Literature update week 22 (2018)

[1] *AlSwafeeri H, ElKenany W, Mowafy M, Karam S*. **Effect of local administration of simvastatin on postorthodontic relapse in a rabbit model**. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 2018; 153:861-871.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29853244

ABSTRACT
INTRODUCTION: Posttreatment relapse is a major challenging clinical issue. The objective of this study was to evaluate the effect of local administration of simvastatin on posttreatment relapse. METHODS: Orthodontic tooth movement was induced in 10 white New Zealand rabbits. After 21 days of active tooth movement, the orthodontic appliances were removed, and the experimental teeth were allowed to relapse for 21 days. During the relapse phase, 1 mandibular quadrant received local simvastatin administration, and the other received the control vehicle solution on a weekly basis. Three-dimensional models of the experimental teeth were created to allow the measurement of experimental tooth movement and posttreatment relapse. The animals were killed at the end of the relapse phase for histomorphometric analysis of alveolar bone remodeling. RESULTS: The mean relapse percentages were 75.83% in the quadrant receiving the control vehicle solution and 62.01% in the quadrant receiving simvastatin. Neither the relapse magnitude nor the relapse percentage showed a significant difference between the 2 quadrants. Histomorphometric analyses showed that local simvastatin administration yielded a significant reduction in the area of active bone-resorptive lacunae and a significant increase in newly formed bone area. CONCLUSIONS: Although local administration of simvastatin aids in bone remodeling associated with posttreatment relapse by reducing the area of active bone resorption and upregulating bone formation, it did not significantly minimize posttreatment relapse.

[2] *Dolci GS, Ballarini A, Gameiro GH et al.* **Atorvastatin inhibits osteoclastogenesis and arrests tooth movement**. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics 2018; 153:872-882.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29853245

ABSTRACT
INTRODUCTION: In addition to their cholesterol-lowering effects, the statin class of drugs appears to enhance osteogenesis and suppress bone resorption, which could be a clinical concern during orthodontic treatment. In this animal study, we aimed to determine whether atorvastatin (ATV) affects orthodontic tooth movement (OTM) through osteoclast inhibition. Furthermore, we analyzed the potential adverse effects of ATV on long-bone turnover and endochondral ossification. METHODS: Rats were administered ATV (15 mg/kg) or saline solution via gavage (n = 12 animals/group), starting 2 weeks before initial OTM. Tooth displacement was measured after 7, 14, and 21 days. Histologic sections of the maxilla and femur were obtained after 14 and 21 days of OTM and stained (hematoxylin and eosin; TRAP assay) for histomorphometric analysis. RESULTS: ATV was associated with significant ($P < 0.05$) reductions in OTM and osteoclast counts. Independently of drug administration, OTM increased the number of osteoclasts and reduced the bone-volume ratio compared with the control maxillae without OTM. Long-term statin administration did not appear to affect femoral endochondral

ossification. CONCLUSIONS: This experimental study showed that the long-term use of ATV can significantly promote osteoclast inhibition and slow the OTM in the first week in rats. Under physiologic conditions, the drug did not affect bone turnover and endochondral ossification.

[3] *Yu P, Qian AS, Chathely KM, Trigatti BL*. **PDZK1 in leukocytes protects against cellular apoptosis and necrotic core development in atherosclerotic plaques in high fat diet fed ldl receptor deficient mice**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29853191
ABSTRACT
BACKGROUND AND AIMS: PDZK1 (Post-synaptic density protein/Drosophila disc-large protein/Zonula occludens protein containing 1) stabilizes the HDL receptor protein, SR-B1, in the liver, and mediates SR-B1 signaling outside of the liver. Complete knockout of pdzk1 increases atherosclerosis in apoE-deficient mice, but the effect of PDZK1 in leukocytes is not known. In this study, we tested the role of leukocyte PDZK1 in atherosclerosis development by using bone marrow transplantation to generate ldlr deficient mice lacking PDZK1 in leukocytes. METHODS: Ldlr(-/-) mice were transplanted with either pdzk1(-/-) or pdzk1(+/+) bone marrow and fed a high-fat diet to induce atherosclerosis. RESULTS: Bone marrow specific pdzk1 knockout slightly increased atherosclerotic plaque sizes but strikingly increased sizes of necrotic cores and cellular apoptosis in within plaques. PDZK1 deficiency prevented HDL dependent protection of macrophages from apoptosis in vitro and sensitized peritoneal macrophages to apoptosis in situ. PDZK1 deficiency in macrophages also impaired their ability to engulf apoptotic cells, and attenuated the IL-4 dependent induction of mannose receptor in vitro and mannose receptor protein levels in macrophages in atherosclerotic plaques. CONCLUSIONS: PDZK1 is required for anti-atherogenic responses in macrophages including HDL dependent protection against apoptosis and macrophage mediated efferocytosis and limits the accumulation of apoptotic cells within atherosclerotic plaques protecting against necrotic core development.

[4] *Ruscica M, Simonelli S, Botta M et al.* **Plasma PCSK9 levels and lipoprotein distribution are preserved in carriers of genetic HDL disorders**. Biochimica et biophysica acta 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29852278
ABSTRACT
Proprotein convertase subtilisin/kexin 9 (PCSK9), a protein regulating the number of cell-surface LDL receptors (LDLR), circulates partially associated to plasma lipoproteins. How this interaction alters PCSK9 plasma levels is still unclear. In the present study, we took advantage of the availability of a large cohort of carriers of genetic HDL disorders to evaluate how HDL defects affect plasma PCSK9 levels and its distribution among lipoproteins. Plasma PCSK9 concentrations were determined by ELISA in carriers of mutations in LCAT, ABCA1, or APOAI genes, and lipoprotein distribution was analyzed by FPLC. Carriers of one or two mutations in the LCAT gene show plasma PCSK9 levels comparable to that of unaffected family controls (homozygotes, 159.4ng/mL (124.9;243.3); heterozygotes, 180.3ng/mL (127.6;251.5) and controls, 190.4ng/mL (146.7;264.4); P for trend=0.33). Measurement of PCSK9 in plasma of subjects carrying mutations in ABCA1 or APOAI genes confirmed normal values. When fractionated by FPLC, PCSK9 peaked in a region between LDL and HDL in control subjects. In

carriers of all HDL defects, lipoprotein profile shows a strong reduction of HDL, but the distribution of PCSK9 was superimposable to that of controls. In conclusion, the present study demonstrates that in genetically determined low HDL states plasma PCSK9 concentrations and lipoprotein distribution are preserved, thus suggesting that HDL may not be involved in PCSK9 transport in plasma.

[5] *Yorulmaz H, Ozkok E, Kaptan E et al.* **Therapeutic Effects of Simvastatin on Galectin-3, and Oxidative Stress parameters in Lung Tissue in Endotoxemia**. Bioscience reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29853535
ABSTRACT
Galectins constitute of a soluble mammalian beta-galactoside binding lectin family, which play homeostatic roles in the regulation of the cell cycle, and apoptosis, in addition to their inflammatory conditions. Galectin-3 has important role in the regulation of various inflammatory conditions including endotoxemia, and airway inflammation. Statins, the key precursor inhibitors of HMG-CoA reductase, may prevent the progression of inflammation in sepsis after prior statin treatment. Endotoxemia leads to the formation of oxidative stress parameters in proteins, carbohydrates, and DNA. In the present study, we aimed to show the effects of simvastatin on Galectin-3, and Glutathione Reductase (GR), Glutathione Peroxidase (GSH-Px), Superoxide dismutase (SOD), and TBARS levels in lung tissue of rats which were treated with lipopolysaccharides (LPS) during the early phase of sepsis. Rats were divided into four groups as the control, LPS (20 mg/kg), Simvastatin (20 mg/kg), and Simvastatin+LPS group. Galectin (Galectin-3) expression in formalin-fixed paraffin-embedded lung tissue sections was demonstrated using by the immunohistochemistry methods. There were reduced densities, and the decreased number of Galectin-3 immunoreactivities in the Simvastatin+LPS group compared with the LPS group in the pneumocytes, and in the bronchial epithelium of lung tissue. In the LPS group, GR, GSH-Px, and SOD were found lower than the levels in Simvastatin treated LPS group ($p<0.05$, $p<0.01$, $p<0.01$, respectively) in the lung tissue. However, TBARS decreased in the Simvastatin+LPS group compared with the levels in LPS group($p<0.001$). Simvastatin attenuates LPS-induced oxidative acute lung inflammation, oxidative stress, and suppresses LPS-induced Galectin-3 expression in the lung tissue.

[6] *Hjelmesaeth J, Asberg A, Andersson S et al.* **Impact of body weight, low energy diet and gastric bypass on drug bioavailability, cardiovascular risk factors and metabolic biomarkers: protocol for an open, non-randomised, three-armed single centre study (COCKTAIL)**. BMJ open 2018; 8:e021878.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29844102
ABSTRACT
INTRODUCTION: Roux-en-Y gastric bypass (GBP) is associated with changes in cardiometabolic risk factors and bioavailability of drugs, but whether these changes are induced by calorie restriction, the weight loss or surgery per se, remains uncertain. The COCKTAIL study was designed to disentangle the short-term (6 weeks) metabolic and pharmacokinetic effects of GBP and a very low energy diet (VLED) by inducing a similar weight loss in the two groups. METHODS AND ANALYSIS: This open, non-randomised, three-armed, single-centre study is performed at a tertiary care centre in Norway. It aims to compare the short-term (6 weeks) and

long-term (2 years) effects of GBP and VLED on, first, bioavailability and pharmacokinetics (24 hours) of probe drugs and biomarkers and, second, their effects on metabolism, cardiometabolic risk factors and biomarkers. The primary outcomes will be measured as changes in: (1) all six probe drugs by absolute bioavailability area under the curve (AUCoral/AUCiv) of midazolam (CYP3A4 probe), systemic exposure (AUCoral) of digoxin and rosuvastatin and drug:metabolite ratios for omeprazole, losartan and caffeine, levels of endogenous CYP3A biomarkers and genotypic variation, changes in the expression and activity data of the drug-metabolising, drug transport and drug regulatory proteins in biopsies from various organs and (2) body composition, cardiometabolic risk factors and metabolic biomarkers. ETHICS AND DISSEMINATION: The COCKTAIL protocol was reviewed and approved by the Regional Committee for Medical and Health Research Ethics (Ref: 2013/2379/REK sorost A). The results will be disseminated to academic and health professional audiences and the public via presentations at conferences, publications in peer-reviewed journals and press releases and provided to all participants. TRIAL REGISTRATION NUMBER: NCT02386917.

[7] *Thorsson B, Eiriksdottir G, Sigurdsson S et al.* **Population distribution of traditional and the emerging cardiovascular risk factors carotid plaque and IMT: the REFINE-Reykjavik study with comparison with the Tromso study**. BMJ open 2018; 8:e019385.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29858406
ABSTRACT
OBJECTIVES: Population statistics for carotid plaque and cardiovascular risk factors reported in scientific journals are usually presented as averages for the population or age and sex adjusted, rather than sex and age groups. Important population differences about atherosclerosis and cardiovascular risk factors may thus be missed. We compare the distribution of cardiovascular risk factors, carotids plaque and carotid intima-media thickness (CIMT) in two population-based studies. METHODS: Carotid artery atherosclerotic plaque prevalence and risk factors levels for cardiovascular disease by sex in 5-year age groups from the Risk Evaluation For Infarct Estimates Reykjavik study (REFINE-Reykjavik study) were compared with data from the Tromso 6 study. RESULTS: The threshold of carotid plaque presence in the Tromso 6 study fell between minimal and moderate plaque defined in the REFINE-Reykjavik study reflecting carotid plaque prevalence. The prevalence of minimal carotid plaque in the REFINE-Reykjavik study was 47% in men (40-69 years old) and 38% in women and 11% in men and 7% in women of moderate plaque. The prevalence of any plaque in the Tromso 6 study was 35% in men and 27% in women. The mean (CIMT) was similar in the studies. In the Tromso 6 study mean systolic blood pressure was 8 mm Hg higher in men and 10 mm Hg higher in women, mean low-density lipoprotein was 0.5 mmol/L higher in men and 0.3 mmol/L higher in women and the prevalence of smoking was 4% higher in men and 9% higher in women. However, body mass index was 0.8 kg/m(2) higher in men and 0.9 kg/m(2) in women in the REFINE-Reykjavik study. CONCLUSION: Comparison between Iceland and Norway revealed differences in the prevalence of carotid plaque, which was assumed to be due to different definition of plaque. However, clinically significant differences in conventional cardiovascular risk factors were seen. This underscores the importance of detailed comparison of population data across different populations.

[8] *Wang Y, Kuang ZM, Feng SJ et al.* **Combined antihypertensive and statin therapy for the prevention of cardiovascular events in patients with hypertension without complications: protocol for a systematic review and meta-analysis**. BMJ open 2018; 8:e019719.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29858408

ABSTRACT

INTRODUCTION: High blood pressure (BP) affects over 40% of adults over the age of 25 worldwide and is the leading global risk factor for death or disability. Hypertension is also the most important risk factor for endovascular atherosclerosis, which, when combined with other cardiovascular risk factors, leads to atherosclerotic cardiovascular disease (ASCVD). Statins are one of the most widely used drugs for the prevention of ASCVD. The recently announced study of Heart Outcomes Prevention Evaluation-3 suggests that cholesterol-lowering agents combined with antihypertensive therapy can prevent cardiovascular events and reduce the combined endpoint. We plan to conduct a systematic review and meta-analysis to evaluate whether combined antihypertensive and statin therapy is more beneficial than antihypertensive therapy alone in patients with hypertension without complications. METHODS AND ANALYSIS: We will perform a comprehensive search for randomised controlled trials evaluating combined antihypertensive and statin therapy for the treatment of patients with hypertension. The following English electronic databases will be searched: The Cochrane Library, EMBASE and PubMed. Outcomes will be categorised as short-term (</=6 months) or long-term (>6 months). When evaluating the effects of combined antihypertensive and statin therapy, a short-term outcome is usually defined as a change in BP or lipid levels, while a long-term outcome is usually defined as cardiovascular benefits or risks. The data screening and extraction will be conducted by two different reviewers. The quality of the RCTs will be assessed according to the Cochrane handbook risk of bias tool. ETHICS AND DISSEMINATION: This review does not require ethics approval and the results of the meta-analysis will be submitted to a peer-review journal. PROSPERO REGISTRATION NUMBER: CRD42017071935.

[9] *Flisiak-Jackiewicz M, Bobrus-Chociej A, Tarasow E et al.* **Predictive Role of Interleukin-18 in Liver Steatosis in Obese Children**. Canadian journal of gastroenterology & hepatology 2018; 2018:3870454.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29854715

ABSTRACT

Introduction: Interleukin-18 (IL-18) is a proinflammatory cytokine associated with metabolic syndrome (MS). Nonalcoholic fatty liver disease (NAFLD) can be recognized as a feature of MS. Material and Methods: Serum IL-18 concentration was evaluated in serum of 108 obese children, determined with ELISA, and referred to degree of liver steatosis in USG or total intrahepatic lipid content assessed by magnetic resonance proton spectroscopy ((1)HMRS). Results: Fatty liver was confirmed in 89 children with USG and in 72 with (1)HMRS. IL-18 concentration demonstrated significantly higher values in patients than in controls. Significant correlations between IL-18 and ALT, GGT, triglycerides, hsCRP, and the degree of liver steatosis were demonstrated. NAFLD children had significantly higher level of IL-18, ALT, GGT, HOMA-IR, waist circumference, and total lipids content in (1)HMRS than other obese children. IL-18 level was also significantly higher in obese children with advanced liver steatosis. Measurement of serum IL-18 showed ability to differentiate children with fatty liver from those without

steatosis. Conclusion: Elevated serum IL-18 concentration and its correlation with hepatocyte injury, systemic inflammation, and degree of liver steatosis support role in NAFLD pathomechanism. IL-18 can be considered to play a role in predicting advanced liver steatosis and fatty liver in obese children.

[10] *Lee H, Choi JM, Cho JY et al.* **Regulation of Endogenic Metabolites by Rosuvastatin in Hyperlipidemia Patients: An Integration of Metabolomics and Lipidomics**. Chemistry and physics of lipids 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29852124
ABSTRACT
Rosuvastatin is a statin used to treat metabolic syndrome conditions, such as hyperlipidemia. It is relatively safe; however, fatal rhabdomyolysis or skeletal myopathy can sometimes occur. Therefore, to investigate the overall effects of rosuvastatin, including lipid lowering and adverse effects, metabolic profiling was performed using metabolomics and lipidomics after rosuvastatin administration. Specifically, the metabolic profiles between healthy subjects and patients with hyperlipidemia were compared and the metabolic changes related to the mechanism of the drug effect were proposed. Healthy volunteers (n=32) and hyperlipidemic patients (n=14) were orally administered rosuvastatin (20mg) once a day for 3-8 weeks, and plasma and urine were collected. Metabolomics and lipidomics were performed using UHPLC-LTQ/Orbitrap/MS/MS for non-targeted analysis and UHPLC-TQ-MS/MS for targeted analysis. Using non-targeted analysis, we successfully profiled and identified 73 and 87 metabolites in healthy subjects and hyperlipidemia subjects, respectively. Through targeted analysis, we have also quantified 188 metabolites, including amino acids, biogenic amines, glycerophospholipids, and sphingolipids. The levels of L-carnitine, diacylglycerol, and acylcarnitines significantly decreased after rosuvastatin administration regardless of the group. The overall levels of fatty acids (FA) and lysophosphatidylcholines (LysoPC) increased, while phosphatidylcholines (PC) decreased only in the patient group. beta-Oxidation decreased overall, while the production of polyunsaturated FA increased only in the hyperlipidemic patients. Using metabolic profiling, we have evaluated the alterations in the biochemical pathways, which may aid in a more detailed understanding of the effect of rosuvastatin. Patient-specific metabolomic and lipidomic profiles may serve as valuable markers for the understanding of the adverse effects associated with statin treatment.

[11] *Sarkkinen E, Lyyra M, Nieminen S et al.* **Cereal-Based Snack Bar with Added Plant Stanol Ester (Benecol(R)) Consumed between Meals Lowers Serum Total and LDL Cholesterol Effectively in Mildly to Moderately Hypercholesterolemic Subjects**. Cholesterol 2018; 2018:1463628.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29854447
ABSTRACT
The cholesterol-lowering effect of foods with added plant sterols or stanols consumed as snacks might be compromised. The purpose of this study was to confirm the cholesterol-lowering efficacy of a specially formulated cereal-based snack bar with added plant stanol ester (1.6 g plant stanols/day) when consumed between meals twice a day. In a double-blind, placebo-controlled, 4-week parallel-design study, 71 mildly to moderately hypercholesterolemic

subjects were randomized into one of two groups, stanol or placebo group. Subjects were advised to replace their ordinary snacks with test products in an isocaloric manner and otherwise keep their habitual diet unchanged. The study showed that a snack bar product with added plant stanol ester lowered LDL and non-HDL cholesterol by 8.6% and 9.2% (mean%-change), respectively, as compared to the placebo product. The change in LDL cholesterol was statistically significantly different (P = 0.001) between the groups while the change in HDL cholesterol or triglycerides did not differ between the groups. In conclusion, the cereal-based snack bar with added plant stanol ester ingested without a meal reduced LDL cholesterol significantly without affecting HDL cholesterol or triglyceride concentrations in mildly hypercholesterolemic men and women. The study is registered as NCT03284918.

[12] *Esmaeilbeigi F, Pope JE*. **Appropriate cardiovascular disease risk assessment in systemic lupus erythematosus may be lacking in rheumatology practice**. Clinical and experimental rheumatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29846162
ABSTRACT
OBJECTIVES: To determine practices regarding cardiovascular (CV) risk assessment in systemic lupus erythematosus (SLE) amongst rheumatologists. METHODS: A questionnaire assessing preventative strategies, risk assessment, and beliefs regarding SLE and CV disease was sent electronically to 425 members of the Canadian Rheumatology Association. Questions were based on published recommendations for CV risk management. Responses were stratified based practitioner's characteristics. RESULTS: Ninety-nine rheumatologists and trainees responded (22% response rate). Nearly all (91%) believed that SLE is a major CV risk factor, and 68% felt rheumatologists should assess CV risk; whereas 42% were not comfortable with guidelines, 97% felt that family physicians are not aware of the CV risk in SLE but 64% did not routinely inform them in their correspondence. For SLE patients followed: 15% did not check blood pressure at every visit, 32% did not order cholesterol and 34% did not screen for diabetes irrespective of the presence of additional risk factors. Half (54%) would stratify SLE patients as intermediate or high risk when deciding on lipid lowering treatment. For SLE, 45% recommended a target blood pressure of 140/90 and 55% recommended 130/80 as the target. CONCLUSIONS: CV risk assessment and preventative measures were inconsistent when rheumatologists monitored SLE patients, indicating a care gap. Improved communication between rheumatologists and family physicians with respect to elevated CVD risk in SLE is needed.

[13] *Kim W, Yoon YE, Shin SH et al.* **Efficacy and Safety of Ezetimibe and Rosuvastatin Combination Therapy Versus Those of Rosuvastatin Monotherapy in Patients With Primary Hypercholesterolemia**. Clinical therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29857919
ABSTRACT
PURPOSE: The aim of this study was to evaluate the safety and efficacy of combination treatment of rosuvastatin with ezetimibe in patients with primary hypercholesterolemia. METHODS: This multicenter, randomized, double-blind study comprised a main study and an extension study. In the main study, the efficacy and safety of a combination of rosuvastatin (5,

10, and 20 mg) with ezetimibe (10 mg) were compared with those of rosuvastatin (5, 10, and 20 mg) alone. The subjects who achieved the National Cholesterol Education Program Adult Treatment Panel III LDL-C goal in the main study and agreed to a further study were enrolled for the extension study. In the extension study, ezetimibe 10 mg was also administered to subjects who had received rosuvastatin (5, 10, and 20 mg) alone in the main study, and the same treatment was continued for subjects who had received a combination of rosuvastatin with ezetimibe in the main study. FINDINGS: At the end of the main study (week 8), LDL-C levels were significantly lower in subjects receiving combination therapy than in those receiving rosuvastatin monotherapy. Other lipid profiles also significantly improved in the combination therapy group. These improvements continued in the extension study. The combination therapy of rosuvastatin and ezetimibe was generally well tolerated. At the end of the main study, more subjects achieved the National Cholesterol Education Program Adult Treatment Panel III LDL-C goal in the combination therapy group than in the monotherapy group. The increased dosage of rosuvastatin was also well tolerated in the combination treatment. IMPLICATIONS: Combination therapy of ezetimibe 10 mg with varying doses of rosuvastatin that are commonly used in the clinical field improved the lipid profile and allowed more subjects to reach the LDL-C goal in primary hypercholesterolemia compared with rosuvastatin monotherapy. In addition, the efficacy of the combination therapy was maintained for the extended period. Additional beneficial changes were also achieved with combination therapy even in patients who responded well to rosuvastatin monotherapy. ClinicalTrials.gov identifier: NCT03288038.

[14] *Mosepele M, Molefe-Baikai OJ, Grinspoon SK, Triant VA*. **Benefits and Risks of Statin Therapy in the HIV-Infected Population**. Current infectious disease reports 2018; 20:20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29804227

ABSTRACT

PURPOSE OF REVIEW: HIV-infected patients face an increased risk for cardiovascular disease (CVD), estimated at 1.5- to 2-fold as compared to HIV-uninfected persons. This review provides a recent (within preceding 5 years) summary of the role of statin therapy and associated role in CVD risk reduction among HIV-infected patients on anti-retroviral therapy. RECENT FINDINGS: Statins remain the preferred agents for reducing risk for CVD among HIV-infected populations based on guidance extrapolated from general population (HIV-uninfected) cholesterol treatment guidelines across different settings globally. However, HIV-infected patients are consistently under prescribed statin therapy when compared to their HIV-uninfected counterparts. The most commonly studied statins in clinical care and small randomized and cohort studies have been rosuvastatin and atorvastatin. Both agents are preferred for their potent lipid-lowering effects and their favorable or neutral pleotropic effects on chronic inflammation, renal function, and hepatic steatosis among others. However, growing experience with the newer glucuronidated pitavastatin suggests that this agent has virtually no adverse drug interactions with ART or effects on glucose metabolism-all marked additional benefits when compared with rosuvastatin and atorvastatin while maintaining comparable anti-lipid effects. Pitavastatin is therefore the statin of choice for the ongoing largest trial (6500 participants) to test the benefits of statin therapy among HIV-infected adults. Statins are underutilized in the prevention of CVD in HIV-infected populations based on criteria in

established cholesterol guidelines. There is a potential role for statin therapy for HIV-infected patients who do not meet guideline criteria which will be further delineated through ongoing clinical trials.

[15] *Oorni K, Lehti S, Sjovall P, Kovanen PT*. **Triglyceride-rich lipoproteins as a source of proinflammatory lipids in the arterial wall**. Curr Med Chem 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29848270
ABSTRACT
Apolipoprotein B -containing lipoproteins include triglyceride-rich lipoproteins (chylomicrons and their remnants, and very low density lipoproteins and their remnants) and cholesterol-rich low-density lipoprotein particles. Of these, lipoproteins having sizes below 70-80 nm may enter the arterial wall, where they accumulate and induce the formation of atherosclerotic lesions. The processes that lead to accumulation of lipoprotein-derived lipids in the arterial wall have been largely studied with focus on the low-density lipoprotein particles. However, recent observational and genetic studies have discovered that the triglyceride-rich lipoproteins and their remnants are linked with cardiovascular disease risk. In this review, we describe the potential mechanisms by which the triglyceride-rich remnant lipoproteins can contribute to the development of atherosclerotic lesions, and highlight the differences in the atherogenicity between low-density lipoproteins and the remnant lipoproteins.

[16] *Kidawa M, Gluba-Brzozka A, Zielinska M et al.* **Cholesterol subfraction analysis in patients with acute coronary syndrome**. Current vascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29852873
ABSTRACT
BACKGROUND: There is a close relationship between lipid metabolism disorders and atherosclerosis. Guidelines focus on lowering low density lipoprotein cholesterol (LDL-C) levels. However, it should be kept in mind that LDL and high density lipoprotein (HDL) consist of subfractions which can affect the progression of atherosclerosis. OBJECTIVE: We assessed the concentration of LDL and HDL subfractions in patients with acute coronary syndromes (ACS). The influence of the presence of type 2 diabetes mellitus on LDL and HDL subfractions was also analysed. METHODS: The study group consisted of 127 patients (62 men, 65 women) with ACS. All patients had coronary angiography and coronary angioplasty and stenting when necessary. Medical history was collected during 12 months of follow-up. HDL and LDL subfraction distribution was measured using Lipoprint (Quantimetrix). RESULTS: No differences in LDL nor HDL subfractions were observed between ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) patients. However, those with restenosis and the necessity of repeated revascularization had higher levels of intermediate-density lipoprotein C (IDL-C) ($p=0.055$) and LDL3 ($p=0.048$) compared with patients without, while level of IDL A (IDLA) was lower than in the latter group ($p=0.036$). In diabetic patients, the percentage share of HDL10 and small-dense HDL was significantly higher while the share of HDL1 (small-dense) ($p=0.028$), HDL4 (intermediate density) ($p=0.052$) and HDL5 (intermediate density) ($p=0.060$) was lower than in patients without DM. CONCLUSIONS: Patients with multi-vessel CAD disease had higher levels of LDL3 subfraction and IDL-C and lower proportion of IDLA.

[17] *Martinez-Lopez S, Sarria B, Mateos R, Bravo-Clemente L*. **Moderate consumption of a soluble green/roasted coffee rich in caffeoylquinic acids reduces cardiovascular risk markers: results from a randomized, cross-over, controlled trial in healthy and hypercholesterolemic subjects**. European journal of nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29858625
ABSTRACT
PURPOSE: Coffee is rich in bioactive compounds with health beneficial properties, with green coffee presenting higher phenol content than roasted. We evaluated the effects of regularly consuming realistic amounts of a green/roasted coffee blend on cardiovascular health-related biomarkers. METHODS: A randomized, cross-over, controlled study was carried out in 25 normocholesterolemic [total cholesterol (TC) < 200 mg/dL] and 27 hypercholesterolemic (TC 200-240 mg/dL) subjects. During 8 weeks, volunteers consumed 6 g/day of soluble green/roasted (35:65) coffee or a control beverage (water or an isotonic drink). Blood pressure, heart rate and body weight were monitored at the end of each intervention, and serum lipids [TC, HDL-C, LDL-C, VLDL-C, triglycerides and phospholipids], cytokines and chemokines (IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, MCP-1, MIP-1beta, TNF-alpha, INF-gamma), adhesion molecules (ICAM-1, VCAM-1), and C-reactive protein were measured. Plasma antioxidant capacity (FRAP, ORAC and ABTS methods), and lipid (malondialdehyde, MDA) and protein (carbonyl groups, CG) oxidation were also determined. RESULTS: Attending to the general lineal model of variance for repeated measures, after the green/roasted coffee intervention significant reductions in TC, LDL-C, VLDL-C and triglycerides levels ($p = 0.006$, 0.001, 0.003 and 0.017, respectively), and a significant group effect were observed (0.001, < 0.001, 0.019 and 0.027, respectively). Only within the hypercholesterolemic group, attending to the Bonferroni test, the aforementioned lipid parameters were significantly lower after regular green/roasted coffee intake compared to baseline values. Moreover, after the coffee stage, plasma antioxidant capacity improved, according to the increase in ORAC and FRAP values ($p < 0.001$ and $p < 0.001$, respectively) and decrease of MDA ($p = 0.015$) and CG ($p < 0.001$) levels, without differences between groups. Systolic ($p = 0.001$) and diastolic ($p < 0.001$) blood pressure, heart rate ($p = 0.035$), and body weight ($p = 0.017$) were reduced in both normo- and hypercholesterolemic groups. CONCLUSION: Regular consumption of moderate amounts of a soluble green/roasted (35:65) coffee blend may contribute to improve cardiovascular health in moderately hypercholesterolemic people, as reducing serum lipids, blood pressure and body weight effects, as well as increasing plasma antioxidant capacity, have been observed. Moreover, positive influences on blood pressure, body weight, and plasma antioxidant capacity were obtained in the healthy group. Therefore, incorporation of green coffee beans into the coffee brew can be recommended as part of a dietary strategy to protect from cardiovascular disease.

[18] *Yu J, Li X, Matei N et al.* **Ezetimibe, a NPC1L1 inhibitor, attenuates neuronal apoptosis through AMPK dependent autophagy activation after MCAO in rats**. Experimental neurology 2018; 307:12-23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29852178
ABSTRACT

Autophagy activation exerts neuroprotective effects in the ischemic stroke model. Ezetimibe (Eze), a Niemann-Pick disease type C1-Like 1 (NPC1L1) pharmacological inhibitor, has been reported to protect hepatocytes from apoptosis via autophagy activation. In this study, we explored whether Eze could attenuate neuronal apoptosis in the rat model of middle cerebral artery occlusion (MCAO), specifically via activation of the AMPK/ULK1/autophagy pathway. Two hundred and one male Sprague-Dawley rats were subjected to transient MCAO followed by reperfusion. Eze was administered 1h after MCAO. To elucidate the underlying molecular mechanism, Dorsomorphin, a selective AMPK inhibitor, and 3-methyladenine (3-MA), an autophagy inhibitor, were injected intracerebroventricularly before MCAO. Infarct volume, neurological score, brain cholesterol levels, immunofluorescence staining, Western blot, and Fluoro-Jade C (FJC) staining were used to evaluate the effects of Eze. The endogenous NPC1L1 expression increased and mainly expressed in neurons after MCAO. Intranasal administration of Eze reduced brain infarct volume at 24 and 72h after MCAO, with improved short and long-term neurological functions after MCAO. Eze reduced brain cholesterol levels (total cholesterol, free cholesterol and cholesteryl esters) and the number of FJC-positive neurons. The expression of phosphorylated AMPK (p-AMPK) and downstream ULK1, Beclin1, LC3BII, Bcl-2, and Bcl-xl increased, while P62 and proapoptotic Bax decreased after treatment with Eze. Pretreatment with Dorsomorphin and 3-MA reversed the beneficial effects of Eze. These findings suggest that intranasal administration of Eze plays neuroprotective role through autophagy activation after MCAO in rats. Lowered cholesterol levels and AMPK activation may act in conjunction to induce autophagy after treatment with Eze. Eze merits further investigation as a potential therapeutic agent in ischemic stroke patients.

[19] *Liu C, Liu Q, Xiao X*. **Effectiveness and safety of combinational therapy compared with intensified statin monotherapy in patients with coronary heart disease**. Experimental and therapeutic medicine 2018; 15:4683-4688.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29805487
ABSTRACT
Reducing the plasma levels of low-density lipoprotein-cholesterol (LDL-C) is critical for patients with coronary heart disease (CHD). Conventional treatment with statins alone may not achieve the goal of lowering LDL-C due to drug intolerance or resistance. The present study evaluated the effectiveness and safety of combining statin with another lipid-lowering agent in the management of dyslipidemia in CHD patients. A total of 180 patients with CHD were divided into three therapeutic groups (n=60 in each): Statin/colesevelam group (20 mg atorvastatin and 10 mg colesevelam daily), statin/ezetimibe group (20 mg atorvastatin and 10 mg ezetimibe daily) and high-intensity statin monotherapy group (30 mg atorvastatin daily). The baseline plasma lipid levels were measured. The duration of the treatment was eight weeks and the side effects were noted at one year's follow-up. After eight weeks' treatment, the mean plasma level of LDL-C was reduced by 45.2, 44.8 and 30.0% in the statin/colesevelam, statin/ezetimibe and statin monotherapy group, respectively. The reduction of LDL-C in the combinational therapy groups was greater than that in the statin monotherapy group ($P<0.05$). The proportion of patients achieving the goal of lowering LDL-C in the combinational therapy groups was higher than that in the statin monotherapy group. The effectiveness of reducing lipids was similar in the two combinational statin/colesevelam and statin/ezetimibe groups. Rates of adverse events

were not significantly different among the three groups. In conclusion, statins combined with colesevelam or ezetimibe were more effective in reducing plasma LDL-C levels than high-intensity statin monotherapy. This combinational therapeutic strategy may be an alternative for patients that are resistant or intolerant to statins.

[20] *Hedrington MS, Davis SN*. **Peroxisome proliferator-activated receptor alpha-mediated drug toxicity in the liver**. Expert opinion on drug metabolism & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29847748
ABSTRACT
INTRODUCTION: Drug-induced hepatic injury is the most common cause of acute liver failure in the United States. Included among the approximately 900 natural and synthetic substances that have shown hepatotoxicity are peroxisome proliferator-activated receptor alpha (PPARalpha)-mediated drugs. Areas covered: This review will focus on fibrates - PPARalpha agonists and their implication in causing liver injury. Expert opinion: Compelling evidence for fibrate-induced hepatotoxicity is not available. Results have been variable with several large randomized clinical trials reporting similar elevations of plasma transaminase levels in fibrate or placebo treated groups. On the other hand, one meta-analysis has reported an increased risk of hepatotoxicity when fibrates are combined with statins. Fibrate induced clinically apparent liver damage has been demonstrated in case reports. However, there are a wide spectrum of clinical phenotypic presentations of these cases (onset of injury, pattern of enzyme elevation, resolution of the symptoms), which reduces the ability to identify specific cause and effect of any putative fibrate-induced hepatotoxicity. Thus, the current recommendations for using fibrates include monitoring of aminotransferase levels especially if combined with statins and discontinuation of the treatment only if the levels persist above 3 times the upper limit of normal.

[21] *Rocha KCE, Pereira BMV, Rodrigues AC*. **An update on efflux and uptake transporters as determinants of statin response**. Expert opinion on drug metabolism & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29842801
ABSTRACT
INTRODUCTION: Statins are used in the treatment of dyslipidemia promoting primary and secondary prevention against detrimental cardiovascular events. ATP-binding cassette (ABC) and solute carrier (SLC) membrane transporters transport statins across the cell membrane. Differences in drug transporter tissue expression and activity contribute to variability in statin pharmacokinetics (PK) and response. Areas covered: The purpose of this review is to discuss factors impacting transporter expression and the effect this has on statin efficacy and safety. Previous studies have demonstrated that genetic polymorphisms, drug-drug interactions (DDI), nuclear receptors and microRNAs affect statin PK and pharmacodynamics. Expert opinion: Genetic variants of ABCG2 and SLCO1B1 transporters affect statin PK and, as a result, the intended lipid-lowering response. However, the effect size is small, limiting its applicability in clinical practice. Furthermore, genetic variants do not totally explain the observed intervariability in statin response. Thus, it is likely that transcriptional and post-transcriptional regulation of drug transporters are also highly involved. Further studies are required to understand the contribution of each of these new factors in statin disposition and toxicity.

Literature update week 22 (2018)

[22] *Chaudry R, Viljoen A, Wierzbicki AS*. **Pharmacological treatment options for severe hypertriglyceridemia and familial chylomicronemia syndrome**. Expert Rev Clin Pharmacol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29842811
ABSTRACT
INTRODUCTION: A spectrum of disorders, ranging from rare severe cases of homozygous null lipoprotein lipase deficiency (LPLD) -familial chylomicronemia syndrome (FCS) to heterozygous missense LPLD or polygenic causes, result in hypertriglyceridemia and pancreatitis. The effects of mutations are exacerbated by environmental factors such as diet, pregnancy and insulin resistance. Areas covered: In this review, authors discuss chronic treatment of FCS by ultra-low fat diets allied with the use of fibrates, omega-3 fatty acids, niacin, statins and insulin-sensitising therapies depending on the extent of residual LPL activity; novel therapies in development target triglyceride-rich lipoprotein particle clearance. Previously, a gene therapy approach to LPL- alipogene tiparvovec showed that direct targeting of LPL function reduced pancreatitis events. An antisense oligonucleotide to apo-C3, volanesorsen has been shown to decrease triglycerides by 70-80% and possibly to reduce rates of pancreatitis admissions. Studies are underway to validate its long-term efficacy and safety. Other approaches investigating the role of LPL modulating proteins such as angiopoietin-like petide-3 (ANGPTL3) are under consideration. Expert Opinion: Current therapeutic options are not sufficient for management of many cases of FCS. The availability of antisense anti-apoC3 therapies and, in the future, ANGPTL3 therapies may remedy this.

[23] *Vlachopoulos C, Koutagiar I, Terentes-Printzios D et al.* **Relationship of PCSK9 levels with indices of vascular function and subclinical atherosclerosis in patients with familial dyslipidaemias**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29807195
ABSTRACT
INTRODUCTION: Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels predict cardiovascular risk. We aimed at determining the correlation of PCSK9 levels with predictors of cardiovascular risk, such as central hemodynamics and carotid intima-media thickness (cIMT) in subjects with familial dyslipidaemias. METHODS: Thirty-three asymptomatic subjects (age 45.4+/-12.3, 21 men) with either familial combined hyperlipidemia or heterozygous familial hypercholesterolemia, free of hypolipidaemic therapy, underwent evaluation of central hemodynamics (aortic augmentation index [AIx@75], augmented pressure [AP]), and cIMT. PCSK9 levels were measured by ELISA. RESULTS: In the univariate model, circulating PCSK9 levels were related to age (r=0.351, P=0.045), AP (r=0.442, P=0.011), AIx@75 (r=0.463, P=0.007), and cIMT (r=0.559, P=0.001). In multivariable analysis, significant positive associations of AP, AIx@75, and cIMT with PCSK9 levels were observed after adjusting for relevant confounders (P=0.018, P=0.002 and P=0.011, respectively). Patients with both high cIMT (>0.81mm) and high AIx@75 (>20%) had significantly increased PCSK9 levels compared with subjects with both low cIMT and low AIx@75 (316 ng/ml vs 155 ng/ml, p=0.037). CONCLUSIONS: In familial dyslipidemias, PCSK9 levels are positively associated with predictors of cardiovascular risk, such as central haemodynamics and cIMT. These relationships may aid in stratification of cardiovascular risk by identifying of a high-risk subgroup within these entities.

[24] *Athyros VG, Doumas M, Imprialos KP et al.* **Diabetes and lipid metabolism**. Hormones (Athens, Greece) 2018; 17:61-67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29858856
ABSTRACT
The authors review the association between diabetes mellitus (DM) and aberrations of lipid metabolism related to DM, diabetic dyslipidemia (DD). DM is considered as a major health burden worldwide and one of the most important modifiable cardiovascular disease (CVD) risk factors. This applies to both the developed and the developing countries, especially the latter. While patients with type 1 DM, 10% of all DM cases, usually do not have dyslipidemia, DD is frequent among patients with type 2 DM (T2DM) (prevalence > 75%) and is mainly a mixed dyslipidemia [increase in triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), and small-dense (atherogenic), low-density lipoprotein cholesterol (LDL-C) particles]. The components of DD, which is characterized by quantitative (mentioned above), qualitative, and kinetic abnormalities all contributing to CVD risk, are mostly related to insulin resistance. Statins, ezetimibe, and PCSK9 inhibitors can be used in monotherapy or consecutively in combinations if needed. Statins compose the main drug. For the residual CVD risk after statin treatment, the use of statin-fibrate combinations is indicated only in patients with mixed dyslipidemia. In conclusion, DD is a major health problem worldwide. It is a significant CVD risk factor and should be treated according to current guidelines. The means today exist to normalize all quantitative, qualitative, and kinetic aberrations of DD, thereby reducing CVD risk.

[25] *Agar R, Markham C, Prendergast M et al.* **A snapshot of lipid levels in the Republic of Ireland in 2017**. Irish journal of medical science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29858796
ABSTRACT
BACKGROUND: Abnormalities in blood lipid levels are causally linked with cardiovascular disease and pancreatitis. Data is limited regarding lipid abnormalities in Ireland. AIMS: As part of a cholesterol awareness campaign, we performed a pilot study of current lipid levels to preliminarily assess the extent and pattern of lipid abnormalities in Ireland. METHODS: Non-fasting, full lipid profiles and glucose measurements were performed in 259 people (32 on lipid-lowering medication and 225 untreated) using a validated Cholestech LDX machine. Untreated participants included 95 men and 130 women, aged 51 +/- 16 years. RESULTS: The mean +/- SD, total, low-density lipoprotein (LDL), high-density lipoprotein cholesterol (HDL) and median(IQR) non-HDL cholesterol and triglyceride levels in untreated individuals were 5.0 +/- 1.1, 2.8 +/- 1.0, 1.5 +/- 0.5 and 3.4 (2.8-4.3), 1.6 (1.0-2.3) mmol/l respectively. Glucose was 5.3 (4.8-5.8) mmol/l. Glucose > 7.8 mmol/l occurred in 10 individuals (4%). Using defined criteria for non-fasting lipid levels, 60% of participants had some form of lipid abnormality with a frequency of 47% having a total cholesterol > 5, 35% with LDL > 3.0, 26% with HDL < 1.0/1.2, 33% with triglycerides > 2.0 and 32% with non-HDL cholesterol > 3.9 mmol/l. Three individuals had untreated LDL > 5 mmol/l (i.e. a ratio of 1:75 of those tested) and eight people had HDLc < 0.7 (1:28) and four had triglyceride above 7.3 mmol/l (1:56). CONCLUSIONS: This pilot study reveals significant lipid abnormalities which require further larger more detailed lipid studies to assess the true burden

of lipid abnormalities in Ireland. Cascade screening and genetic testing of relatives of those with severe lipid abnormalities should be considered.

[26] *Jamilian M, Samimi M, Mirhosseini N et al.* **The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome**. Journal of affective disorders 2018; 238:32-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29859385
ABSTRACT
OBJECTIVE: The aim of this study was to evaluate the effect of the co-administration of vitamin D and omega-3 fatty acid on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome (PCOS). METHODS: This randomized, double-blinded, placebo-controlled clinical trial was conducted on 60 subjects, aged 18-40 years old with PCOS. Subjects were randomly allocated to take either 50,000 IU vitamin D every 2 weeks plus 2000mg/day omega-3 fatty acid from fish oil (n=30) or placebo (n=30) for 12 weeks. Gene expression analysis of inflammatory cytokines was conducted on peripheral blood mononuclear cells (PBMCs) of PCOS women using RT-PCR method. RESULTS: Vitamin D and omega -3 fatty acid co-supplementation significantly decreased serum total testosterone levels (-0.2+/-0.5vs.+0.1+/-0.4ng/mL, P=0.02) compared with the placebo. In addition, vitamin D and omega-3 fatty acid co-supplementation resulted in a significant improvement in beck depression inventory (-1.4+/-1.6 vs. -0.5+/-0.6, P=0.01), general health questionnaire scores (-4.5+/-4.3 vs. -1.9+/-2.3, P=0.005) and depression anxiety and stress scale scores (-5.0+/-5.1 vs. -2.3+/-3.5, P=0.01) compared with the placebo. Additionally, vitamin D and omega-3 fatty acid co-administration significantly decreased serum high-sensitivity C-reactive protein (hs-CRP) (-1.2+/-1.9vs.+0.1+/-0.7mg/L, P=0.001) and malondialdehyde (MDA) levels (-0.4+/-0.4vs.+0.2+/-0.6micromol/L, P<0.001), and significantly increased plasma total antioxidant capacity (TAC) levels (+114.6+/-122.2 vs. -2.4+/-168.2mmol/L, P=0.003) compared with the placebo. Results of RT-PCR demonstrated that vitamin D and omega-3 fatty acid co-supplementation significantly downregulated gene expression of interleukin-1 (IL-1) (P=0.03), and upregulated vascular endothelial growth factor (VEGF) (P=0.004) in PBMCs of subjects with PCOS, when compared with placebo. CONCLUSIONS: Overall, the co-administration of vitamin D and omega-3 fatty acid for 12 weeks had beneficial effects on mental health parameters, serum total testosterone, hs-CRP, plasma TAC and MDA levels, and gene expression of IL-1 and VEGF among women with PCOS.

[27] *Jenkins DJA, Spence JD, Giovannucci EL et al.* **Supplemental Vitamins and Minerals for CVD Prevention and Treatment**. Journal of the American College of Cardiology 2018; 71:2570-2584.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29852980
ABSTRACT
The authors identified individual randomized controlled trials from previous meta-analyses and additional searches, and then performed meta-analyses on cardiovascular disease outcomes and all-cause mortality. The authors assessed publications from 2012, both before and including the U.S. Preventive Service Task Force review. Their systematic reviews and meta-analyses showed generally moderate- or low-quality evidence for preventive benefits (folic acid for total cardiovascular disease, folic acid and B-vitamins for stroke), no effect (multivitamins,

vitamins C, D, beta-carotene, calcium, and selenium), or increased risk (antioxidant mixtures and niacin [with a statin] for all-cause mortality). Conclusive evidence for the benefit of any supplement across all dietary backgrounds (including deficiency and sufficiency) was not demonstrated; therefore, any benefits seen must be balanced against possible risks.

[28] *Lamprecht DG, Jr., Shaw PB, King JB et al.* **Trends in high-intensity statin use and low-density lipoprotein cholesterol control among patients enrolled in a clinical pharmacy cardiac risk service**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29803357
ABSTRACT
BACKGROUND: Although high-intensity statin therapy (HIST) is recommended for most patients between 21 and 75 years of age with atherosclerotic cardiovascular disease (ASCVD), several recent analyses examining contemporary statin use trends have identified a clinical care gap in the utilization of HIST. OBJECTIVE: The objective of this study was to assess secular trends in lipid management for patients with ASCVD enrolled in a clinical pharmacy program within an integrated health care delivery system. METHODS: We performed serial cross-sectional studies over time, comprising 18,006 adults with both acute and chronic ASCVD, to assess trends in statin use and low-density lipoprotein cholesterol (LDL-C) levels from 2007 to 2016. RESULTS: Although the use of statin therapy (any intensity) remained relatively consistent throughout the 10-year study period (89% in 2007, 87% in 2016), the proportion of patients receiving HIST increased over time (44% in 2007, 67% in 2016; P < .001 for trend). Population mean LDL-C levels ranged from 73 to 83 mg/dL with a downward trend over the 10-year study period (P < .001 for trend). By 2016, the proportion of patients attaining an LDL-C <100 mg/dL and <70 mg/dL was 85% and 54%, respectively. Nonstatin lipid-lowering therapy use decreased over the study period, which was primarily driven by decreased use of ezetimibe (24% in 2007, 2% in 2016; P < .001 for trend). CONCLUSIONS: Among adults with ASCVD enrolled in a clinical pharmacy cardiac risk reduction service, guideline-directed use of HIST significantly increased over the past 10 years and coincided with decreased population LDL-C levels.

[29] *Scorsone A, Saura G, Fleres M et al.* **Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus Also Receiving Metformin: A Real-Life Experience**. Journal of diabetes research 2018; 2018:8501418.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29854825
ABSTRACT
Introduction: This study aimed at evaluating the efficacy and safety of dapagliflozin in patients with type 2 diabetes (T2D) who also received metformin in clinical practice in Italy. Methods: This was a retrospective observational study and it included data from patients who received dapagliflozin 10 mg once daily in conjunction with metformin for 12 months (DAPA + MET). In those with inadequate glycemic control, insulin or glimepiride was added after 30 days (DAPA + MET + other glucose-lowering drugs). Efficacy assessments included glycosylated hemoglobin (HbA1c) levels at 6 and 12 months, as well as body mass index (BMI) and lipid parameters at 12 months. Safety was also assessed. Results: Data on 66 patients were included. In both groups, HbA1c was significantly reduced at 6 and 12 months compared with baseline and significant reductions in HbA1c were observed at 12 months compared with 6 months. Over the 12-month

treatment period, dapagliflozin significantly reduced BMI in both groups. No significant changes in lipid parameters were observed in either group and no detrimental effects on renal function were detected. Conclusions: Dapagliflozin is effective and safe in patients with T2D also receiving metformin. Glycemic control was already achieved with dapagliflozin + metformin, and add-on therapy was not associated with further improvements.

[30] *Bandyopadhyay D, Qureshi A, Ghosh S et al.* **Safety and Efficacy of Extremely Low LDL-Cholesterol Levels and Its Prospects in Hyperlipidemia Management**. Journal of lipids 2018; 2018:8598054.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29850255
ABSTRACT
The risk of cardiovascular disease has been reported to have a linear relationship with LDL levels. Additionally, the currently recommended LDL target goal of 70 mg/dl does not diminish the CV risk entirely leaving behind some residual risk. Previous attempts to maximally lower the LDL levels with statin monotherapy have met dejection due to the increased side effects associated with the treatment. Nevertheless, with the new advancements in clinical medicine, it has now become possible to bring down the LDL levels to as low as 15 mg/dl using PCSK9 monoclonal antibodies alone or in combination with statins. The development of inclisiran, siRNA silencer targeting PCSK9 gene, is a one step forward in these endeavors. Moreover, various studies aiming to lower the CV risk and mortality by lowering LDL levels have demonstrated encouraging results. The current challenge is to explore this arena to redefine the target LDL levels, if required, to avoid any suboptimal treatment. After thorough literature search in the PubMed, Embase, Scopus, and Google Scholar, we present this article to provide a brief overview of the safety and efficacy of lowering LDL below the current goal.

[31] *van den Bos F, Emmelot-Vonk MH, Verhaar HJ, van der Schouw YT*. **Links between Atherosclerosis and Osteoporosis in Middle Aged and Elderly Men**. The journal of nutrition, health & aging 2018; 22:639-644.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29806852
ABSTRACT
BACKGROUND: Although the incidences of osteoporosis and atherosclerosis increase with age, there is growing evidence that the coincidental occurrence of both diseases may be independent of age. In general, studies in men are scarce and results are inconsistent. OBJECTIVE: to investigate the relationship between atherosclerosis and bone mineral density, and the influence of insulin sensitivity and low grade inflammation on this relationship in 332 men without CVD. METHODS: Aortic Pulse wave velocity (PWV), augmentation index (AIX) and measurements of carotid intima media thickness (CIMT) were assessed. BMD measurements were performed with dual-X-ray absorptiometry (DEXA), subcutaneous fat by ultrasonography. Serum concentrations of lipids, hsCRP, glucose and insulin were measured. Insulin sensitivity was calculated by use of the quantitative insulin sensitivity (QUICKI). We used multivariate linear regression models to examine the association of hsCRP, insulin sensitivity, PWV, Aix, CIMT with BMD. RESULTS: A higher CIMT was significantly associated with higher BMD after multivariate adjustment (ss 99.7; p=0.02). Further adjustment for weight attenuated the estimates towards non-significant. No association was found between PWV or AIX and BMD.

Lower insulin sensitivity was associated with higher BMD (ss -645.1; p<0.01). After adjustment for weight this association was no longer significant. A similar effect was seen for the association between hsCRP and BMD. CONCLUSION: In this population of healthy, non-obese, men without a history of cardiovascular disease the positively association between cardiovascular parameters and BMD was mainly explained by weight, suggesting that in this population weight plays a protective role in the development of osteoporosis.

[32] *Degala S, Bathija NA*. **Evaluation of the Efficacy of Simvastatin in Bone Regeneration after Surgical Removal of Bilaterally Impacted Third Molars-A Split-Mouth Randomized Clinical Trial**. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29859160
ABSTRACT
PURPOSE: Simvastatin has been reported to promote osteoblastic activity, inhibit osteoclastic activity, and support osteoblast differentiation induced by bone morphogenetic protein. This split-mouth randomized clinical trial evaluated the effect of local application of simvastatin (10 mg) on bone regeneration after surgical removal of bilaterally impacted mandibular third molars. MATERIALS AND METHODS: A randomized, split-mouth, single-blinded, single-center trial was performed in 30 patients 18 to 40 years old requiring surgical extraction of bilaterally impacted mandibular third molars. These patients underwent 2 surgical sessions, with extraction of 1 third molar during each session. Each participant was randomly assigned to receive Gelfoam soaked with normal saline or with the drug simvastatin (10 mg) at the first session and were blinded to the use of drug for that particular socket. The alternate regimen was used during the second session. The study was conducted over a period of 3 months. Patients were evaluated for pain, postoperative swelling, and bone density measurement and analysis using intraoral periapical radiographs at the end of 1, 4, 8 and 12 weeks, respectively. In addition, cone-beam computed tomographic (CBCT) images were obtained for every fifth patient at the end of 12 weeks. RESULTS: Mean gray-level histographic values were significantly higher for the study sockets at the end of 1, 4, 8, and 12 weeks (P = .001) compared with the control sockets (30 sockets each). CBCT analysis further substantiated accelerated bone regeneration in the study sockets. CONCLUSION: The study was statistically and radiographically in favor of the drug, indicating that local application of simvastatin could be a cost-effective and simple way to stimulate and hasten osseous regeneration.

[33] *Volpe M*. **What is the role of PCSK9 inhibitors in treating hypercholesterolemia?** JAAPA : official journal of the American Academy of Physician Assistants 2018; 31:14-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29846311
ABSTRACT
PCSK9 inhibitors are a novel medical therapy for treating hypercholesterolemia. This article reviews the basic properties of PCSK9 inhibitors, including their mechanism of action, indications, contraindications, adverse reactions, and efficacy.

[34] *Bagdade JD, Jilma B, Hudgins LC et al.* **LpA-II:B:C:D:E: a new immunochemically-defined acute phase lipoprotein in humans**. Lipids in health and disease 2018; 17:127.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29807532

ABSTRACT

BACKGROUND: Previous studies of lipoproteins in patients with sepsis have been performed on density fractions isolated by conventional ultracentrifugation that are heterogeneous and provide no information about the cargo of apoproteins present in the immunochemically distinct subclasses that populate the density classes. Since apoproteins are now known to have important roles in host defense, we have separated these subclasses according to their apoprotein content and characterized their changes during experimental endotoxemia in human volunteers. METHODS: We have studied apoB- and apoA containing lipoprotein subclasses in twelve healthy male volunteers before and for 8 h after a single dose of endotoxin (ET; 2 mug/kg) to stimulate inflammation. RESULTS: After endotoxin, TG, TC, apoB and the apoB-containing lipoprotein cholesterol-rich subclass LpB and two of the three triglyceride-rich subclasses (TGRLP: Lp:B:C, LpB:C:E+ LpB:E) all declined. In contrast, the third TGRLP, LpA-II:B:C:D:E ("complex particle"), after reaching a nadir at 4 h rose 49% above baseline, p = .006 at 8 h and became the dominant particle in the TGRLP pool. This increment exceeds the threshold of > 25% change required for designation as an acute phase protein. Simultaneous decreases in LpA-I:A-II and LpB:C:E + LpB:E suggest that these subclasses undergo post-translational modification and contribute to the formation of new LpA-II:B:C:D:E particles. CONCLUSIONS: We have identified a new acute phase lipoprotein whose apoprotein constituents have metabolic and immunoregulatory properties applicable to host defense that make it well constituted to engage in the APR.

[35] *Jiang LY, Jiang YH, Qi YZ et al.* **Integrated analysis of long noncoding RNA and mRNA profiling ox-LDL-induced endothelial dysfunction after atorvastatin administration**. Medicine (Baltimore) 2018; 97:e10949.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29851839

ABSTRACT

BACKGROUND: Long noncoding RNAs (lncRNAs) play a key role in the development of endothelial dysfunction. However, few lncRNAs associated with endothelial dysfunction after atorvastatin administration have been reported. METHODS: In the present study, differentially expressed (DE) genes in ox-LDL versus control and ox-LDL + atorvastatin versus control were detected. Bioinformatics analysis and integrated analysis of mRNAs and lncRNAs were conducted to study the mechanisms of endothelial dysfunction after atorvastatin administration and to explore the regulation functions of lncRNAs. RESULTS: Here, 532 DE mRNAs and 532 DE lncRNAs were identified (among them, 195 mRNAs and 298 lncRNAs were upregulated, 337 mRNAs and 234 lncRNAs were downregulated) after ox-LDL treatment for 24 hours (fold change >/=2.0, P < .05). After ox-LDL treatment following atorvastatin administration, 750 DE mRNAs and 502 DE lncRNAs were identified (among them, 149 mRNAs and 218 lncRNAs were upregulated and 601 mRNAs and 284 lncRNAs were downregulated). After atorvastatin administration, 167 lncRNAs and 262 mRNAs were still DE. Q-PCR validated the results of microarrays. CONCLUSION: Chronic inflammatory response, nitric oxide biosynthetic process, microtubule cytoskeleton, cell proliferation and cell migration are regulated by lncRNAs, which also participated in the mainly molecular function and biological processes underlying endothelial dysfunction. Atorvastatin partly improved endothelial

dysfunction, but the aspects beyond recovery were mainly concentrated in cell cycle, mitosis, and metabolism. Further exploration is required to explicit the mechanism by which lncRNAs participate in endothelial dysfunction.

[36] *Wang L, Lin R, Guo L, Hong M*. **Rosuvastatin relieves myocardial ischemia/reperfusion injury by upregulating PPARgamma and UCP2**. Molecular medicine reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29845235
ABSTRACT
The present study aimed to investigate whether pretreatment with rosuvastatin (RS) can provide cardioprotection in a myocardial ischemia/reperfusion (MI/R) model. The protective effect of RS on myocardial oxygenglucose deprivation/reperfusion (OGD/R) injury was also evaluated by upregulating peroxisome proliferatoractivated receptorgamma (PPARgamma). In the present study, MI/R model was established and activities of superoxide dismutase (SOD), lactate dehydrogenase (LDH), creatine kinasemuscle/brain (CKMB), malondialdehyde (MDA), and troponin I/T were measured. The infarct size was measured using Evans blue staining and cell viability was measured by MTT assay. Reactive oxygen species (ROS) levels were assessed by flow cytometry. Caspase9, cytochrome c (cyt c), mitochondrial uncoupling protein 2 (UCP2) and PPARgamma expression levels were detected by reverse transcriptionquantitative polymerase chain reaction and western blotting. The results indicated that RS increased SOD activity, and decreased LDH, CKMB, MDA and troponin I/T activities. The effect of RS was reversed by atractyloside (ATR). RS inhibited myocardial infarct size, downregulated expression of caspase9 and cyt c and upregulated expression of UCP2 and PPARgamma by inhibiting ATR. Furthermore, the results indicated that RS promoted cardiomyocyte viability, inhibited LDH release, reduced ROS production, decreased expression of caspase9 and cyt c, and increased expression of UCP2 and PPARgamma following OGD/R damage. Therefore, the present study demonstrated that RS protects primary myocardial cells against OGD/R injury by regulating PPARgamma and UCP2. RS may be a promising therapeutic agent for treatment of MI/R injury.

[37] *Yoshida Y, Hiwasa T, Machida T et al.* **Elevation of Autoantibody in Patients with Ischemic Stroke**. Neurologia medico-chirurgica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29848906
ABSTRACT
Recent clinical research has revealed a significant correlation between atherosclerosis, one of the primary etiologies of ischemic stroke, and the immune system. Assuming that "disease-specific autoantibodies are produced in the sera of patients with ischemic stroke," we investigated multiple arteriosclerosis-related antibodies using the serological identification of antigens by recombinant cDNA expression cloning (SEREX), an established method for identifying antigenic proteins. We either screened a human aortic endothelial cell cDNA library or conducted protein array screening using the sera from patients with ischemic stroke, such as carotid artery stenosis or transient ischemic attack (TIA). Next, we measured serum antibody levels using amplified luminescent proximity homogeneous assay-linked immunosorbent assay (AlphaLISA) in patient/healthy donor (HD) cohorts and identified several antigens, the antibody levels of which were significantly higher in patients with ischemic stroke than in HDs. This review introduced the method of identifying antigens by the SEREX and protein microarray and

summarized antigenic proteins. In particular, it focused on anti-replication protein A2 antibody and anti-programmed cell death 11 antibody, which are significantly related to atherosclerotic plaque and ischemic brain tissue, respectively, and proposed the mechanism of elevated autoantibody levels against them. Furthermore, this review suggests a possibility of clinical application as an atherosclerotic disease diagnostic marker for TIA or cerebral infarction.

[38] *Uransilp N, Chaiyawatthanananthn P, Muengtaweepongsa S*. **Efficacy of High-Dose and Low-Dose Simvastatin on Vascular Oxidative Stress and Neurological Outcomes in Patient with Acute Ischemic Stroke: A Randomized, Double-Blind, Parallel, Controlled Trial**. Neurology research international 2018; 2018:7268924.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29850244
ABSTRACT
Backgrounds: Stroke is the leading cause of death and long-term disability. Oxidative stress is elevated during occurrence of acute ischemic stroke (AIS). Soluble LOX-1 (sLOX-1) and NO are used as biomarkers for vascular oxidative stress that can reflect stabilization of atherosclerotic plaque. Previous study showed that simvastatin can reduce oxidative stress and LOX-1 expression. Objectives: To evaluate neurological outcomes and serum sLOX-1 and NO levels in patients with AIS treatment with low dose 10 mg/day and high dose 40 mg/day of simvastatin. Methods: 65 patients with AIS within 24 hours after onset were randomized to treatment with simvastatin 10 mg/day or 40 mg/day for 90 days. Personal data and past history of all patients were recorded at baseline. The blood chemistries were measured by standard laboratory techniques. Serum sLOX-1 and NO levels and neurological outcomes including NIHSS, mRS, and Barthel index were tested at baseline and Day 90 after simvastatin therapy. Results: Baseline characteristics were not significantly different in both groups except history of hypertension. Serum sLOX-1 and NO levels significantly reduce in both groups (sLOX-1 = 1.19 +/- 0.47 and 0.98 +/- 0.37 ng/ml; NO = 49.28 +/- 7.21 and 46.59 +/- 9.36 mumol/l) in 10 mg/day and 40 mg/day simvastatin groups, respectively. Neurological outcomes including NIHSS, mRS, and Barthel index significantly improve in both groups. However, no difference in NO level and neurological outcomes was found at 90 days after treatment as compared between low dose 10 mg/day and high dose 40 mg/day of simvastatin. Conclusion: High-dose simvastatin might be helpful to reduce serum sLOX-1. But no difference in clinical outcomes was found between high- and low-dose simvastatin. Further more intensive clinical trial is needed to confirm the appropriate dosage of simvastatin in patients with acute ischemic stroke. This trial is registered with ClinicalTrials.gov ID: NCT03402204.

[39] *Cho KH, Kim SJ, Yadav D et al.* **Consumption of Cuban Policosanol Improves Blood Pressure and Lipid Profile via Enhancement of HDL Functionality in Healthy Women Subjects: Randomized, Double-Blinded, and Placebo-Controlled Study**. Oxidative medicine and cellular longevity 2018; 2018:4809525.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29854085
ABSTRACT
Policosanol has been reported to improve blood pressure, lipid profile, and HDL functionality via inhibition of cholesteryl ester transfer protein (CETP) both in vitro and in vivo in zebrafish and human models. However, there are limited reports and randomized, double-blinded trials

on policosanol that could advocate the blood pressure-lowering effect in prehypertensive participants. Therefore, we performed in vitro, in vivo, and ex vivo experiments to provide more substantial and concrete data on the blood pressure-lowering effect of policosanol. Consumption of policosanol for 8 weeks enhanced plasma antioxidant activity. In the policosanol group, plasma total cholesterol (TC) and triglyceride (TG) levels were reduced up to 20% and 14%, respectively, and HDL-C level was elevated up to 1.3-fold compared to that at week 0. TG/HDL-C and cholesteryl ester transfer protein (CETP) activities were reduced up to 36% and 20%, respectively. Uptake of oxidized LDL in macrophages was reduced as oxidized species levels were reduced, and HDL2-associated paraoxonase activities were enhanced by 60% compared to those at week 0. Encapsulation of policosanol into reconstituted HDL (PCO-rHDL) enhanced cholesterol efflux activity and insulin secretion capacity. In conclusion, consumption of policosanol for 8 weeks in healthy female subjects resulted in lowered blood pressure and CETP activity via elevation of HDL/apoA-I contents and enhancement of HDL functionalities, including cholesterol efflux and insulin secretion. These functional enhancements of HDL can contribute to the prevention of aging-related diseases, hypertension, and stroke.

[40] *Bartlett LE, Pratt NL, Roughead EE*. **Prior experience with cardiovascular medicines predicted longer persistence in people initiated to combinations of antihypertensive and lipid-lowering therapies: findings from two Australian cohorts**. Patient preference and adherence 2018; 12:835-843.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29805251
ABSTRACT
Purpose: Many studies of persistence involving fixed dose combinations (FDCs) of cardiovascular medicines have not adequately accounted for a user's prior experience with similar medicines. The aim of this research was to assess the effect of prior medicine experience on persistence to combination therapy. Patients and methods: Two retrospective cohort studies were conducted in the complete Pharmaceutical Benefits Scheme prescription claims dataset. Initiation and cessation rates were determined for combinations of: ezetimibe/statin; and amlodipine/statin. Initiators to combinations of these medicines between April and September 2013 were classified according to prescriptions dispensed in the prior 12 months as either: experienced to statin or calcium channel blocker (CCB); or naive to both classes of medicines. Cohorts were stratified according to formulation initiated: FDC or separate pill combinations (SPC). Cessation of therapy over 12 months was determined using Kaplan-Meier survival analysis. Risk of cessation, adjusted for differences in patient characteristics was assessed using Cox proportional hazard models. Results: There were 12,169 people who initiated combinations of ezetimibe/statin; and 26,848 initiated combinations of amlodipine/statin. A significant proportion of each cohort were naive initiators: ezetimibe/statin cohort, 1,964 (16.1%) of whom 81.9% initiated a FDC; and amlodipine/statin cohort, 5,022 (18.7%) of whom 55.4% initiated a FDC. Naive initiators had a significantly higher risk of ceasing therapy than experienced initiators regardless of formulation initiated: ezetimibe/statin cohort, naive FDC versus experienced FDC HR=3.0 (95% CI 2.8, 3.3) and naive SPC versus experienced SPC HR=4.4 (95% CI 3.8, 5.2); and amlodipine/statin cohort naive FDC versus experienced FDC HR=2.0 (95% CI 1.8, 2.2) and naive SPC versus experienced SPC HR=1.5

(95% CI 1.4, 1.6). Conclusion: Prescribers are initiating people to combinations of two cardiovascular medicines without prior experience to at least one medicine in the combination. This is associated with a higher risk of ceasing therapy than when combination therapy is initiated following experience with one component medicine. The use of FDC products does not overcome this risk.

[41] *Poli A, Barbagallo CM, Cicero A et al.* **Nutraceuticals and functional foods for the control of plasma cholesterol levels. An Intersociety position paper**. Pharmacological research : the official journal of the Italian Pharmacological Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29859248
ABSTRACT
Current evidence shows that cholesterol management either reduces the likelihood of cardiovascular disease (CVD) or slows down its progression. Hence, it is important that all health professionals make appropriate use of all the available intervention strategies to control risk factors: from dietary improvement and positive lifestyle changes to the use of functional foods, food supplements, and drugs. This review examines the effect of the most frequently occurring cholesterol-lowering substances in functional foods or in supplements across Europe, namely plant sterols and stanols, monacolin K found in red yeast rice, berberine and beta-glucans. We conclude that currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5 to 25%, either alone or in combination. Suitable candidates for these products are mainly individuals at low absolute cardiovascular risk at a young age or according to classic algorithms. Of note, despite being freely available for purchase, these products should be used following shared agreement between the caring physician and the patient ("concordance").

[42] *Bekkelund SI, Johnsen SH*. **Creatine kinase is associated with reduced inflammation in a general population: The Tromso study**. PloS one 2018; 13:e0198133.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29813131
ABSTRACT
BACKGROUND: Creatine kinase (CK) has been associated with reduced inflammation in obesity while inflammation is associated with obesity-related cardiovascular diseases. We investigated the relationship between CK and high sensitive C-reactive protein (hs-CRP) in a general population. METHODS: CK and hs-CRP were measured in the population-based Tromso study that included entire birth cohorts and random samples of citizens between 30-87 years of age. The analyses were performed sex-stratified in 5969 men and 6827 women. RESULTS: CK correlated negatively with hs-CRP in men (r = -0.08, P <0.001) and women (r = -0.06, P <0.001). In univariable regression analyses, CK associated negatively with hs-CRP in men (ss = -0.14, 95% CI -0.19 to -0.10, P <0.001) and women (ss = -0.13, 95% CI -0.18 to -0.08, P <0.001). Mean CK declined from the 2. to the 4. quartiles of hs-CRP in both genders (P <0.001 for trends). There were positive correlations between CK and body mass index (BMI) in men (r = 0.10, P <0.001) and women (r = 0.07, P <0.001). Multiple regression analyses showed a 0.13 unit decrease in hs-CRP (mg/dl) per unit CK increase in men (95% CI -0.35 to -0.20) and 0.29 mg/dl in women (95% CI -0.36 to -0.21) when adjusted for age, BMI, lipids, s-glucose, s-creatinine, transaminases and coronary heart disease. CONCLUSION: CK were inversely and independently associated

with hs-CRP in a general population. These data provide evidence that CK might have anti-inflammatory properties, but the mechanism and clinical implications are unclarified.

[43] *Winkler K, Contini C, Konig B et al.* **Treatment of very preterm preeclampsia via heparin-mediated extracorporeal LDL-precipitation (H.E.L.P.) apheresis: The Freiburg preeclampsia H.E.L.P.-Apheresis study**. Pregnancy hypertension 2018; 12:136-143.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29858106
ABSTRACT
OBJECTIVE: Soluble Fms-like tyrosine kinase-1 (sFlt-1) is thought to be causative in the pathogenesis of preeclampsia (PE) and specific removal of sFlt-1 via dextran sulfate cellulose (DSC)-apheresis was suggested as cure to allow prolongation of pregnancy in preterm PE. However, in addition a deranged lipoprotein metabolism may impact endothelial and placental function in PE. Lipoprotein-apheresis by heparin-mediated extracorporeal LDL-precipitation (H.E.L.P.) was previously applied and has been shown to alleviate symptoms in PE. This clinical trial reevaluates the clinical efficacy of H.E.L.P.-apheresis in PE considering sFlt-1. STUDY DESIGN: Open pilot study assessing the prolongation by H.E.L.P.-apheresis in 6 women (30-41years) with very preterm PE (24+4 to 27+0 gestational weeks (GW)) (NCT01967355) compared to a historic control-group matched for GW at admission (<28GW; n=6). Clinical outcome of mothers and babies, and pre- and post H.E.L.P.-apheresis levels of sFlt-1 and PlGF were monitored. MAIN OUTCOME MEASURES: In apheresis patients (2-6 treatments), average time from admission to birth was 15.0days (6.3days in controls; p=0.027). Lung maturation was induced in all treated cases, and all children were released in healthy condition. Apheresis reduced triglycerides and LDL-cholesterol by more than 40%. Although H.E.L.P.-apheresis induced a transient peak baseline levels did not change and rather stabilized sFlt-1 levels at pre-apheresis levels throughout treatments, with sFlt-1/PLGF ratio remaining unaffected. CONCLUSIONS: H.E.L.P.-apheresis proved again to be safe and prolongs pregnancies in PE. However, without changing sFlt-1 levels below baseline lowering lipids or other yet undefined factors appear to be of more relevance than reducing sFlt-1.

[44] *Chiavaroli L, Nishi SK, Khan TA et al.* **Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-Analysis of Controlled Trials**. Prog Cardiovasc Dis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29807048
ABSTRACT
BACKGROUND: The evidence for the Portfolio dietary pattern, a plant-based dietary pattern that combines recognized cholesterol-lowering foods (nuts, plant protein, viscous fibre, plant sterols), has not been summarized. OBJECTIVE: To update the European Association for the Study of Diabetes clinical practice guidelines for nutrition therapy, we conducted a systematic review and meta-analysis of controlled trials using GRADE of the effect of the Portfolio dietary pattern on the primary therapeutic lipid target for cardiovascular disease prevention, low-density lipoprotein cholesterol (LDL-C), and other established cardiometabolic risk factors. METHODS: We searched MEDLINE, EMBASE, and The Cochrane Library through April 19, 2018. We included controlled trials >/= 3-weeks assessing the effect of the Portfolio dietary pattern on cardiometabolic risk factors compared with an energy-matched control diet free of Portfolio dietary pattern components. Two independent reviewers extracted data and assessed risk of

bias. The primary outcome was LDL-C. Data were pooled using the generic inverse-variance method and expressed as mean differences (MDs) with 95% confidence intervals (CIs). Heterogeneity was assessed (Cochran Q statistic) and quantified (I(2)-statistic). GRADE assessed the certainty of the evidence. RESULTS: Eligibility criteria were met by 7 trial comparisons in 439 participants with hyperlipidemia, in which the Portfolio dietary pattern was given on a background of a National Cholesterol Education Program (NCEP) Step II diet. The combination of a portfolio dietary pattern and NCEP Step II diet significantly reduced the primary outcome LDL-C by ~17% (MD, -0.73mmol/L, [95% CI, -0.89 to -0.56 mmol/L]) as well as non-high-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, triglycerides, systolic and diastolic blood pressure, C-reactive protein, and estimated 10-year coronary heart disease (CHD) risk, compared with an NCEP Step 2 diet alone (P<0.05). There was no effect on high-density lipoprotein cholesterol or body weight. The certainty of the evidence was high for LDL-cholesterol and most lipid outcomes and moderate for all others outcomes. CONCLUSIONS: Current evidence demonstrates that the Portfolio dietary pattern leads to clinically meaningful improvements in LDL-C as well as other established cardiometabolic risk factors and estimated 10-year CHD risk.

[45] *Parsons C, Agasthi P, Mookadam F, Arsanjani R*. **Reversal of coronary atherosclerosis: Role of life style and medical management**. Trends in cardiovascular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29807666

ABSTRACT

Atherosclerotic coronary artery disease continues to be a major global health burden in developing and developed nations. Newer imaging techniques afford an accurate assessment of plaque burden and characteristics as well as the effects of treatment. Lifestyle interventions and pharmacotherapy remain the mainstay of non-interventional treatment of coronary atherosclerosis, with reversal seen in many studies. In addition, control of modifiable risk factors can be beneficial. As a better understanding of atherosclerosis pathophysiology is achieved, new therapeutic targets and combination therapies may join the armamentarium that promotes regression of atherosclerotic plaque. We present a review of the literature regarding lifestyle and medical therapies that can promote the reversal of coronary atherosclerosis.