of simvastatin against apoptosis was related to its anti-mitophagy activity. Experiments in the rat model of induced apical periodontitis supported the laboratory findings. Simvastatin treatment mitigated periapical bone loss and reduced the activities of apoptosis and mitophagy in regional osteoblasts. CONCLUSIONS: The results suggest that modulation of osteoblast mitophagy may help diminish bone loss associated with inflammation and has potential as an auxiliary therapy for apical periodontitis.

[44] *Bonaccio M, Di Castelnuovo A, Costanzo S et al.* **Interaction between Mediterranean diet and statins on mortality risk in patients with cardiovascular disease: Findings from the Moli-sani Study**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527993
ABSTRACT
BACKGROUND: Statins are prescribed for patients with cardiovascular disease (CVD), along with the recommendation of adopting healthy diets. We evaluated the independent and the combined effect of statins and Mediterranean diet (MD) towards mortality risk in patients with previous CVD by using real-life data from a population-based prospective cohort. METHODS: Longitudinal analysis on 1180 subjects (mean age 67.7+/-10) with prior CVD at enrollment in

the Moli-sani Study and followed up for 7.9y (median). Adherence to MD was appraised by a Mediterranean diet score. Hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated by multivariable Cox regression and competing risk models. RESULTS: Multivariable risk estimates associated with a 2-point increase in MD score were 0.84 (95% CI 0.70-1.00), 0.77 (0.61-0.97) and 0.70 (0.52-0.93) for overall, cardiovascular and coronary artery disease (CAD)/cerebrovascular deaths, respectively. Statins were not associated with death risk. Subjects combining statins and average-high adherence to MD had much lower than expected risk of cardiovascular and CAD/cerebrovascular mortality (p for interaction=0.045 and 0.0015, respectively) as compared to those neither using statins nor having average-high MD. The combination of average-high MD and statins was associated in a likely synergistic way with reduced low-grade inflammation, but not with blood cholesterol. CONCLUSIONS: MD lowered the risk of all-cause, cardiovascular and CAD/cerebrovascular mortality CVD patients, net of statins. In the same population, statins reduced CVD death risk only in combination with MD. Low-grade inflammation, rather than lipids, is likely to be on the pathway of the interaction between MD and statins towards mortality risk.

[45] *Rodriguez-Granillo GA, Campisi R, Reynoso E et al.* **Atherosclerotic plaque burden evaluated from neck to groin: effect of gender and cardiovascular risk factors**. The international journal of cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30547317
ABSTRACT
We explored the impact of gender and cardiovascular risk factors (RF) in the distribution and burden of coronary and extra-coronary atherosclerotic plaques among patients undergoing ECG-gated thoracoabdominal computed tomography angiography (CTA) from the supra-aortic trunks to the femoral arteries. We included a consecutive cohort of patients who underwent ECG-gated thoracoabdominal aortic CTA from the supra-aortic trunks to the pubic symphysis. We evaluated the number of coronary segments with plaques [segment-involvement score (SIS)]; and the extra-coronary atherosclerotic plaque burden, comprising the aorta and supra-aortic trunks, iliofemoral arteries, and visceral arteries (extra-coronary SS). A total of 3400 vascular segments were evaluated in 100 patients (mean age 67.0 +/- 12.6 years, 66% male). Seventy-two (72%) patients had evidence of atherosclerosis in the coronary tree (coronary SIS >/= 1), of which 32% was extensive (coronary SIS > 5). Males had a significantly higher prevalence of coronary SIS >/= 1 [53 (80%), vs. 19 (56%), p = 0.018], and coronary SIS > 5 [24 (36%) vs. 8 (24%), p = 0.035] than females. Extra-coronary SS was similar between genders (males 10.2 +/- 5.8 vs. females 9.7 +/- 5.4, p = 0.70), irrespective of the location along the different vascular beds. The number of coronary RF was significantly related to the coronary SIS (p = 0.038), and hypertension and diabetes were consistently related to coronary and extra-coronary plaque burden. In the present study involving analysis of multiple vascular beds from the supra-aortic trunks to the femoral arteries, we identified significant sex-related differences in coronary plaque burden, whereas extra-coronary plaque burden was similar between genders irrespective of the vascular bed assessed.

[46] *Inacio MD, Rafacho A, de Paula Camaforte NA et al.* **Prevention of Elevation in Plasma Triacylglycerol with High-Dose Bezafibrate Treatment Abolishes Insulin Resistance and**

Attenuates Glucose Intolerance Induced by Short-Term Treatment with Dexamethasone in Rats. Int J Endocrinol 2018; 2018:3257812.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532777
ABSTRACT
Objective: Fibrates are used as lipid-lowering drugs and are well tolerated as cotreatments when glucose metabolism disturbances are also present. Synthetic glucocorticoids (GCs) are diabetogenic drugs that cause dyslipidemia, dysglycemia, glucose intolerance, and insulin resistance when in excess. Thus, we aimed to describe the potential of bezafibrate in preventing or attenuating the adverse effects of GCs on glucose and lipid homeostasis. Methods: Male Wistar rats were treated with high-dose bezafibrate (300 mg/kg, body mass (b.m.)) daily for 28 consecutive days. In the last five days, the rats were also treated with dexamethasone (1 mg/kg, b.m.). Results: Dexamethasone treatment reduced the body mass gain and food intake, and bezafibrate treatment exerted no impact on these parameters. GC treatment caused an augmentation in fasting and fed glycemia, plasma triacylglycerol and nonesterified fatty acids, and insulinemia, and bezafibrate treatment completely prevented the elevation in plasma triacylglycerol and attenuated all other parameters. Insulin resistance and glucose intolerance induced by GC treatment were abolished and attenuated, respectively, by bezafibrate treatment. Conclusion: High-dose bezafibrate treatment prevents the increase in plasma triacylglycerol and the development of insulin resistance and attenuates glucose intolerance in rats caused by GC treatment, indicating the involvement of dyslipidemia in the GC-induced insulin resistance.

[47] *Chen Q, Xiang J, Gong R et al.* **Atorvastatin downregulates HSP22 expression in an atherosclerotic model in vitro and in vivo**. International journal of molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30535427
ABSTRACT
One of the pathological functions of heat shock protein 22 (HSP22) is the association with inflammatory diseases and atherosclerosis. However, the effects of a highfat diet (HFD) or oxidized lowdensity lipoprotein (oxLDL) combined with atorvastatin (ATV) on HSP22 expression are entirely unknown. The present study investigated the effects of ATV on HSP22 expression in HFDinduced atherosclerotic apolipoprotein Edeficient (ApoE/) mice and in oxLDLinduced human umbilical vein endothelial cells (HUVECs). Furthermore, the influence of HSP22knockdown on the HFD- or oxLDLinduced atherosclerotic model was also examined. It was found that HFD or oxLDL treatment significantly increased HSP22 expression in the serum and aorta, accompanied by decreased phosphorylated (p)endothelial nitric oxide synthase (p-eNOS) activity and activated p38 mitogenactivated protein kinase (MAPK). However, these effects were suppressed by treatment with ATV. Furthermore, HSP22-knockdown showed reduced oxLDLinduced lesions, evidenced by increased peNOS activity and inactivated p38 MAPK, while suppression of cell proliferation inhibition and cell cycle arrest were also observed. Taken together, the results of this study suggest that HFD or oxLDL increased the expression of HSP22 and pp38 MAPK, and decreased the peNOS activity in vitro and in vivo, and ATV could reduce the effects by downregulating HSP22 expression.

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[48] *Gaudio LT, Veltri P, De Rosa S et al.* **Model and Application to Support the Coronary Artery Diseases (CAD): Development and Testing**. Interdisciplinary sciences, computational life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30535963
ABSTRACT
Cardiovascular diseases are among the main causes of morbidity, disability, and mortality. Most of them occur because of an atherosclerotic plaque developing within a coronary artery, which can cause a narrowing of the vessel lumen (coronary stenosis) or even break it. It is, therefore, useful to evaluate the role of the stress state of the endothelial layer of the arterial tissue, both for the maintenance of the blood circulation and for the implications in presence of a pathology that can lead to thromboembolic complications. The aim of the following study was to develop and test an application that is able to evaluate specific hemodynamic shear stress indicators in coronary arteries at different percentages of stenosis and in different patients' specific conditions. The application, based on Java, allows users to view the results of simulations performed on a coronary anatomy that can be customized with a stenosis of different degrees and positions. Being in possession of a predictive tool for disturbed flow factors may be important for the location and development of atherosclerotic plaque. Moreover, the application can be a valid tool to help in the evaluation of the condition and in the follow-up of the coronary affected by pathology.

[49] *Poggio P, Songia P, Cavallotti L et al.* **PCSK9 Involvement in Aortic Valve Calcification**. Journal of the American College of Cardiology 2018; 72:3225-3227.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30545459
ABSTRACT

[50] *Rosenson RS, Colantonio LD, Burkholder GA et al.* **Trends in Utilization of Statin Therapy and Contraindicated Statin Use in HIV--Infected Adults Treated With Antiretroviral Therapy From 2007 Through 2015**. Journal of the American Heart Association 2018; 7:e010345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30526249
ABSTRACT
Background HIV is associated with an increased risk for atherosclerotic cardiovascular disease, which may result in many people living with HIV taking a statin. Some statins are contraindicated with certain antiretroviral therapies (ART) and other medications commonly used by HIV -infected patients. Methods and Results We analyzed trends in the use of statins, including contraindicated statins, between 2007 and 2015 among HIV -infected patients aged >/=19 years taking ART who had employer-sponsored or Medicare supplemental health insurance in the Marketscan database (n=186 420). Statin use was identified using pharmacy claims. Contraindicated statin use was defined by a pharmacy claim for HIV protease inhibitors, cobicistat, hepatitis C protease inhibitors, anti-infectives, calcium channel blockers, amiodarone, gemfibrozil, or nefazodone followed by a fill for a contraindicated statin type and dosage within 90 days. The percentage of beneficiaries with HIV taking a statin remained unchanged between 2007 (24.6%) and 2015 (24.7%). Among those taking a statin, the percentage taking a contraindicated statin declined from 16.3% in 2007 to 9.0% in 2014 and then increased to 9.8% in 2015. The proportion of contraindicated statin fills attributable to HIV

protease inhibitors declined from 63.9% in 2007 to 51.0% in 2015, while those attributable to cobicistat increased from 0% before 2012 to 20.6% in 2015. Conclusions Changes in ART regimens resulted in a decline in contraindicated statin use from 2007 to 2014, but this favorable trend was attenuated in 2015 because of increased use of cobicistat-containing ART regimens.

[51] *Farsani BE, Karimi S, Mansouri E*. **Pravastatin attenuates testicular damage induced by doxorubicin - a stereological and histopatological study**. Journal of basic and clinical physiology and pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30530881
ABSTRACT
Background The aim of this study is to investigate the effects of pravastatin (PS) against doxorubicin (DOX)-induced testicular toxicity. Methods A total of 24 healthy male Sprague-Dawley rats were equally divided into four groups. Group I received normal saline, Group II received PS (20 mg/kg b.w.) by gavage, Group III was treated with DOX alone (15 mg/kg b.w., i.p.) and Group IV received the combination of DOX and PS. Results After 8 weeks, the results displayed that DOX caused a decrease in testicular volume and index, epididymal sperm count, seminiferous tubule diameter and germinal epithelium. DOX also reduced the number of spermatogonia, spermatoctyes and Sertoli cells as well as increased the lumen diameter of seminiferous tubules ($p<0.05$) and the incidence of histopathological changes of the testis. Moreover, elevated malondialdehyde (MDA) levels and declined glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities were observed ($p<0.05$). On the contrary, PS treatment significantly ameliorated nearly all of these abnormalities ($p<0.05$). Conclusions PS protects against DOX-induced testicular toxicity in rats, which is likely via the inhibition of oxidative stress and the increase of antioxidant enzyme activity.

[52] *Shiga Y, Miura SI, Nishikawa H et al.* **Regression of coronary plaque after coronary artery bypass graft**. Journal of cardiology cases 2012; 5:e92-e95.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532913
ABSTRACT
A 62-year-old woman complained of sudden chest pain and 64-multidetector row computed tomography (MDCT) was performed. The volume-rendered image showed severe stenosis of the left main coronary trunk artery (LMT). The mean density of the plaque was 32.4 hounsfield units (HU), which indicated soft plaque. Coronary angiography (CAG) showed significant focal stenosis of the LMT. Since the patient had experienced chest pain, and since focal stenosis of the LMT was demonstrated, lipid-lowering therapy using statin and coronary artery bypass graft (CABG, right internal mammary artery-left anterior descending branch, left internal mammary artery-obtuse marginal branch) were applied. Three years after treatment, 64-MDCT showed mild stenosis and a regression of plaque in the LMT. The mean density of the plaque was 73.1 HU (intermediate plaque). CAG showed a degradation of CABG flow, in addition to mild stenosis of the LMT. In conclusion, lipid-lowering therapy with statins may stabilize soft coronary plaque. In addition, non-invasive MDCT is a useful tool for diagnosing coronary artery disease, and for evaluating the size and properties of coronary plaque.

[53] *Yamaguchi K, Wakatsuki T, Niki T et al.* **Observation of short-term atorvastatin-induced changes in coronary arterial plaque properties using integrated backscatter intravascular ultrasound in a patient**. Journal of cardiology cases 2011; 3:e111-e114.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532851
ABSTRACT
Integrated backscatter intravascular ultrasound (IB-IVUS) capable of assessing plaque properties has recently become clinically applicable. We observed short-term atorvastatin-induced changes in coronary arterial plaque properties using IB-IVUS. The patient was a 57-year-old man who underwent coronary angiography when admitted to our hospital for cerebrovascular surgery, and lesions were observed in 2 branches: 99% and 90% stenoses in the proximal anterior descending branch (LAD) and middle region of the circumflex, respectively. Stenting was performed for the LAD on November 4, 2009 and for the circumflex on December 9. Oral atorvastatin administration at 10 mg/day was initiated on November 5 because the LDL-cholesterol level was high (160 mg/dl). A region about 5 mm in length proximal to the stent placed in the LAD was analyzed using IB-IVUS. Atorvastatin lowered the LDL cholesterol level from 160 to 79 mg/dl. On IB image analysis, although the period was as short as about 1 month, a marked decrease in the fatty component (44% --> 26%) and an increase in the fibrous component (53% --> 66%) were observed in the plaque. It was suggested that atorvastatin changes the tissue properties of coronary arterial plaques from a very early phase. It might be associated with the stabilization of coronary plaque.

[54] *Gao G, Jiang S, Ge L et al.* **Atorvastatin improves doxorubicin-induced cardiac dysfunction by modulating Hsp70, Akt and MAPK signalling pathways**. Journal of cardiovascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30540688
ABSTRACT
Atorvastatin is a lipid-regulating drug that is commonly used in clinical practice and can stabilize plaques. Increasing evidence shows that statins have anti-heart failure effects, but their specific mechanism is not clear. The purpose of this study was to investigate the cardioprotective effects of atorvastatin on heart failure in rats and its mechanism. Continuous intraperitoneal injection of 2.5 mg/kg/w doxorubicin for 6 weeks, with a cumulative dose of 15 mg/kg, was used to induce a rat model of heart failure. Then, the rats were treated with low-dose atorvastatin, high-dose atorvastatin or saline for 4 weeks. In the doxorubicin-treated groups, echocardiography showed decreases in LVEF and FS and increases in LVEDd and LVPWd compared with those in the control group, and increased levels of BNP and Hsp70 were also found in the doxorubicin-treated groups. Compared with saline intervention, atorvastatin ameliorated LVEF, FS, LVEDd and LVPWd (a significant difference was observed only in the high-dose group) and reduced serum BNP. HE staining showed that atorvastatin ameliorated myocardial injury. The improvement in cardiac function induced by atorvastatin was accompanied by increased Hsp70 expression, decreased p-ERK and p-JNK expression and a reduction in myocardial fibrosis shown by Masson staining. In addition, atorvastatin had a protective effect on the myocardial apoptosis signalling pathway, with increased p-Akt expression and downregulated cleaved caspase-3 expression, and the reduction in myocardial apoptosis was confirmed by a TUNEL assay. Therefore, our experiments demonstrated that

atorvastatin may protect cardiac function by modulating Hsp70, p-Akt, p-ERK, and p-JNK signalling to reduce myocardial fibrosis and myocardial apoptosis.

[55] *Akbari H, Asadikaram G, Vakili S, Masoumi M*. **Atorvastatin and losartan may upregulate renalase activity in hypertension but not coronary artery diseases: The role of gene polymorphism**. Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30548657
ABSTRACT
The aim is to explore the treatment effect of coronary artery disease (CAD) and hypertension on plasma levels of renalase activity and also the possible association of renalase rs10887800 gene polymorphism with CAD and hypertension. A total of 286 patients who received coronary angiography were included in the study. Subjects were divided into four groups including (1) hypertensive with no CAD (H-Tens, n = 60); (2) CAD with hypertension (CAD + H-Tens, n = 71); (3) CAD with no hypertension (CAD, n = 61); and (4) nonhypertensive with no CAD as a control group (Con, n = 69). The plasma renalase activity was measured using the Amplex Red Monoamine Oxidase Assay Kit. Renalase rs10887800 single-nucleotide polymorphisms (SNPs) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Atorvastatin (P = 0.005), losartan (P < 0.001), and captopril (P = 0.001) were administered significantly more in case groups compared with the Con group. Significant higher and lower levels of renalase activity were observed in H-Tens and CAD patients compared with control subjects (P < 0.001 for both comparisons). Furthermore, no significant differences were obtained in the risk or protective effects of renalase rs10887800 SNP against hypertension and/or CAD in both recessive and dominant genetic models (P > 0.05). According to the findings of the present study, atorvastatin and losartan therapy assumes considerable significance in alleviating hypertension, but not CAD, by increasing the renalase activity. Furthermore, it was found that renalase rs10887800 is less likely a predisposing factor for susceptibility to hypertension and/or CAD in an Iranian southeast population.

[56] *Lorza-Gil E, de Souza JC, Garcia-Arevalo M et al.* **Coenzyme Q10 protects against beta-cell toxicity induced by pravastatin treatment of hypercholesterolemia**. Journal of cellular physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30536661
ABSTRACT
New onset of diabetes is associated with the use of statins. We have recently demonstrated that pravastatin-treated hypercholesterolemic LDL receptor knockout (LDLr(-/-)) mice exhibit reductions in insulin secretion and increased islet cell death and oxidative stress. Here, we hypothesized that these diabetogenic effects of pravastatin could be counteracted by treatment with the antioxidant coenzyme Q 10 (CoQ 10), an intermediate generated in the cholesterol synthesis pathway. LDLr (-/-) mice were treated with pravastatin and/or CoQ 10 for 2 months. Pravastatin treatment resulted in a 75% decrease of liver CoQ 10 content. Dietary CoQ 10 supplementation of pravastatin-treated mice reversed fasting hyperglycemia, improved glucose tolerance (20%) and insulin sensitivity (>2-fold), and fully restored islet glucose-stimulated insulin secretion impaired by pravastatin (40%). Pravastatin had no effect on insulin secretion of wild-type mice. In vitro, insulin-secreting INS1E cells cotreated with CoQ 10 were

protected from cell death and oxidative stress induced by pravastatin. Simvastatin and atorvastatin were more potent in inducing dose-dependent INS1E cell death (10-15-fold), which were also attenuated by CoQ 10 cotreatment. Together, these results demonstrate that statins impair beta-cell redox balance, function and viability. However, CoQ 10 supplementation can protect the statins detrimental effects on the endocrine pancreas.

[57] *Alfian SD, Pradipta IS, Hak E, Denig P*. **A systematic review of measures estimates adherence and persistence to multiple medications**. J Clin Epidemiol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30537541
ABSTRACT
OBJECTIVES: We reviewed measures used to estimate adherence and persistence to multiple cardiometabolic medications from prescription data, particularly for blood pressure-lowering, lipid-lowering, and/or glucose-lowering medication, and give guidance on which measures to choose. STUDY DESIGN AND SETTING: A literature search of Medline, Embase, and PsycINFO databases was conducted to identify studies assessing medication adherence and/or persistence for patients using multiple cardiometabolic medications. Two reviewers performed the study selection process independently. RESULTS: From the 54 studies assessing adherence, only 36 (67%) clearly described the measures used. Five measures for adherence were identified, including adherence to 'all', to 'any', to 'both' medication, 'average adherence' and 'highest/lowest adherence'. From the 22 studies assessing persistence, only 6 (27%) clearly described the measures used. Three measures for persistence were identified, including persistence with 'all', with 'both', and with 'any' medication. Less than half of the studies explicitly considered medication switches when relevant. CONCLUSION: From the identified measures, the "any medication" measure is most suitable for identifying patients in need of an intervention, whereas the "all medication" measure is useful for assessing the effect of interventions. More attention is needed for adequate measurement definitions when reporting on and interpreting adherence or persistence estimates to multiple medications.

[58] *Backes JM, Melton BL, Ruisinger JF et al.* **Comparing patients' prescribed, self-reported, and actual intake of supplemental eicosapentaenoic acid + docosahexaenoic acid**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30551972
ABSTRACT
BACKGROUND: Dietary fish oil supplements containing the omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are frequently used for cardiovascular benefit. However, several factors may limit the intake of prescribed doses. OBJECTIVE: The objective of this study is to compare the prescribed, patient self-reported, and actual intake of supplemental EPA + DHA doses in a lipid-specialty clinic and identify common barriers and influences to therapy. METHODS: Seventy-six patients prescribed supplemental fish oil were randomly selected to participate in a 28-item cross-sectional survey for evaluating patient knowledge and intake of prescribed supplemental EPA + DHA doses. Self-reported data were collected during a follow-up clinic visit, whereas actual intake was determined when patients had access to their fish oil bottle. These data were compared with their chart-documented prescribed EPA + DHA dose. RESULTS: Many patients were well-educated and had

attended the lipid-specialty clinic for approximately 2 years but only 28.9% were confident that they could accurately recall their daily EPA + DHA dose. There were statistically significant differences between the prescribed doses and patients' self-reported doses (3600 mg vs 2750 mg, P = .014), as well as between prescribed doses and actual intake (3600 mg vs 1575 mg, P < .001). Patients reported multiple barriers and influences to explain their use of fish oil products. CONCLUSION: Most patients using supplemental fish oil in a lipid-specialty clinic were not taking the prescribed amount of EPA + DHA, with many using markedly lower than prescribed doses. This is likely because of several factors including the complexities of supplemental fish oil doses and labeling, product availability, and discount sales. These findings suggest that supplemental fish oil requires continuous education and dosing guidance.

[59] *Marcovina SM, Moriarty PM, Koschinsky ML, Guyton JR*. **JCL roundtable-Lipoprotein(a): The emerging risk factor**. Journal of clinical lipidology 2018; 12:1335-1345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527801
ABSTRACT
Lipoprotein(a), or Lp(a), is a major risk factor for atherothrombotic events along with low-density lipoprotein cholesterol and, inversely, high-density lipoprotein cholesterol. Lp(a) also contributes to the progression of calcific aortic stenosis and to the rare occurrence of arterial thrombotic strokes without atherosclerosis in children and younger women. Much has been learned about the inheritance of Lp(a) levels and the relationship between apolipoprotein(a) structure and function. Recent work suggests an intriguing interaction between oxidized phospholipids on Lp(a) and inflammatory interleukin-1 genotypes. New pharmaceutical approaches with antisense and RNA interference technology may achieve up to 90% lowering of Lp(a). This Roundtable includes practical considerations for clinically measuring and responding to Lp(a) levels.

[60] *Wang Y, Guo YL, Dong QT, Li JJ*. **Severe aortic valve stenosis in a 14-year-old boy with sitosterolemia**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30528907
ABSTRACT
We report a 14-year-old boy finally diagnosed with sitosterolemia, presenting with severe aortic valve stenosis. Genetic analysis revealed homozygous null mutation c.1336 C > T (p.R446X) in ABCG5 gene. His cardiac ultrasound presented aortic valve stenosis and moderate aortic regurgitation. His whole aorta computed tomography angiogram scan revealed aortic stenosis superior to the aortic valve, followed by ascending aorta dilation, whereas his coronary and peripheral arteries appeared normal. His maximum total cholesterol and low-density lipoprotein-cholesterol levels dropped dramatically after diet control, and ezetimibe was prescribed for treatment. The current case indicated that sitosterolemia may be a heterogeneous disease in clinical phenotype.

[61] *Pelham JH, Hanks L, Aslibekyan S et al.* **Higher hemoglobin A1C and atherogenic lipoprotein profiles in children and adolescents with type 2 diabetes mellitus**. Journal of clinical & translational endocrinology 2019; 15:30-34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30547005

ABSTRACT
Aim: Significant knowledge gaps exist regarding lipoprotein profiles in children with type 2 diabetes mellitus (T2DM). The primary objective was to analyze the type and nature of lipoprotein abnormalities present in children with T2DM and to identify determinants of adverse lipoprotein profiles. The secondary objective was to assess associations with elevated glycated hemoglobin (HbA1C), i.e., <8% vs. >/=8.0% and pediatric dyslipidemias in the setting of T2DM. Methods: This retrospective chart review included children with T2DM who had undergone lipoprotein analysis and were not on lipid lowering medications (n=93). Results: The participants (mean age 15.2+/-2.7y) were 71% female and 78% African American (AA). Adjusted for age, sex, and race, BMI z-score was positively associated with LDL-pattern B (pro-atherogenic profile with small dense LDL particles) (P=0.01), and negatively associated with total HDL-C (P=0.0003). HbA1C was robustly positively associated with the LDL-C, apoB and LDL pattern B (all P<0.001). Patients with an HbA1C >8% had significantly higher total cholesterol (191.4 vs. 158.1mg/dL, P=0.0004), LDL-C (117.77 vs. 92.3mg/dL, P=0.002), apoB (99.5 vs. 80.9mg/dL, P=0.002), non-HDL-C (141.5 vs. 112.5, P=0.002), and frequency of LDL pattern B (57% vs. 20%, P=0.0008). Conclusion: HbA1C and BMI were associated with adverse lipoprotein profiles, and may represent two major modifiable cardiovascular risk factors in the pediatric T2DM population. Patients with an HbA1C higher than 8.0% had significantly worse atherogenic lipid profile, i.e., higher LDL-C, non-HDL-C, apoB and LDL pattern B, suggesting adequate glycemia may improve adverse lipoprotein profiles.

[62] *Pahor M, Anton SD, Beavers DP et al.* **Effect of losartan and fish oil on plasma IL-6 and mobility in older persons. The ENRGISE Pilot randomized clinical trial**. J Gerontol A Biol Sci Med Sci 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30541065

ABSTRACT
BACKGROUND: Low-grade chronic inflammation, characterized by elevations in plasma Interleukin-6 (IL-6), is an independent risk factor of impaired mobility in older persons. Angiotensin receptor blockers and omega-3 polyunsaturated fatty acids (omega-3) may reduce IL-6 and may potentially improve physical function. To assess the main effects of the angiotensin receptor blocker losartan and omega-3 as fish oil on IL-6 and 400 m walking speed, we conducted the ENRGISE Pilot multicenter randomized clinical trial. METHODS: The ENRGISE Pilot enrolled participants between April 2016 and June 2017, who participated for 12 months. Participants were aged >=70 years with mobility impairment, had IL-6 between 2.5 and 30 pg/ml, and were able to walk 400 meters at baseline. Participants were randomized in three strata 2 X 2 factorial to: a) losartan 50 to 100 mg/day or placebo (n=43), b) fish oil 1400 to 2800 mg/day or placebo (n=180), and c) with both (n=66). RESULTS: 289 participants were randomized (mean ag/e 78.3 years, 47.4% women, 17.0% black). There was no effect of losartan (difference of means=-0.065+/-0.116 [SE], 95% CI: -0.293 to 0.163, P=0.58) or fish oil (-0.020+/-0.077, 95% CI: -0.171 to 0.132, P=0.80) on the log of IL-6. Similarly, there was no effect of losartan (-0.025+/-0.026, 95% CI: -0.076 to 0.026, P=0.34) or fish oil (0.010+/-0.017, 95% CI: -0.025 to 0.044, P=0.58) on walking speed (m/s). CONCLUSIONS. These results do not support use of these interventions to prevent mobility loss in older adults at risk of disability with low-grade chronic inflammation. REGISTRATION: Clinicaltrials.gov NCT02676466.

[63] *Rinella ME, Trotter JF, Abdelmalek MF et al.* **Rosuvastatin improves the FGF19 analogue NGM282-associated lipid changes in patients with nonalcoholic steatohepatitis**. Journal of hepatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30529590
ABSTRACT
BACKGROUND: NGM282, an engineered analogue of the gut hormone FGF19, improves hepatic steatosis and fibrosis biomarkers in patients with nonalcoholic steatohepatitis (NASH). However, NGM282 increases serum cholesterol levels by inhibiting CYP7A1, which encodes the rate-limiting enzyme in the conversion of cholesterol to bile acids. Here, we investigate whether administration of a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor can manage the cholesterol increase seen in NASH patients treated with NGM282. METHODS: In this phase 2, 12-week, open-label, multi-center study, patients with biopsy-confirmed NASH were treated with subcutaneous NGM282 once daily. After 2 weeks, rosuvastatin was added in stepwise, biweekly incremental doses to a maximum of 40 mg daily. Both drugs were continued until end of treatment at week 12. We evaluated plasma lipids, lipoprotein particles and liver fat content. RESULTS: In 66 patients who received NGM282 0.3 mg (n=23), NGM282 1 mg (n=21), or NGM282 3 mg (n=22), circulating cholesterol increased from baseline at week 2. Initiation of rosuvastatin resulted in rapid decline in plasma levels of total cholesterol and LDL-C. At week 12, reductions from baseline in total cholesterol levels of up to 18% (P<0.001), LDL-C of up to 28% (P<0.001), triglycerides of up to 34% (P<0.001) and an increase in HDL-C of up to 16% (P<0.001), with similar changes in lipoprotein particles, were observed in these patients. Robust decreases from baseline in 7alpha-hydroxy-4-cholesten-3-one (P<0.001) and liver fat content (P<0.001) were also observed. Rosuvastatin was safe and well-tolerated in patients co-administered with NGM282. CONCLUSIONS: In this multi-center study, NGM282-associated elevation of cholesterol was effectively managed with rosuvastatin. Co-administration of rosuvastatin with NGM282 may be a reasonable strategy to optimize cardiovascular risk profile in patients with NASH. LAY SUMMARY: Non-alcoholic steatohepatitis (NASH) represents a large and growing public health concern with no approved therapy. NGM282, an engineered analogue of the gut hormone FGF19, reduces liver fat, liver injury and inflammation in patients with NASH. However, NGM282 increases cholesterol levels. Here we show that co-administration of a statin can manage the cholesterol increase seen in NASH patients treated with NGM282, producing a favorable overall lipid profile.

[64] *de Las Marinas Alvarez MD, Lopez Calatayud V, Solaz Garrido B et al.* **Moderate Asymptomatic Subacute Eosinophilia Secondary to Simvastatin Therapy**. J Investig Allergol Clin Immunol 2018; 28:434-436.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30530396
ABSTRACT

[65] *Miyashita K*. **Prevention of Fish Oil Oxidation**. Journal of oleo science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30542006
ABSTRACT

Literature update week 50 (2018)

The benefit of fish oil to health has been widely recognized because of the high contents of functional EPA (20:5n-3) and DHA (22:6n-3) in the oil; however, the application of fish oil has been limited by its high susceptibility to oxidation. This review reports the characteristics of EPA and DHA oxidation compared with those of other fatty acids such as linoleic acid (18:2n-6). In addition, effective approaches to protect against oxidation are discussed, focusing on the unique antioxidant potential of amine compounds. Finally, the exceptionally high oxidative stability of EPA and DHA in biological systems is discussed. Understanding the protective mechanism against EPA and DHA oxidation in such systems may be useful for the development of an effective antioxidant procedure for fish oil that is rich in EPA and DHA.

[66] *Mysliwiec P, Choromanska B, Winnicka MM et al.* **Interleukin-6 deficiency modifies the effect of high fat diet on myocardial expression of fatty acid transporters and myocardial lipids**. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society 2018; 69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30552304
ABSTRACT
Chronic inflammation is a critical feature of obesity in the development of myocardial dysfunction. The observations that interleukin-6 (IL-6) is implicated in lipid and glucose homeostasis as well as its connection with the pathogenesis of insulin resistance might suggest the involvement of this cytokine in metabolic disorders of the failing heart. In the present study we aimed to assess the effects of IL-6 ablation in mice fed with normal and high fat diet on the myocardial expression of glucose and fatty acid transporting proteins, and to evaluate the paralleled alterations in lipid content. We demonstrated that mice devoid of IL-6 exert reduced glucose transporter type 4 (GLUT-4) expression (-26%) and plasma membrane abundance (-43%), with no effect on glucose transporter type 1 (GLUT-1) content. Although there were no significant alterations in fatty acid translocase (FAT/CD36) and plasma membrane-associated fatty acid-binding protein (FABPpm) levels, we revealed a substantial decline in intramyocardial triacylglycerol level (-49%). Challenging of IL-6 knockout (KO) mice with high fat diet evoked an increase in FAT/CD36 expression (+19%) concomitantly with a trend for its reduced amount in plasma and mitochondrial membranes. Additionally, an increase in triacylglycerol level (+56%) was noticed, simultaneously with elevated content of saturated (+62%), monounsaturated (+69%) and polyunsaturated (+38%) fatty acids in this lipid fraction. The presented data reflect different roles of IL-6 in cardiomyocytes under selected conditions (i.e., normal and excessive lipid supply).

[67] *Nonaka K, Ozaki Y, Ito K et al.* **Endurance exercise increases the protein levels of PGC-1alpha and respiratory chain complexes in mouse skeletal muscle during atorvastatin administration**. The journal of physiological sciences : JPS 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30536041
ABSTRACT
Statins and exercise reduce cardiovascular disease incidence. We investigated whether endurance exercise in mice induces mitochondrial adaptation in skeletal muscle and muscle injury during administration of atorvastatin, a member of the statin medication class. Male C57BL mice were assigned to one of three groups: control (Con), statin (Statin), or statin and

exercise (Statin + Ex). Atorvastatin was administered, and exercise performed on a treadmill for 8 weeks. The levels of mitochondria-associated proteins, PGC-1alpha, and respiratory chain complex, (COX) I-V, in the quadriceps femoris, and serum creatine kinase, a muscle injury marker, were measured. PGC-1alpha and COX I-V were upregulated in the Statin + Ex group compared to those in the Statin and Con groups; serum creatine kinase levels were similar. Endurance training in mice induced mitochondrial adaptation in skeletal muscle without causing muscle injury, during atorvastatin administration.

[68] *Cao YX, Wu NQ, Sun D et al.* **Application of expanded genetic analysis in the diagnosis of familial hypercholesterolemia in patients with very early-onset coronary artery disease**. Journal of translational medicine 2018; 16:345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30526649
ABSTRACT
BACKGROUND: Patients with monogenic familial hypercholesterolemia (FH) have high risk for coronary artery disease (CAD). A recent FH Expert Panel suggested that FH was underdiagnosed and undertreated which needs early diagnosis. Moreover, the proportion of DNA-confirmed FH patients hospitalized with very early-onset (</= 35 years) CAD remains uncertain. METHODS: One hundred and five patients with age </= 35 years and LDL-C >/= 3.4 mmol/L were tested for 9 genes (LDLR, APOB, PCSK9, APOE, STAP1, LIPA, LDLRAP1, ABCG5/8). Dutch Lipid Clinic Network (DLCN) and Simon Broome (SB) criteria for FH were also performed. RESULTS: The prevalence of genetically confirmed FH was 38.1% (n = 40) in 105 patients. DLCN categorized 26.7% patients to probable and definite FH while SB identified 17.1% of patients with possible to definite FH. Twenty-five (62.5%) and seventeen (42.5%) patients with pathogenic mutations were undiagnosed according to SB and DLCN criteria. FH variant carriers, especially homozygotes, had significantly higher plasma LDL-C levels. The best LDL-C threshold for genetically confirmed FH was 4.56 mmol/L in the present study. CONCLUSIONS: FH is really a common cause for very young CAD patients (</= 35 years) with a 38.1% of causative mutations in China and best LDL-C threshold for predicting mutations was 4.56 mmol/L. The underdiagnostic rate of clinical criteria was around 42.5-62.5%, suggesting that the expanded genetic testing could indeed promote the diagnosis of FH.

[69] *Qamar A, Giugliano RP, Keech AC et al.* **Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction With Evolocumab: An Analysis of FOURIER Trial Data**. JAMA cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30540337
ABSTRACT
Importance: Little is known about the heterogeneity in low-density lipoprotein cholesterol levels (LDL-C) lowering with proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor medications. Objective: To evaluate the interindividual variability in LDL-C reduction with the PCSK9 inhibitor drug evolocumab. Design, Setting, and Participants: We examined the percentage change in LDL-C levels from baseline in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, a placebo-controlled randomized clinical trial of the PCSK9 inhibitor evolocumab in patients with stable atherosclerotic cardiovascular disease who were taking statin medications. Patients in either

treatment arm who had high baseline LDL-C variability during screening and either did not receive the study drug, altered their background lipid-lowering therapy regimen, or had no LDL-C level sample in week 4 were excluded from the primary analysis. Analyses in the patients were stratified by treatment arm. Data was collected from 2013 to 2016, and data were analyzed from January 2018 to November 2018. Main Outcomes and Measures: Interindividual variation in percent reduction in LDL-C with evolocumab. Results: There were 27564 individuals in the cohort; after exclusions for baseline variability (n = 3524) or alterations in background lipid therapy and other causes (n = 2272), 21768 patients remained. At week 4, the median percent reduction in LDL-C levels from baseline was 66% (interquartile range, 54%-76%; median [interquartile range] baseline value, 90 [79-105] mg/dL; postchange value, 31 [21-44] mg/dL) with evolocumab. During the first year, a total of 10325 of 10902 patients in the evolocumab group (94.7%) had a reduction 50% or greater in LDL-C levels, 10669 of 10902 (97.9%) had a reduction 30% or more, and 10849 of 10902 (99.5%) had any reduction in LDL-C levels. Fifty-three patients (0.5%) had no apparent reduction in LDL-C levels. In the placebo arm, the median LDL-C reduction was 4% (interquartile range, 6% increase to 13% reduction; baseline median [IQR] value, 90 [79-106] mg/dL; postchange value, 87 [74-103] mg/dL) at 4 weeks. Waterfall plots showed notable variability in the top and bottom 5% of patients for both evolocumab and placebo groups, with large changes in LDL-C levels in the placebo group (increases of >/=25%, 531 patients [4.9%]; decreases of >/=25%, 985 patients [9.1%]). At 4 weeks, the placebo-adjusted reductions in LDL-C levels with evolocumab were 50% or greater in 9839 of 10866 patients (90.5%) and 30% or greater in 10846 of 10866 patients (99.8%). Results were consistent across clinically relevant subgroups. Conclusions and Relevance: There appears to be a highly consistent robust reduction in LDL-C levels with evolocumab use. Trial Registration: ClinicalTrials.gov identifier: NCT01764633.

[70] *Ruuth M, Soronen J, Kaiharju E et al.* **USF1 deficiency alleviates inflammation, enhances cholesterol efflux and prevents cholesterol accumulation in macrophages**. Lipids in health and disease 2018; 17:285.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30545366
ABSTRACT
BACKGROUND: The focus of studies on high-density lipoproteins (HDL) has shifted from HDL-cholesterol (HDL-C) to HDL function. We recently demonstrated that low USF1 expression in mice and humans associates with high plasma HDL-C and low triglyceride levels, as well as protection against obesity, insulin resistance, and atherosclerosis. Here, we studied the impact of USF1 deficiency on HDL functional capacity and macrophage atherogenic functions, including inflammation, cholesterol efflux, and cholesterol accumulation. METHODS: We used a congenic Usf1 deficient mice in C57Bl/6JRccHsd background and blood samples were collected to isolate HDL for structural and functional studies. Lentiviral preparations containing the USF1 silencing shRNA expression vector were used to silence USF1 in human THP-1 and Huh-7 cells. Cholesterol efflux from acetyl-LDL loaded THP-1 macrophages was measured using HDL and plasma as acceptors. Gene expression analysis from USF1 silenced peritoneal macrophages was carried out using Affymetrix protocols. RESULTS: We show that Usf1 deficiency not only increases HDL-C levels in vivo, consistent with elevated ABCA1 protein expression in hepatic cell lines, but also improves the functional capacity of HDL particles. HDL particles derived from

Usf1 deficient mice remove cholesterol more efficiently from macrophages, attributed to their higher contents of phospholipids. Furthermore, silencing of USF1 in macrophages enhanced the cholesterol efflux capacity of these cells. These findings are consistent with reduced inflammatory burden of USF1 deficient macrophages, manifested by reduced secretion of pro-inflammatory cytokines MCP-1 and IL-1beta and protection against inflammation-induced macrophage cholesterol accumulation in a cell-autonomous manner. CONCLUSIONS: Our findings identify USF1 as a novel factor regulating HDL functionality, showing that USF1 inactivation boosts cholesterol efflux, reduces macrophage inflammation and attenuates macrophage cholesterol accumulation, linking improved macrophage cholesterol metabolism and inflammatory pathways to the antiatherogenic function of USF1 deficiency.

[71] *Zhang X, Liu H, Hao Y et al.* **Coenzyme Q10 protects against hyperlipidemia-induced cardiac damage in apolipoprotein E-deficient mice**. Lipids in health and disease 2018; 17:279.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30526612

ABSTRACT

BACKGROUND: Hyperlipidemia is a well-established risk factor for cardiac damage, which can lead to cardiovascular diseases. Many studies have shown that Coenzyme Q10(CoQ10) protects against cardiac damage in vivo. The aim of this study was to investigate the possible protective effects of CoQ10 against cardiac damage in apolipoprotein E-deficient (ApoE(-/-)) mice. METHODS: Eight-week-old male C57BL/6 and ApoE(-/-) mice were randomly divided into four groups: C57BL/6 mice fed a normal diet (C57BL/6 group); C57BL/6 mice fed a normal diet + CoQ10 (C57BL/6 + CoQ10 group); ApoE(-/-) mice fed a high-fat diet (ApoE(-/-) HD group), and ApoE(-/-) mice fed a high-fat diet + CoQ10 (ApoE(-/-) HD + CoQ10 group). All groups were fed the different diets for 16 weeks. Blood samples were obtained from the inferior vena cava and collected in serum tubes. The samples were then stored at - 80 degrees C until used. Coronal sections of heart tissues were fixed in 10% formalin and then embedded in paraffin for histological evaluation. The remainder of the heart tissues was snap-frozen in liquid nitrogen for mRNA or immunohistochemical analysis. RESULTS: The metabolic parameters such as total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-c), and triglycerides (TG) levels were lower in ApoE(-/-)HD + CoQ10 mice than in ApoE(-/-) HD mice. There were significant pathophysiological changes (H&E, PAS, Masson and CD68 staining) in ApoE(-/-) mice in the HD group compared with those in the HD + CoQ10 group. CoQ10 reduced HD-induced cardiac tissue damage via autophagy (p62 and LC3), as evidenced by immunoblotting, immunohistochemistry, and RT-qPCR. CoQ10 also inhibited inflammation (IL-6 and TNF-alpha) gene expression in ApoE(-/-) mice. CONCLUSIONS: These results indicate that CoQ10 is a potential therapeutic target for cardiac damage caused by hyperlipidemia.

[72] *Ung MH, MacKenzie TA, Onega TL et al.* **Statins associate with improved mortality among patients with certain histological subtypes of lung cancer**. Lung cancer (Amsterdam, Netherlands) 2018; 126:89-96.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527197

ABSTRACT

OBJECTIVES: To measure the association between statin exposure and mortality in lung cancer patients belonging to different categories of histological subtype. MATERIALS AND METHODS: A

cohort of 19,974 individuals with incident lung cancer between 2007 and 2011 was identified using the SEER-Medicare linked database. Statin exposure both pre- and post-diagnosis was analyzed to identify a possible association with cancer-specific mortality in patients stratified by histological subtype. Intention-to-treat analyses and time-dependent Cox regression models were used to calculate hazard ratios and 95% confidence intervals (95% CIs) corresponding to statin exposure both pre- and post-diagnosis, respectively. RESULTS: Overall baseline statin exposure was associated with a decrease in mortality risk for squamous-cell carcinoma patients (HR = 0.89, 95% CI = 0.82-0.96) and adenocarcinoma patients (HR = 0.87, 95% CI = 0.82-0.94), but not among those with small-cell lung cancer. Post-diagnostic statin exposure was associated with prolonged survival in squamous-cell carcinoma patients (HR = 0.68, 95% CI = 0.59-0.79) and adenocarcinoma patients (HR = 0.78, 95% CI = 0.68-0.89) in a dose-dependent manner. CONCLUSION: There is consistent evidence indicating that baseline or post-diagnostic exposure to simvastatin and atorvastatin is associated with extended survival in non-small-cell lung cancer subtypes. These results warrant further randomized clinical trials to evaluate subtype-specific effects of certain statins in patient cohorts with characteristics similar to those examined in this study.

[73] *Mukai H, Dai L, Chen Z et al.* **Inverse J-shaped relation between coronary arterial calcium density and mortality in advanced chronic kidney disease**. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30534995
ABSTRACT
Background: The coronary artery calcium (CAC) score from cardiac computed tomography (CT) is a composite of CAC volume and CAC density. In the general population, CAC volume is positively and CAC density inversely associated with cardiovascular disease (CVD) events, implying that decreased CAC density reflects atherosclerotic plaque instability. We analysed associations of CAC indices with mortality risk in patients with end-stage renal disease [chronic kidney disease Stage 5 (CKD5)]. Methods: In 296 CKD5 patients undergoing cardiac CT (median age 55 years, 67% male, 19% diabetes, 133 dialysed), the Framingham risk score (FRS), presence of CVD and protein-energy wasting (PEW; subjective global assessment) and high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) were determined at baseline. During follow-up for a median of 35 months, 51 patients died and 75 patients underwent renal transplantation. All-cause mortality risk was analysed with competing-risk regression models. Vascular calcification was analysed in biopsies of the arteria epigastrica inferior in 111 patients. Results: Patients in the middle tertile of CAC density had the highest CAC score, CAC volume, age, CVD, PEW, FRS, hsCRP and IL-6. In competing risk analysis, the middle {subhazard ratio [sHR] 10.7 [95% confidence interval (CI) 2.0-57.3]} and high [sHR 8.9 (95% CI 1.5-51.8)] tertiles of CAC density associated with increased mortality, independent of CAC volume. The high tertile of CAC volume, independent of CAC density, associated with increased mortality [sHR 8.9 (95% CI 1.5-51.8)]. Arterial media calcification was prominent and associated with CAC volume and CAC density. Conclusions: In CKD5, mortality increased linearly with higher CAC score and CAC volume whereas for CAC density an inverse J-shaped pattern was observed, with the crude

mortality rate being highest for the middle tertile of CAC density. CAC volume and CAC density were associated with the extent of arterial media calcification.

[74] *Nitta S, Kasao M*. **[Use of lipid-lowering therapy in patient with acute coronary syndrome]**. Nihon Rinsho Men'eki Gakkai kaishi = Japanese journal of clinical immunology 2016; 74 Suppl 6:114-118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30540382
ABSTRACT

[75] *Nilholm C, Roth B, Hoglund P et al.* **Dietary intervention with an Okinawan-based Nordic diet in type 2 diabetes renders decreased interleukin-18 concentrations and increased neurofilament light concentrations in plasma**. Nutrition research (New York, N.Y.) 2018; 60:13-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527256
ABSTRACT
Food may induce inflammation and favor development of metabolic diseases, which have been associated with increased inflammation and potential risk of cognitive impairment. It is customary to know whether food or disease promote inflammation. Our hypothesis was that Okinawan-based Nordic (O-BN) diet leads to decreased circulating concentrations of inflammatory and neural biomarkers. The objectives of this study were to examine the effects of the O-BN diet on inflammatory and neural responses. First, 2 different breakfasts; one standard and another O-BN-based, were given in random order to 19 healthy volunteers. Second, a 12-week O-BN-dietary intervention was performed in type 2 diabetes mellitus (T2DM), where the participants were followed for another 16-weeks, with registration of anthropometry and metabolic parameters. Non-diabetic subjects served as controls at baseline. Plasma was analyzed for cytokines by a 10-plex Luminex assay and neurofilament light (NfL) by an ultrasensitive Single molecule assay. Cytokine levels decreased after a single breakfast intake, independent of diet composition. Cytokine levels were higher in T2DM than in controls. Anthropometric and metabolic parameters were improved by the dietary intervention. In parallel, cytokine levels were lowered, although only significantly for IL-18 (P=.001), with a tendency of significance for IL-12p70 (P=.07). Levels of IL-18 correlated with glucose, HbA1c and lipids, but not with body mass index, insulin or blood pressure. NfL levels increased during the intervention (P=.049). O-BN-based diet does not affect postprandial cytokine levels in health, whereas it renders decreased circulating IL-18 levels along with metabolic biomarkers in T2DM, with no beneficial effect on NfL.

[76] *Mrowczynski OD, Madhankumar AB, Sundstrom JM et al.* **Exosomes impact survival to radiation exposure in cell line models of nervous system cancer**. Oncotarget 2018; 9:36083-36101.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30546829
ABSTRACT
Radiation is utilized in the therapy of more than 50% of cancer patients. Unfortunately, many malignancies become resistant to radiation over time. We investigated the hypothesis that one method of a cancer cell's ability to survive radiation occurs through cellular communication via

exosomes. Exosomes are cell-derived vesicles containing DNA, RNA, and protein. Three properties were analyzed: 1) exosome function, 2) exosome profile and 3) exosome uptake/blockade. To analyze exosome function, we show radiation-derived exosomes increased proliferation and enabled recipient cancer cells to survive radiation in vitro. Furthermore, radiation-derived exosomes increased tumor burden and decreased survival in an in vivo model. To address the mechanism underlying the alterations by exosomes in recipient cells, we obtained a profile of radiation-derived exosomes that showed expression changes favoring a resistant/proliferative profile. Radiation-derived exosomes contain elevated oncogenic miR-889, oncogenic mRNAs, and proteins of the proteasome pathway, Notch, Jak-STAT, and cell cycle pathways. Radiation-derived exosomes contain decreased levels of tumor-suppressive miR-516, miR-365, and multiple tumor-suppressive mRNAs. Ingenuity pathway analysis revealed the most represented networks included cell cycle, growth/survival. Upregulation of DNM2 correlated with increased exosome uptake. To analyze the property of exosome blockade, heparin and simvastatin were used to inhibit uptake of exosomes in recipient cells resulting in inhibited induction of proliferation and cellular survival. Because these agents have shown some success as cancer therapies, our data suggest their mechanism of action could be limiting exosome communication between cells. The results of our study identify a novel exosome-based mechanism that may underlie a cancer cell's ability to survive radiation.

[77] *Saaguchi M, Hasegawa T, Ehara S et al.* **Cardio-ankle Vascular Index Associated with Coronary Plaque Burden not Plaque Morphology**. Osaka city medical journal 2016; 62:47-57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30550710
ABSTRACT
Background Cardio-ankle vascular index (CAVI) is a marker that reflects the overall stiffness of the aorta, femoral artery, and tibial artery. Several previous reports have shown the usefulness of CAVI for coronary artery disease (CAD) presence and severity. According to coronary angiography (CAG) and intracoronary imaging such as optical coherence tomography (OCT), coronary plaque burden and morphology as predictors of all-cause and cardiovascular mortality were previously evaluated. The aim of our study was to assess the correlation between CAVI value and Gensini's score for the coronary plaque burden as well as CAVI value and plaque morphology by using OCT. Methods A total of 548 consecutive patients who underwent CAG were enrolled in this study. CAVI value was evaluated in all patients, and OCT was performed in 89 of the 548 patients. CAVI ratio is calculated as CAVI/CAVIex (expected normal value of CAVI, which is calculated using patient age and sex). Results On multivariable analysis, sex, age, hypertension, diabetes mellitus, and CAVI were significantly correlated with logarithmized Gensini's score. CAVI values were significantly higher in the groups with CAD, which were 1 vessel disease (VD), 2VD, and 3VD, than in the OVD group ($p<0.001$). However, there was no statistical significance between CAVI ratio and OCT findings in terms of plaque morphology. Conclusions CAVI might be useful as a routine test for the detection of CAD and the evaluation of atherosclerotic plaque burden but not coronary plaque vulnerability.

[78] *Clifton PM*. **Diet, exercise and weight loss and dyslipidaemia**. Pathology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30528924
ABSTRACT

There is a large amount of controversy relating dietary fat intake and coronary artery disease. It has been strongly suggested that saturated fat is not harmful and that polyunsaturated fat is either not beneficial or even harmful. Given that dietary lipids and fibre can influence serum lipids which are strongly linked to the risk of coronary artery disease I have reviewed recent evidence linking diet and serum lipids to confirm a diet-heart disease link. Over 84 studies have been included in a recent meta-analysis and meta-regression which examined the effects of changes in fat type on lipid levels. An absolute 1% reduction in saturated fat or trans fat intake as a percentage of energy with replacement by n-6 polyunsaturated fat would lead to a reduction in low density lipoprotein (LDL) cholesterol of 0.05 mmol/L. In most Western countries the difference in intake between the highest quintile and the lowest quintile of saturated fat is about 7%, so moving from the highest to the lowest quintile should lower LDL cholesterol by 0.35 mmol/L or about 10%. This change should lower cardiovascular disease rates by at least 10%. Replacing this amount of saturated fat with carbohydrate of average quality would lower LDL cholesterol by 0.21 mmol/L and increase fasting triglyceride by 0.17 mmol/L. This combination of effects would have a neutral effect on cardiovascular disease rates. However, replacement of trans fat appears to reduce disease rates and total mortality. Substituting low glycaemic index carbohydrates for high glycaemic index carbohydrates will lower triglyceride by 15-25% and reduce cardiovascular risk. Large doses of fish oil will lower triglyceride with a mean lowering of 0.45 mmol/L for a 3.5 g/day amount. Large doses of soluble fibre (3.5-7.0 g/day) lower LDL cholesterol by 0.2-0.35 mmol/L with Konjac glucomannan being the most effective per gram. Plant sterols or stanols lower LDL cholesterol by about 10% for a 2 g/day dose, while exercise and weight loss lower cardiovascular risk predominantly by lowering fasting triglyceride. In conclusion, diet lowers LDL cholesterol and triglyceride and dietary changes should be ultimately linked to a reduced risk of heart disease.

[79] *Dyrbus K, Gasior M, Desperak P et al.* **Characteristics of lipid profile and effectiveness of management of dyslipidaemia in patients with acute coronary syndromes - Data from the TERCET registry with 19,287 patients**. Pharmacological research : the official journal of the Italian Pharmacological Society 2018; 139:460-466.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30527895

ABSTRACT

Despite well-defined therapeutic low-density lipoprotein cholesterol (LDL-C) target in the highest-risk population, low percentage of patients is administered with intensive lipid-lowering therapy and achieves recommended levels. Therefore, based on the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) Registry data we investigated the characteristics of lipid profile and management of dyslipidemia in acute coronary syndrome (ACS) patients. 19,287 consecutive patients hospitalized between 2006 and 2016 have been included in the study. The lipid profile on admission and long-term laboratory effects (namely the efficacy of achievement of the therapeutic target of LDL-C <70 mg/dl [1.8 mmol/L]) after follow-up of twelve months were assessed. Acute coronary syndromes occurred in 36.1% of the Registry patients including 14.3% with ST-elevated myocardial infarction (STEMI), 10.2% with NSTEMI and 9,9% with unstable angina (UA). The highest LDL-C concentration on admission was observed in the STEMI subgroup (mean level: 127.0 mg/dL [3.28 mmol/L]). In 76.6% of the Registry patients LDL-C concentration was lower than 130 mg/dL and in 20.7% was lower than

70 mg/dL at baseline. The patients with baseline LDL < 70 mg/dL were usually presented with the worst clinical profile. In 91,6% of the patients admitted due to acute coronary syndrome, statin treatment was administered at discharge. Among them, 37.6% received intensive statin therapy. In the 12-month follow-up, in 32.4% of patients admitted due to STEMI, LDL-C concentration was lower than 70 mg/dL, compared to 29.9% in patients with NSTEMI and 27.8% in patients with UA. In conclusion, STEMI patients are less clinically burdened with concomitant risk factors and comorbidities, but present significantly worse baseline lipid profile values. Among the patients already treated with statins, patients with ACS regardless of its type have significantly higher LDL-C than patients with SA. Despite discrepancies in the clinical profile on admission, achievement of the therapeutic target equalizes the outcomes in 12-month follow-up, however with the best results for STEMI patients.

[80] *Juarez-Rojas JG, Posadas-Romero C, Martinez-Alvarado R et al.* **Type 2 Diabetes Mellitus is Associated with Carotid Artery Plaques in Patients with Premature Coronary Heart Disease**. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion 2018; 70:301-309.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532096
ABSTRACT
Background: In subjects without a history of coronary heart disease (CHD), type 2 diabetes mellitus (T2DM) is associated with carotid artery plaques (CAP), which is a better marker than high carotid intima-media thickness (hCIMT) for predicting first or recurrent cardiovascular events. Objective: The objective of this study is to analyze the association of T2DM with CAP and hCIMT in premature CHD patients. Methods: Premature CHD was considered before the age of 55 years in men and before 65 in women. T2DM was defined according to the American Diabetes Association criteria. CAP was defined as a focal structure encroaching the arterial lumen by at least 50% of the surrounding IMT value or with a thickness > 1.5 mm. Results: Among 1196 patients (CHD duration 1.5 years [interquartile range: 0.4-5.6]), 37.2% had T2DM, and 97.8% were on antihypertensive, 94.4% on lipid-lowering, and 97.3% on anti-aggregate treatment. hCIMT prevalence was similar in patients with or without T2DM, whereas CAP prevalence was higher among T2DM patients (17.7% vs. 30.9%; $p < 0.001$). T2DM showed association with CAP, independently of CHD evolution and glycemic control (odds ratio: 1.57; 95% confidence interval: 1.09-2.26). Conclusions: T2DM has an independent association with CAP. Early detection of recurrent cardiovascular events, with CAP identification, could be useful to prevent complications in patients with CHD.

[81] *Angelino D, Tassotti M, Brighenti F et al.* **Niacin, alkaloids and (poly)phenolic compounds in the most widespread Italian capsule-brewed coffees**. Scientific reports 2018; 8:17874.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30552404
ABSTRACT
Coffee is one of the most popular beverages worldwide and, nowadays, one of the most practical way for its preparation is by prepacked capsules. The aim of this study was comparing the content in caffeine, trigonelline, N-methylpyridinium (NMP), niacin, and chlorogenic acids of 65 different capsule-brewed coffees, commercialised by 5 of the most representative brands in Italy. Coffees were prepared from capsules following manufacturer's instructions and

analysed with an optimized UHPLC-MS/MS method able to assess all these phytochemicals in one single run. Inter-lot and capsule variability were also studied for a subset of coffee capsules. Except for decaffeinated coffees, caffeine amount accounted between 54 and 208 mg/serving. Regular espresso coffees showed higher trigonelline, NMP, and niacin concentrations than large (lungo) and decaffeinated samples, with average serving amounts of 17.96, 1.78, and 0.66 mg, respectively. Regarding chlorogenic acids, caffeoylquinic acids were the most relevant ones (20-117 mg/serving). Feruloylquinic acids were quantified between 8 and 50 mg/serving. Coumaroylquinic acids, hydroxycinnamate dimers, caffeoylshikimic acids, and caffeoylquinic lactones were also present at lower concentrations. Multivariate analysis provided comprehensive information on the phytochemical profile of the different types of coffee, showing a great variability among coffees with some brand-related insights. This study supports the need for accurately characterizing espresso coffees while investigating the beneficial effects of coffee on human health.

[82] *Al-Taani GM, Al-Azzam SI, Alzoubi KH, Aldeyab MA*. **Which drugs cause treatment-related problems? Analysis of 10,672 problems within the outpatient setting**. Therapeutics and clinical risk management 2018; 14:2273-2281.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532550
ABSTRACT
Background: Treatment-related problems (TRPs) may pose risks for patients if unaddressed. With the increased complexity of health care, it is important to target pharmacists' efforts to patients that are at high risk for TRPs. Objectives: The present study aimed to identify medications most commonly associated with TRPs. Setting: Outpatient departments of five public and teaching hospitals in Jordan. Method: TRPs and drugs most commonly implicated with TRPs were assessed for patients recruited from outpatient clinics in five major hospitals in Jordan using a standardized and validated pharmaceutical care manual. Main outcome measure: Drugs associated with different types of TRPs. Results: Ultimately, 2,747 patients, with a total of 10,672 TRPs, were included in the study. The medication groups most commonly associated with TRPs were cardiovascular (53.0%), endocrine (18.1%), and gastrointestinal (7.7%) drugs. The most common specific drugs associated with TRPs from any category were atorvastatin (12.5%), metformin (8.5%), simvastatin (6.2%), and enalapril (5.9%). Cardiovascular medications were the most common drugs implicated with multiple subtypes of TRPs - most commonly, allergic reaction or undesirable effect (88.5%), drug product not available (87.3%), safety interaction issues (81.8%), a need for additional or more frequent monitoring (78.0%), and more effective drugs available (77.2%). Hypertension, diabetes mellitus, and dyslipidemia were the most common diseases associated with different subtypes of TRPs. Conclusion: The present study identified high-risk drugs for TRPs, which can be used as identification of targeting approach TRPs. Such an approach would improve care provided to patients and can inform health care policies.

[83] *Jiang J, Zhou YJ, Li JJ et al.* **Uncontrolled hyperlipidemia in Chinese patients who experienced acute coronary syndrome: an observational study**. Therapeutics and clinical risk management 2018; 14:2255-2264.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30532548

ABSTRACT

Objective: Despite current standard of care, the overall lipid goal attainment rate for hyperlipidemia patients, especially those who have experienced acute coronary syndrome (ACS), is suboptimal, which predisposes them to a higher residual risk of atherothrombotic events. This study aimed to describe characteristics of Chinese patients who recently experienced an ACS event and were on lipid-lowering treatment, yet failing to reach targeted goal. Methods: A multicenter, cross-sectional study was conducted to recruit 2,034 Chinese patients who experienced an ACS (ST segment elevation myocardial infarction [STEMI], non-STEMI, or unstable angina) event within the past 4-40 weeks and were on statin treatment (>2 weeks) from March 2015 to December 2016. All eligible patients underwent a fasting lipid test after enrollment and data on medical history were collected. Results: The mean age of 1,994 eligible patients was 61.0+/-9.84 years. Among them, 1,493 (74.9%) patients received intensive statin therapy (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 mg per protocol) and 499 (25.0%) patients were on maximum tolerated dose statin. Of the 1,994 eligible subjects, 1,273 (63.8%) patients did not achieve the lipid goal at the time of enrollment. Among the not-at-goal patients, 910 (71.5%) received intensive statin therapy; the majority (73.4%) of them were male; the mean age was 61.2+/-10.1 years old; 699 (54.9%) patients had a history of hypertension; 25.3% had diabetes mellitus; and 29.5% were current smokers. The mean low-density lipoprotein-cholesterol (LDL-C), non-high-density lipoprotein-cholesterol (non-HDL-C), and ApoB levels at enrollment of this group of patients were 2.460+/-0.7139 mmol/L, 3.094+/-0.8861 mmol/L, and 0.840+/-0.3015 g/L, respectively. Conclusion: The study result demonstrates that overall more than half of the patients who recently (4-40 weeks) experienced ACS who were treated did not reach the guideline-recommended LDL-C and non-HDL-C goal. These results highlight the potential necessity for a new drug beyond statins to further reduce disease burden in the future.