Literature update week 30 (2019)

[1] *Fatehi Hassanabad A, McBride SA*. **Statins as Potential Therapeutics for Lung Cancer: Molecular Mechanisms and Clinical Outcomes**. American journal of clinical oncology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31335352
ABSTRACT
Lung cancer is the most common cancer worldwide. It also has the highest malignancy-associated mortality rate. Treatment options are limited by cancer and tumor heterogeneity, resistance to treatment options, and an advanced stage at time of diagnosis, all of which are common. Statins are a class of lipid-lowering medications that have been studied for their antitumor effects in various types of cancers. Multiple mechanisms have been proposed to explain their observed off-target effects. Most of these hypotheses focus largely on statin-induced upregulation of proapoptotic signaling pathways and mediators, and the downregulation of antineoplastic factors secondary to statin use. Preclinical and clinical studies support their use for conferring a mortality benefit and improving treatment effect in some chemotherapy-resistant subtypes of lung cancer. However, their exact mechanism of action, class-dependent effect, dose-dependent effect, potential use as adjuvant chemotherapeutics, and markers of statin-sensitivity in specific lung cancer subtypes remain areas of ongoing investigation. Herein, we review the latest literature pertinent to the role statins can play in the management of lung cancers.

[2] *Vahid F, Hekmatdoost A, Mirmajidi S et al.* **Association Between Index of Nutritional Quality and Nonalcoholic Fatty Liver Disease: The Role of Vitamin D and B Group**. The American journal of the medical sciences 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31326093
ABSTRACT
BACKGROUND: Numerous studies have revealed that diet has been considered as an important pathogenic factor for nonalcoholic fatty liver disease (NAFLD). The Index of Nutritional Quality (INQ) is a method of quantitative and qualitative evaluation of single foods and diets, which has special significance in recognizing clinical nutritional problems. MATERIALS AND METHODS: This study included 295 patients with NAFLD and 704 controls. The dietary intake was assessed through a valid and reliable food frequency questionnaire. INQ was calculated from the questionnaire data and was compared between the 2 groups. RESULTS: The controls had higher INQ of vitamin D, vitamin E, thiamin, riboflavin, niacin, vitamin B12; biotin, pantothenic acid, magnesium and zinc compared to the patients with NAFLD. After controlling for several covariates, positive associations were observed between NAFLD risk and INQs of riboflavin (ORriboflavin=0.49, 95% confidence interval [CI]: 0.28-0.78; ORbiotin=0.35, 95% CI: 0.18-0.76; ORpantothenic=0.28, 95% CI: 0.12-0.64; ORmagnesium=0.28, 95% CI: 0.11-0.75; ORzinc=0.15 95% CI: 0.05-0.42). CONCLUSIONS: Findings of the present study suggest that subjects who follow a more healthy and nutrient-rich diet, especially in terms of vitamins D, B1, B2, B12, B3 and zinc, are at a lower risk of NAFLD compared to those who consume unhealthy and nutrient-poor diet.

[3] *Cannon EC, Zadvorny EB, Sutton SD et al.* **Value of Pharmacy Students Performing Population Management Activity Interventions as an Advanced Pharmacy Practice Experience**. American journal of pharmaceutical education 2019; 83:6759.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31333253

ABSTRACT

Objective. To assess the value of an advanced pharmacy practice experience in which students engaged in population health management (PHM) activities for a managed care setting. Methods. Students were provided with a list of patients, trained on the requirements for each PHM activity and completed them independently. The students reviewed the electronic record for each patient on their list to identify those who were non-adherent to dual antiplatelet therapy (DAPT) within one year of coronary stent placement, non-adherent to beta blockers (BB) within six months post-acute myocardial infarction, or with renal dysfunction and requiring dose adjustment of lipid-lowering therapy. Students coded each intervention based on predefined categories such as patient education, medication discontinuation, or medication reconciliation, and then if necessary were reviewed with the pharmacy preceptor. The primary investigator determined the intervention to be either actionable or non-actionable. The primary outcome was the proportion and type of interventions made by each student. The secondary outcome was clinical pharmacist time offset. A retrospective, data-only pilot study was conducted to determine the outcomes from the program over four years. Results. Forty-six students made 3,774 interventions over the study period, 37% of which were categorized as actionable. The most common actionable interventions were providing patient education (52%), verifying prescription adherence (23%), and medication therapy adjustment (10.5%). Over the study period, an estimated 765.6 hours of clinical pharmacist time was offset, or approximately 191.4 hours per academic year. Conclusion. This study demonstrated that a population health management approach can be used successfully within an APPE. This approach can result in offset pharmacist time for precepting organizations, while offering meaningful clinical interventions for patients and learning opportunities for students.

[4] *Dodos I, Georgopoulos S, Dodos K et al.* **Correlation of glycosylated hemoglobin (HbA1c) levels with histological and ultrasound characteristics of the carotid plaque in diabetic and non-diabetic patients**. Annals of vascular surgery 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31344464

ABSTRACT

PURPOSE: The purpose of this study is to investigate the correlation of HbA1c levels with histological characters of atherosclerotic plaque that make it vulnerable, as well as ultrasound criteria that can contribute to the prognosis of carotid disease. MATERIAL AND METHODS: This is a single center prospective study. Our study population consists of 74 diabetic and non-diabetic patients with carotid atherosclerosis who underwent carotid endarterectomy in our department. Patient categorization was based on the following criteria: levels of HbA1c, gender and risk factors (smoking, hypertension), carotid stenosis rate, symptomatic or asymptomatic carotid disease, histological examination of the atherosclerotic plaque and ultrasound morphological criteria of the plaque. RESULTS: The mean age of the patients was 68.2 years (TA = 7.8), 58.1% were smokers, 71.6% had arterial hypertension, 37.8% had symptomatic carotid disease and 64.9% had atherosclerotic plaque type 6. Futhermore, 95.9% of the patients had a carotid stenosis rate greater of 70% and 4.1% had from 50% to 69%. Older patients had more frequently type 7 and 8 atherosclerotic plaque based on AHA scoring system compared to younger patients (p = 0.041). The relative likelihood of atherosclerotic plaque type 7 and 8 was

1.12 times higher in older patients (OR = 1.12, p = 0.029). Patients with higher levels of glycosylated hemoglobin were more likely to have type 6 atherosclerotic plaque than those with atherosclerotic lesions type 7 and 8 (p <0.001). Specifically, increasing the level of HbA1c by 1mg/dl increases the likelihood of the presence of vulnerable plaque by 2.55%. Moreover, the relative likelihood of a Type 6 atherosclerotic plaque was 10.4 times higher in the older patients (OR = 10.4, p <0.001). CONCLUSION: This study demonstrates that levels of HbA1c and advanced age are two factors that may be correlated with the presence of vulnerable carotid plaques in diabetic population. Moreover, HbA1c is an independent factor that could possibly be used as a prognostic marker for carotid artery disease. Though, further studies are needed to explore this association in order to elucidate the precise role of HbA1c.

[5] *Kattoor AJ, Goel A, Mehta JL*. **LOX-1: Regulation, Signaling and Its Role in Atherosclerosis**. Antioxidants (Basel, Switzerland) 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31336709
ABSTRACT
Atherosclerosis has long been known to be a chronic inflammatory disease. In addition, there is intense oxidative stress in atherosclerosis resulting from an imbalance between the excess reactive oxygen species (ROS) generation and inadequate anti-oxidant defense forces. The excess of the oxidative forces results in the conversion of low-density lipoproteins (LDL) to oxidized LDL (ox-LDL), which is highly atherogenic. The sub-endothelial deposition of ox-LDL, formation of foamy macrophages, vascular smooth muscle cell (VSMC) proliferation and migration, and deposition of collagen are central pathophysiologic steps in the formation of atherosclerotic plaque. Ox-LDL exerts its action through several different scavenger receptors, the most important of which is LOX-1 in atherogenesis. LOX-1 is a transmembrane glycoprotein that binds to and internalizes ox-LDL. This interaction results in variable downstream effects based on the cell type. In endothelial cells, there is an increased expression of cellular adhesion molecules, resulting in the increased attachment and migration of inflammatory cells to intima, followed by their differentiation into macrophages. There is also a worsening endothelial dysfunction due to the increased production of vasoconstrictors, increased ROS, and depletion of endothelial nitric oxide (NO). In the macrophages and VSMCs, ox-LDL causes further upregulation of the LOX-1 gene, modulation of calpains, macrophage migration, VSMC proliferation and foam cell formation. Soluble LOX-1 (sLOX-1), a fragment of the main LOX-1 molecule, is being investigated as a diagnostic marker because it has been shown to be present in increased quantities in patients with hypertension, diabetes, metabolic syndrome and coronary artery disease. LOX-1 gene deletion in mice and anti-LOX-1 therapy has been shown to decrease inflammation, oxidative stress and atherosclerosis. LOX-1 deletion also results in damage from ischemia, making LOX-1 a promising target of therapy for atherosclerosis and related disorders. In this article we focus on the different mechanisms for regulation, signaling and the various effects of LOX-1 in contributing to atherosclerosis.

[6] *Kronenberg F*. **Therapeutic lowering of lipoprotein(a): How much is enough?** Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31327477
ABSTRACT

[7] *Vallejo-Vaz AJ, Ray KK, Ginsberg HN et al.* **Associations between lower levels of low-density lipoprotein cholesterol and cardiovascular events in very high-risk patients: Pooled analysis of nine ODYSSEY trials of alirocumab versus control**. Atherosclerosis 2019; 288:85-93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31349086

ABSTRACT

BACKGROUND AND AIMS: Guidelines recommend high-intensity statins for patients with atherosclerotic cardiovascular disease (ASCVD). Subgroups with comorbidities that increase cardiovascular risk, such as diabetes mellitus (DM), chronic kidney disease (CKD) or polyvascular disease (PoVD), may derive greater absolute benefit from addition of non-statin therapies. We assessed the relationship between lower low-density lipoprotein cholesterol (LDL-C) and major adverse cardiovascular events (MACE) risk reduction during alirocumab phase III ODYSSEY trials among these subgroups. METHODS: Patient data were pooled from nine trials comparing alirocumab with control (placebo/ezetimibe), predominantly on background maximally tolerated statin. Patients with baseline ASCVD were stratified into subgroups with DM, CKD or PoVD, or without comorbidities, and between-group relative and absolute benefits were compared. RESULTS: Among 3505 patients with ASCVD, 1573 had no comorbidities, 981 had DM, 660 had CKD and 943 had PoVD, with overlap between comorbidities; mean baseline LDL-C levels were 119 (ASCVD overall), 123, 117, 114 and 113mg/dL, respectively. Overall, each 39mg/dL lower on-study LDL-C was associated with a 25% lower MACE risk, hazard ratio 0.75 (95% confidence interval, 0.62-0.90, p=0.0023), with a similar lower risk observed in each very high-risk subgroup (DM, CKD or PoVD; 30-35%) but not in the subgroup without these comorbidities (9%). Absolute benefits were greater for very high-risk subgroups; lowering LDL-C from 120 to 40mg/dL would result in 2.76-4.35 fewer MACE/100 patient-years versus 0.3 for no comorbidities. CONCLUSIONS: Among patients with ASCVD and mean baseline LDL-C >100mg/dL, patients with DM, CKD or PoVD appeared to derive greater absolute cardiovascular benefits from further LDL-C reduction than those without.

[8] *S CT, Meor Anuar Shuhaili MFR, Chew BH et al.* **A Pilot Study on the Association between SLCO1B1 RS4363657 Polymorphism and Muscle Adverse Events in Adults with Newly Diagnosed Dyslipidaemia who were prescribed a Statin: The Malaysian Primary Health Care Cohort**. Biomarkers 2019:1-20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31342800

ABSTRACT

Introduction: Statin, the first-line treatment for dyslipidaemia, may have suboptimal adherence due to its associated muscle adverse events. This data however, remains limited. Aim: To determine the association of serum creatine kinase(CK) and SLCO1B1 rs4363657 polymorphism with statin-associated muscle adverse events(SAMAE) among dyslipidaemia participants. Methods: This was a prospective cohort study at government health clinics involving newly diagnosed adults with dyslipidaemia. SAMAE were recorded based on the patient's complaint after a month on statin. CK was taken at baseline and follow-up. Genetic profiling was performed for SLCO1B1 rs4363657 polymorphism. Results: Among 118 participants, majority were Malay(72%) males(61%) with a mean age of 49 +/- 12.2 years old and prescribed lovastatin(61.9). There was a significant association between statin types(lovastatin and

simvastatin) and SAMAE(p = 0.0327); no significant association noted between CK and SAMAE(p = 0.5637). The SLCO1B1 rs4363657 polymorphism was significantly associated SAMAE(p < 0.0001). Conclusions: In this first pilot study of a multiethnic Malaysian population, the incidence of SAMAE was 18.6%. SAMAE were significantly higher in subjects on lovastatin compared to simvastatin. SLCO1B1 rs4363657 polymorphism was a significant risk factor for SAMAE.

[9] *Glicksberg BS, Amadori L, Akers NK et al.* **Integrative analysis of loss-of-function variants in clinical and genomic data reveals novel genes associated with cardiovascular traits**. BMC medical genomics 2019; 12:108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31345219
ABSTRACT
BACKGROUND: Genetic loss-of-function variants (LoFs) associated with disease traits are increasingly recognized as critical evidence for the selection of therapeutic targets. We integrated the analysis of genetic and clinical data from 10,511 individuals in the Mount Sinai BioMe Biobank to identify genes with loss-of-function variants (LoFs) significantly associated with cardiovascular disease (CVD) traits, and used RNA-sequence data of seven metabolic and vascular tissues isolated from 600 CVD patients in the Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task (STARNET) study for validation. We also carried out in vitro functional studies of several candidate genes, and in vivo studies of one gene. RESULTS: We identified LoFs in 433 genes significantly associated with at least one of 10 major CVD traits. Next, we used RNA-sequence data from the STARNET study to validate 115 of the 433 LoF harboring-genes in that their expression levels were concordantly associated with corresponding CVD traits. Together with the documented hepatic lipid-lowering gene, APOC3, the expression levels of six additional liver LoF-genes were positively associated with levels of plasma lipids in STARNET. Candidate LoF-genes were subjected to gene silencing in HepG2 cells with marked overall effects on cellular LDLR, levels of triglycerides and on secreted APOB100 and PCSK9. In addition, we identified novel LoFs in DGAT2 associated with lower plasma cholesterol and glucose levels in BioMe that were also confirmed in STARNET, and showed a selective DGAT2-inhibitor in C57BL/6 mice not only significantly lowered fasting glucose levels but also affected body weight. CONCLUSION: In sum, by integrating genetic and electronic medical record data, and leveraging one of the world's largest human RNA-sequence datasets (STARNET), we identified known and novel CVD-trait related genes that may serve as targets for CVD therapeutics and as such merit further investigation.

[10] *Bonaventura A, Grossi F, Carbone F et al.* **Serum PCSK9 levels at the second nivolumab cycle predict overall survival in elderly patients with NSCLC: a pilot study**. Cancer immunology, immunotherapy : CII 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31327024
ABSTRACT
Monoclonal antibodies targeting PD-1 are used for treating NSCLC. To date, proprotein convertase subtilisin/kexin type 9 (PCSK9) has been poorly investigated in the oncologic field. Here, we aimed at evaluating whether serum PCSK9 might represent a predictive factor for OS in older patients with advanced NSCLC under nivolumab treatment. Among 78 patients with

advanced, pre-treated NSCLC previously enrolled in a prospective study at Ospedale Policlinico San Martino in Genoa (Italy), 44 patients have been included in this sub-analysis due to the availability of serum samples for the measurement of PCSK9. Before each nivolumab administration, clinical information and blood samples were collected. Median age was 71, with a prevalence of the male sex. The most represented histological type of lung cancer was adenocarcinoma. The majority of patients were former smokers (72.1%). Median PCSK9 levels were 123.59 (86.32-169.89) ng/mL and 117.17 (80.46-147.79) ng/mL at cycle 1 and 2, respectively. Based on a receiver operating characteristic curve analysis, a PCSK9 value at cycle 2 of 95 ng/mL was found as the best cutoff point for OS. Kaplan-Meier analysis demonstrated that patients below the PCSK9 cutoff (< 95 ng/mL) experienced a better OS, as confirmed by Cox proportional hazard regression analysis. In this pilot study, circulating levels of PCSK9 < 95 ng/mL at the time of the second cycle of nivolumab treatment could independently predict a better OS in elderly patients with advanced, pre-treated NSCLC. However, further studies are warranted to validate these preliminary results.

[11] *Fung BM, Heinze ER, Wong AL*. **Statin-Associated Necrotizing Autoimmune Myositis Complicated by an Uncommon Adverse Effect to Treatment**. Case reports in medicine 2019; 2019:4601304.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31341481
ABSTRACT
Statin-associated necrotizing autoimmune myositis (NAM) is an autoimmune condition characterized by severe acute-onset proximal muscle weakness, a very high creatinine kinase (CK) level, and prominent myofiber necrosis and minimal lymphocytic infiltration on muscle biopsy. Unlike self-limited statin myopathy, this condition usually requires aggressive immunomodulation therapy to assist recovery and prevent future disability. In this case report, we present a patient who developed progressive muscle weakness after taking atorvastatin for one year. At initial presentation, her CK level was 28,000 U/L. She was diagnosed with statin-associated NAM and started on high-dose intravenous solumedrol, mycophenolate, and intravenous immunoglobulin (IVIG) therapy. However, she subsequently developed acute bilateral vision loss and right side hemineglect; she was diagnosed with posterior reversible encephalopathy syndrome (PRES), thought to be a possible delayed adverse reaction to IVIG. IVIG was discontinued, and the patient was treated with supportive therapy. At six-month follow-up, she had significant improvement in muscle strength and vision.

[12] *Qian L, Zhu K, Lin Y et al.* **Insulin Secretion Impairment Induced by Rosuvastatin partly though Autophagy in INS-1E Cells**. Cell Biol Int 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31342626
ABSTRACT
Statins are used extensively for the clinical treatment of cardiovascular diseases. Recent studies suggest that statins increase the risk of new-onset diabetes mellitus (NODM). However, the mechanisms of statin-induced NODM remain unclear. The present study investigated the effects of autophagy on insulin secretion impairment induced by rosuvastatin in INS-1E cells. INS-1E cells were cultured and treated with rosuvastatin at different concentrations (0.2-20 muM) for 24 h. Insulin secretion in INS-1E cells was detected by ELISA, and the co-localization of

microtubule-associated protein light chain 3 (LC3) and lysosome-associated membrane protein 2 (LAMP-2) was observed by immunofluorescence staining. Western blotting was used to assess the conversion of LC3 and p62. The results showed that the insulin secretion and cell viability decreased induced by rosuvastatin treatment for 24 h occurred in a dose-dependent manner in INS-1E cells. Rosuvastatin significantly inhibited the expression of LC3-II but increased the protein expression of p62. Simultaneously, rosuvastatin diminished the co-localization of LC3-II and Lamp2 fluorescence signals. These results suggested that rosuvastatin inhibited autophagy in INS-1E cells. Rapamycin, an autophagy agonist, reversed the insulin secretion and cell viability suppression induced by rosuvastatin in INS-1E cells. Rosuvastatin also decreased the phosphorylation of mammalian target of rapamycin (mTOR). The results indicated that rosuvastatin impairs insulin secretion in INS-1E cells, which may be partly due to the inhibition of autophagy via a mTOR-dependent pathway.

[13] *Myers KD, Farboodi N, Mwamburi M et al.* **Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes**. Circulation. Cardiovascular quality and outcomes 2019; 12:e005404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331194

ABSTRACT

BACKGROUND: Atherosclerotic cardiovascular disease remains a major cause of death and disability, especially for high-risk familial hypercholesterolemia individuals. PCSK9i (proprotein convertase subtilisin kexin type 9 inhibitors) reduce low-density lipoprotein cholesterol levels and cardiovascular event rates. However, PCSK9i prescriptions are rejected at high rates by payers, and use is often delayed or eventually abandoned as a treatment option. We tested the hypothesis that acute coronary syndromes, coronary interventions, stroke, and cardiac arrest are more prevalent in patients with rejected or abandoned PCSK9i prescriptions than for those with paid PCSK9i prescriptions. METHODS AND RESULTS: We identified 139 036 individuals aged >/=18 years who met the following 3 criteria: prescribed PCSK9i between August 2015 and December 2017, had claims history, and had an established date of exposure for paid, rejected, or abandoned status. To compare the effects of rejected versus paid and abandoned versus paid status, propensity score matching was performed to minimize confounding because of baseline differences in patient groups. Cox regression analyses and incidence density rates for cardiovascular events were estimated on the propensity score-matched cohorts. Patients who received 168 or more days of paid PCSK9i medication within a 12-month period were defined as paid. The hazard ratios for composite cardiovascular events outcome in propensity score-matched analyses were 1.10 (95% CI, 1.01-1.19; P=0.02) for rejected versus paid and 1.12 (95% CI, 1.01-1.24; P=0.03) for abandoned versus paid. In a stricter analysis where paid patients were defined by receiving 338 or more days of therapy within 12-months, hazard ratio was 1.16 (95% CI, 1.02-1.30; P=0.04) for rejected versus paid and 1.21 (95% CI, 1.04-1.38; P=0.03) for the abandoned versus paid status. Higher PCSK9i rejection rates were observed with women, racial minorities, and lower-income groups. CONCLUSIONS: Individuals in the rejected and abandoned cohorts had significantly increased risk of cardiovascular events compared with those in the paid cohort. Rejection, abandonment, and disparities related to PCSK9i prescriptions are related to higher cardiovascular outcome rates.

[14] *Nasir K, Angraal S, Virani SS*. **PCSK9 Inhibitors Prior Authorization**. Circulation. Cardiovascular quality and outcomes 2019; 12:e005910.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331186
ABSTRACT

[15] *Tada H, Okada H, Nomura A et al.* **Rare and Deleterious Mutations in ABCG5/ABCG8 Genes Contribute to Mimicking and Worsening of Familial Hypercholesterolemia Phenotype**. Circulation journal : official journal of the Japanese Circulation Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31327807
ABSTRACT
BACKGROUND: A substantial proportion of patients clinically diagnosed as having familial hypercholesterolemia (FH) do not manifest causative mutation(s) in the FH genes such asLDLR,APOB, andPCSK9. We aimed to evaluate the effect of rare and deleterious mutation(s) inABCG5/ABCG8on hyper-low-density lipoprotein (LDL) cholesterolemia in individuals who meet the clinical criteria for FH.Methods and Results:We compared the LDL cholesterol (LDL-C) values among 487 subjects with FH; the subjects were grouped according to the presence of mutation(s) in FH andABCG5/ABCG8genes. We identified 276 individuals with a deleterious mutation in 1 FH gene (57%, monogenic FH), but found no causative mutations in 156 individuals (32%, mutation-negative). A total of 37 individuals had deleterious mutations inABCG5orABCG8, but not in FH genes (8%,ABCG5/ABCG8mutation carriers). Among these, 3 individuals had sitosterolemia (0.6%) with double mutations. We also identified 18 individuals with deleterious mutations in an FH gene andABCG5orABCG8(4%,ABCG5/ABCG8-oligogenic FH). Subjects without mutations had significantly higher polygenic scores than those in any other groups. LDL-C levels in oligogenic FH subjects were significantly higher than in the monogenic FH subjects. Moreover, sitosterol/lathosterol levels were significantly affected by those mutations. CONCLUSIONS: The results suggested that rare and deleterious mutations inABCG5/ABCG8contribute substantially to mimicking and exacerbation of the FH phenotype.

[16] *Hopewell JC, Ibrahim M, Hill M et al.* **Impact of ADCY9 Genotype on Response to Anacetrapib**. Circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331193
ABSTRACT
BACKGROUND: Exploratory analyses of previous randomized trials generated a hypothesis that the clinical response to CETP inhibitor therapy differs by ADCY9 genotype, prompting the ongoing dal-GenE trial in individuals with a particular genetic profile. The randomized placebo-controlled REVEAL trial demonstrated the clinical efficacy of the CETP inhibitor anacetrapib among patients with pre-existing atherosclerotic vascular disease. In the present study, we have examined the impact of ADCY9 genotype on response to anacetrapib within the REVEAL trial. METHODS: Individuals with stable atherosclerotic vascular disease, who were treated with intensive atorvastatin therapy, received either anacetrapib 100 mg daily or matching placebo. Cox proportional hazards models, adjusted for the first 5 principal components of ancestry, were used to estimate the effects of allocation to anacetrapib on major vascular events (a composite of coronary death, myocardial infarction, coronary revascularization or presumed

ischaemic stroke) and the interaction with ADCY9 rs1967309 genotype. RESULTS: Among 19,210 genotyped individuals of European ancestry, 2,504 (13.0%) had a first major vascular event during 4 years median follow-up: 1,216 (12.6%) among anacetrapib-allocated participants and 1,288 (13.4%) among placebo-allocated participants. Proportional reductions in the risk of major vascular events with anacetrapib did not differ significantly by ADCY9 genotype: HR = 0.92 (95% CI, 0.81-1.05) for GG; HR = 0.94 (95% CI, 0.84-1.06) for AG; and HR = 0.93 (95% CI, 0.76-1.13) for AA genotype carriers respectively; genotypic p for interaction = 0.96. Furthermore, there were no associations between ADCY9 genotype and the proportional reductions in the separate components of major vascular events, or meaningful differences in lipid response to anacetrapib. CONCLUSIONS: The REVEAL trial is the single largest study to date evaluating the ADCY9 pharmacogenetic interaction. It provides no support for the hypothesis that ADCY9 genotype is materially relevant to the clinical effects of the CETP inhibitor anacetrapib. The ongoing dal-GenE study will provide direct evidence as to whether there is any specific pharmacogenetic interaction with dalcetrapib. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov Unique Identifier: NCT01252953; URL: http://www.isrctn.com Unique Identifier: ISRCTN48678192; URL: https://www.clinicaltrialsregister.eu Unique Identifier: 2010-023467-18.

[17] *Sun YY, Liu LY, Sun T et al.* **Prophylactic atorvastatin prior to intra-arterial administration of iodinated contrast media for prevention of contrast-induced acute kidney injury: A meta-analysis of randomized trial data**. Clinical nephrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31347493
ABSTRACT
BACKGROUND: The efficacy of high-dose atorvastatin pretreatment in reducing the incidence of contrast-induced nephropathy in patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) has been examined in some randomized studies. However, the results across the trials remain controversial. OBJECTIVE: This study sought to perform a meta-analysis to evaluate the effect of high-dose atorvastatin in the prevention of contrast-induced nephropathy (CIN) while undergoing CAG or PCI. MATERIALS AND METHODS: Comprehensive literature searches for randomized controlled trials (RCTs) comparing high-dose atorvastatin vs. low-dose statin or placebo pretreatment for prevention of contrast-induced acute kidney injury in patients undergoing CAG were performed using PubMed, Embase, and the Cochrane library updated to June 2017. The primary outcome was the incidence of CIN. RESULTS: A total of 11 RCTs were included in this analysis. The high-dose atorvastatin treatment can significantly reduce the incidence of CIN (OR 0.46, 95% CI 0.35 - 0.62, $p < 0.00001$). The benefit was consistent in comparison with the low-dose group (OR 0.41, 95% CI 0.25 - 0.66, $p = 0.0003$) and the placebo group (OR 0.50, 95% CI 0.26 - 0.98, $p = 0.04$). CONCLUSION: Our study demonstrates that high-dose statin pretreatment shows a benefit specifically in reducing the incidence of contrast-induced acute kidney injury in patients undergoing CAG, especially compared with low-dose statin pretreatment..

[18] *Brandts J, Muller-Wieland D*. **PCSK9 Inhibition: New Treatment Options and Perspectives to Lower Atherogenic Lipoprotein Particles and Cardiovascular Risk**. Current atherosclerosis reports 2019; 21:40.

Literature update week 30 (2019)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31350672

ABSTRACT

PURPOSE OF REVIEW: To summarize latest clinical studies and to put them into perspectives for clinical relevant subgroups and new therapeutic options. RECENT FINDINGS: Have investigated PCSK9 inhibitors in patients with very high cardiovascular risk and insufficient LDL cholesterol lowering under current maximal tolerated lipid-lowering therapy, patients with statin intolerance, or genetic forms of familiar hypercholesterolemia, and patients on LDL apheresis. Purpose of recent cardiovascular endpoint trials has proven cardiovascular benefit of this new approach. PCSK9 inhibition with fully humanized antibodies has proven to be effective, safe, and well-tolerated in reducing cardiovascular risk by LDL cholesterol lowering. Therefore, research interests are to elucidate additional roles and effects of PCSK9 modulation on inflammation and cellular processes of the atherosclerotic plaque and to develop alternative therapeutic strategies addressing PCSK9 as a proven and therefore promising drug target.

[19] *Stulnig TM, Morozzi C, Reindl-Schwaighofer R, Stefanutti C*. **Looking at Lp(a) and Related Cardiovascular Risk: from Scientific Evidence and Clinical Practice**. Current atherosclerosis reports 2019; 21:37.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31350625

ABSTRACT

PURPOSE OF REVIEW: A considerable body of data from genetic and epidemiological studies strongly support a causal relationship between high lipoprotein(a) [Lp(a)] levels, and the development of atherosclerosis and cardiovascular disease. This relationship is continuous, unrelated to Lp(a) threshold, and independent of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels. Unfortunately, the mechanism(s) through which Lp(a) promotes atherosclerosis are not clarified yet. Suggested hypotheses include: an increased Lp(a)-associated cholesterol entrapment in the arterial intima followed by inflammatory cell recruitment, abnormal upload of proinflammatory oxidized phospholipids, impaired fibrinolysis by inhibition of plasminogen activation, and enhanced coagulation, through inhibition of the tissue factor pathway inhibitor. This review is aimed at summarizing the available evidence on the topic. RECENT FINDINGS: There are two clinical forms, isolated hyperlipidemia(a) [HyperLp(a)] with acceptable LDL-C levels (< 70 mg/dL), and combined elevation of Lp(a) and LDL-C in plasma. To date, no drugs that selectively decrease Lp(a) are available. Some novel lipid-lowering drugs can lower Lp(a) levels, but to a limited extent, as their main effect is aimed at decreasing LDL-C levels. Significant Lp(a) lowering effects were obtained with nicotinic acid at high doses. However, adverse effects apart, nicotinic acid is no longer prescribed and available in Europe for clinical use, after European Agency of Medicines (EMA) ban. The only effective therapeutic option for now is Lipoprotein Apheresis (LA), albeit with some limitations. Lastly, it is to be acknowledged that the body of evidence confirming that reducing plasma isolated elevation of Lp(a) brings cardiovascular benefit is still insufficient. However, the growing bulk of clinical, genetic, mechanistic, and epidemiological available evidence strongly suggests that Lp(a) is likely to be the smoking gun.

[20] *Feingold KR*. **Maximizing the benefits of cholesterol-lowering drugs**. Current opinion in lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31335331
ABSTRACT
PURPOSE OF REVIEW: Drugs to lower LDL-C levels are very widely used. In this brief review, I will use selected recent studies to delineate several important principles that provide a rationale for how to maximize the benefits of using LDL-C lowering drugs to reduce cardiovascular disease. The focus will be on using statins, ezetimibe, and PCSK9 monoclonal antibodies as recent studies have predominantly utilized these agents. RECENT FINDINGS: The key principles to consider when using LDL-C-lowering drugs to reduce cardiovascular disease are: the lower the LDL-C the better; the sooner and the longer one lowers LDL-C the better; the higher the risk of cardiovascular disease the greater the absolute benefit; the higher the baseline LDL-C the greater the absolute benefit; and compared with the benefits of cholesterol-lowering drugs on reducing cardiovascular disease the risk of side effects is very modest. SUMMARY: Understanding and employing these key concepts in caring for patients will allow one to use cholesterol-lowering drugs wisely to maximize the reduction of cardiovascular events.

[21] *Kajikawa M, Higashi Y*. **Triglycerides and endothelial function: molecular biology to clinical perspective**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31348023
ABSTRACT
PURPOSE OF REVIEW: Recently, a high level of triglycerides has attracted much attention as an important residual risk factor of cardiovascular events. We will review and show the mechanisms underlying the association of endothelial dysfunction with hypertriglyceridemia and present clinical evidence for a relationship between endothelial function and triglycerides. RECENT FINDINGS: Clinical studies have shown that hypertriglyceridemia is associated with endothelial dysfunction. It is likely that hypertriglyceridemia impairs endothelial function through direct and indirect mechanisms. Therefore, hypertriglyceridemia is recognized as a therapeutic target in the treatment of endothelial dysfunction. Although experimental and clinical studies have shown that fibrates and omega-3 fatty acids not only decrease triglycerides but also improve endothelial function, the effects of these therapies on cardiovascular events are controversial. SUMMARY: Accumulating evidence suggests that hypertriglyceridemia is an independent risk factor for endothelial dysfunction. Triglycerides should be considered more seriously as a future target to reduce cardiovascular events. Results of ongoing studies may show the benefit of lowering triglycerides and provide new standards of care for patients with hypertriglyceridemia possibly through improvement in endothelial function.

[22] *Sabatine MS*. **PCSK9 inhibitors: what we know, what we should have understood, and what is to come**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31334749
ABSTRACT

[23] *Kuroda K, Otake H, Shinohara M et al.* **Effect of Rosuvastatin and Eicosapentaenoic Acid on Neoatherosclerosis: The LINK-IT Trial**. EuroIntervention : journal of EuroPCR in collaboration

with the Working Group on Interventional Cardiology of the European Society of Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31334703
ABSTRACT
AIMS: We assessed the effect of 10 mg/day of rosuvastatin plus eicosapentaenoic acid (EPA) versus 2.5 mg/day of rosuvastatin on the extent of neoatherosclerosis using optical coherence tomography (OCT). METHODS AND RESULTS: We randomly assigned 50 patients with non-obstructive neoatherosclerotic plaques detected on OCT to receive either rosuvastatin 10 mg/day and EPA 1800 mg/day (intensive-therapy group) or rosuvastatin 2.5 mg (standard-therapy group). Follow-up OCT was performed 1 year later to evaluate serial changes of neoatherosclerosis. Serum low-density lipoprotein cholesterol (LDL-C) level decreased significantly from baseline to the 12-month follow-up in the intensive-therapy group (89 mg/dL to 70 mg/dL; P < 0.001), while no change occurred in the standard-therapy group. Lipid index change and percent changes in macrophage grade were significantly lower in the intensive-therapy group than in the standard-therapy group (-53.6 vs. 310.1, P = 0.001; -37.0% vs. 35.3%, P < 0.001; respectively). Percent changes in lipid index and macrophage grade were positively correlated with the changes in serum LDL-C and C-reactive protein levels, and negatively correlated with the change in serum eicosapentaenoic acid/arachidonic acid and 18-hydroxyeicosapentaenoic acid (EPA bioactive metabolite) level. CONCLUSIONS: Compared with rosuvastatin 2.5 mg/day, rosuvastatin 10 mg/day and EPA 1800 mg/day significantly stabilized non-obstructive neoatherosclerotic plaques.

[24] *Katsiki N, Mikhailidis DP, Banach M*. **Lipid-lowering agents for concurrent cardiovascular and chronic kidney disease**. Expert opinion on pharmacotherapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31344332
ABSTRACT
Introduction: Cardiovascular disease (CVD) frequently co-exists with chronic kidney disease (CKD). Patients with concomitant CVD and CKD are at very high risk of CVD events. Areas covered: This narrative review discusses the use of hypolipidaemic drugs in patients with both CVD and CKD. Current guidelines are considered together with the evidence from randomised controlled clinical trials. Expert opinion: Statins are the first-line lipid-lowering therapy in patients with CVD and CKD. Some statins require dose adjustments based on renal function, whereas atorvastatin does not. Ezetimibe can be prescribed in patients with CVD and CKD, usually combined with a statin. According to current guidelines, statin+/-ezetimibe therapy should not be initiated, but should be continued, in dialysis-treated CKD patients. Fenofibrate (dose adjusted or contra-indicated according to renal function) and omega 3 fatty acids lower triglyceride levels; whether they also exert cardiorenal benefits in patients with CVD and CKD remains to be established. The use of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, cholesterol-reducing nutraceuticals, bempedoic acid and apabetalone in such patients should be investigated. Patients with concomitant CVD and CKD should be treated, in terms of lipid-lowering therapy, early and intensively to minimize their very high risk and possibly, progression of CKD.

Literature update week 30 (2019)

[25] *Abdalla M, Akwo EA, Bluemke DA et al.* **Association between reduced myocardial contraction fraction and cardiovascular disease outcomes: The Multi-Ethnic Study of Atherosclerosis**. International journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31327521
ABSTRACT
BACKGROUND: The myocardial contraction fraction (MCF: stroke volume to myocardial volume) is a volumetric measure of left ventricular myocardial shortening. We examined the relationship of MCF, measured by cardiac magnetic resonance imaging (cMRI), to incident cardiovascular (CV) events within the Multi-Ethnic Study of Atherosclerosis (MESA). METHODS: Participants (n=5000, aged 45-84years) underwent cMRI. PRIMARY OUTCOME: CVD events (myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease: CHD death, and stroke death). SECONDARY OUTCOMES: CHD and heart failure (HF) events. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for outcomes. RESULTS: There were 299 incident CVD, 188 CHD, and 151 HF events over 10.2years. The lowest MCF quartile was associated with an increased risk for incident CVD [HR 2.42, CI: 1.58-3.72], CHD [HR 2.32, CI: 1.36-3.96] and HF events [HR 1.99, CI: 1.15-3.44]. In a model adjusted for demographics, CV risk factors, antihypertensive and lipid-lowering medication use, each standard deviation decrease in MCF was associated with incident CVD [HR 1.42, CI: 1.23-1.64], CHD [HR 1.40, CI: 1.17-1.67] and HF [HR 1.58, CI: 1.30-1.94]. In a subgroup analysis of participants with preserved ejection fraction and without left ventricular hypertrophy, the lowest MCF quartile and each standard deviation decrease in MCF was also associated with an increased risk for incident CVD in fully-adjusted analyses. CONCLUSIONS: MCF is a novel measure that can be measured using cMRI. In this multi-ethnic cohort, MCF is a measure that can be used to predict incident CVD events.

[26] *Chen LW, Lin CS, Tsai MC et al.* **Pitavastatin Exerts Potent Anti-Inflammatory and Immunomodulatory Effects via the Suppression of AP-1 Signal Transduction in Human T Cells**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31330988
ABSTRACT
Statins inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase are the standard treatment for hypercholesterolemia in atherosclerotic cardiovascular disease (ASCVD), mediated by inflammatory reactions within vessel walls. Several studies highlighted the pleiotropic effects of statins beyond their lipid-lowering properties. However, few studies investigated the effects of statins on T cell activation. This study evaluated the immunomodulatory capacities of three common statins, pitavastatin, atorvastatin, and rosuvastatin, in activated human T cells. The enzyme-linked immunosorbent assay (ELISA) and quantitative real time polymerase chain reaction (qRT-PCR) results demonstrated stronger inhibitory effects of pitavastatin on the cytokine production of T cells activated by phorbol 12-myristate 13-acetate (PMA) plus ionomycin, including interleukin (IL)-2, interferon (IFN)-gamma, IL-6, and tumor necrosis factor alpha (TNF-alpha). Molecular investigations revealed that pitavastatin reduced both activating protein-1 (AP-1) DNA binding and transcriptional activities. Further exploration showed the selectively inhibitory effect of pitavastatin on the signaling pathways of extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK), but not c-Jun N-

terminal kinase (JNK). Our findings suggested that pitavastatin might provide additional benefits for treating hypercholesterolemia and ASCVD through its potent immunomodulatory effects on the suppression of ERK/p38/AP-1 signaling in human T cells.

[27] *Trinder M, Li X, DeCastro ML et al.* **Risk of Premature Atherosclerotic Disease in Patients With Monogenic Versus Polygenic Familial Hypercholesterolemia**. Journal of the American College of Cardiology 2019; 74:512-522.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31345425
ABSTRACT
BACKGROUND: A pathogenic variant in LDLR, APOB, or PCSK9 can be identified in 30% to 80% of patients with clinically-diagnosed familial hypercholesterolemia (FH). Alternatively, approximately 20% of clinical FH is thought to have a polygenic cause. The cardiovascular disease (CVD) risk associated with polygenic versus monogenic FH is unclear. OBJECTIVES: This study evaluated the effect of monogenic and polygenic causes of FH on premature (age <55 years) CVD events in patients with clinically diagnosed FH. METHODS: Targeted sequencing of genes known to cause FH as well as common genetic variants was performed to calculate polygenic scores in patients with "possible," "probable," or "definite" FH, according to Dutch Lipid Clinic Network Criteria (n = 626). Patients with a polygenic score >/=80th percentile were considered to have polygenic FH. We examined the risk of unstable angina, myocardial infarction, coronary revascularization, or stoke. RESULTS: A monogenic cause of FH was associated with significantly greater risk of CVD (adjusted hazard ratio: 1.96; 95% confidence interval: 1.24 to 3.12; p = 0.004), whereas the risk of CVD in patients with polygenic FH was not significantly different compared with patients in whom no genetic cause of FH was identified. However, the presence of an elevated low-density lipoprotein cholesterol (LDL-C) polygenic risk score further increased CVD risk in patients with monogenic FH (adjusted hazard ratio: 3.06; 95% confidence interval: 1.56 to 5.99; p = 0.001). CONCLUSIONS: Patients with monogenic FH and superimposed elevated LDL-C polygenic risk scores have the greatest risk of premature CVD. Genetic testing for FH provides important prognostic information that is independent of LDL-C levels.

[28] *Reddy LL, Ashavaid TF*. **Familial Hypercholesterolemia (FH) Awareness Amongst Physicians in Mumbai, India**. The Journal of the Association of Physicians of India 2018; 66:66-69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331139
ABSTRACT
Background: Familial Hypercholesterolemia (FH) is a common genetic disorder affecting low density lipoprotein cholesterol (LDL-C) metabolism. Prolong exposure to elevated LDL-C results in the development of atherosclerotic lesions and a substantially increased risk of Coronary Artery Disease (CAD). In contrast, early detection and effective treatment of FH can result in a significant improvement in clinical outcomes. Despite these data, FH remains largely underdiagnosed and untreated. Objective: To assess the awareness, knowledge, and clinical practices of FH by General Physicians (GPs) in Mumbai. Methods: Physicians were requested to complete a survey comprising Multiple Choice questions (MCQs) on FH. The questionnaire inquired about; familiarity and awareness of the disorder, clinical description, prevalence,

inheritance and their opinions on FH clinical services. Results: Of the 79 GPs surveyed, 31% of them correctly described FH and only 28% knew about its prevalence. 51% perceived themselves to have an above moderate familiarity with this disorder. 46% of them were aware of the risk of cardiovascular disease (CVD) associated with FH. 80% of GPs were unsure or unaware of whether they had FH patients under their care. 50% and 33% of physicians identified statins as monotherapy and statin & ezetimibe as a combination therapy for FH respectively. Conclusion and Interpretation: Immediate attention should be focused on increasing awareness and knowledge about FH in India. Establishment of lipid clinic network will aid in improving care and clinical practices.

[29] *Bing R, Driessen RS, Knaapen P, Dweck MR*. **The clinical utility of hybrid imaging for the identification of vulnerable plaque and vulnerable patients**. Journal of cardiovascular computed tomography 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31345766
ABSTRACT
Despite decades of research and major innovations in technology, cardiovascular disease remains the leading cause of death globally. Our understanding of major cardiovascular events and their prevention is centred around the atherosclerotic plaque and the processes that ultimately lead to acute plaque rupture. Recent advances in hybrid imaging technology allow the combination of high spatial resolution and anatomical detail with molecular assessments of disease activity. This provides the ability to identify vulnerable plaque characteristics and differentiate active and quiescent disease, with the potential to improve patient risk stratification. Combined positron emission tomography and computed tomography is the prototypical non-invasive hybrid imaging technique for coronary artery plaque assessment. In this review we discuss the current state of play in the field of hybrid coronary atherosclerosis imaging.

[30] *Ferdinand KC, Jacobson TA, Koren A et al.* **Alirocumab efficacy and safety by race and ethnicity: Analysis from 3 ODYSSEY phase 3 trials**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331789
ABSTRACT
BACKGROUND: Differences in lipid and cardiovascular risk profiles have been observed in African-American/black (AA/B), white (W), and Hispanic/Latino (H/L) individuals. Efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, may vary by race and ethnicity and has not been analyzed. OBJECTIVE: This post hoc analysis evaluated alirocumab efficacy and safety vs control in 3 pooled ODYSSEY phase 3 trials (COMBO I, COMBO II, and LONG TERM) by race (AA/B [n = 154] vs W [n = 1982]) and ethnicity (H/L [n = 174] vs non-H/L [n = 3149]). METHODS: Patients with elevated low-density lipoprotein cholesterol (LDL-C) despite maximally tolerated statin received alirocumab (75 mg up to 150 mg every 2 weeks [COMBO I & II] or 150 mg every 2 weeks [LONG TERM]) or control (placebo [COMBO I and LONG TERM] or ezetimibe [COMBO II]). RESULTS: At baseline, LDL-C levels were similar across treatment groups; median lipoprotein(a) levels were higher in AA/B (33.0-120.0 mg/dL) vs W (7.1-66.3 mg/dL) and lower in H/L (5.0-38.3 mg/dL) vs non-H/L (7.7-69.0 mg/dL). At week 24, alirocumab significantly reduced LDL-C vs control. Alirocumab also reduced lipoprotein(a)

compared with control across the subgroups. Treatment-emergent adverse events were similar between alirocumab (68.9-85.0%) and control (70.6-82.4%) regardless of race and ethnicity. CONCLUSION: Alirocumab significantly reduced LDL-C and Lp(a) levels compared with control, regardless of race and ethnicity, with overall safety comparable to control across most of the racial and ethnic groups analyzed.

[31] *Zwol WV, Rimbert A, Kuivenhoven JA*. **The Future of Lipid-lowering Therapy**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31340607
ABSTRACT
The recent introduction of inhibitors of proprotein convertase subtilisin/kexin 9 to lower low-density lipoprotein (LDL) cholesterol on top of statins or as monotherapy is rapidly changing the landscape of treatment of atherosclerotic cardiovascular disease (ASCVD). However, existing lipid-lowering drugs have little impact on lipoprotein(a) (Lp(a)) or plasma triglycerides, two other risk factors for ASCVD. This review summarizes the evidence and the rationale to target Lp(a) and triglycerides and provides an overview of currently tested strategies to lower Lp(a), apolipoprotein C-III and angiopoietin-like protein 3. In addition, it summarizes new findings on the use of omega-3 fatty acids (OM3FA) to fight ASCVD. With the exception of OM3FA supplementation, the promise of the experimental drugs discussed here depends on the long-term safety and efficacy of monoclonal antibodies and/or antisense oligonucleotides Clinical outcome trials will ultimately prove whether these new therapeutic modalities will reduce ASCVD risk.

[32] *Hallett PJ, Engelender S, Isacson O*. **Lipid and immune abnormalities causing age-dependent neurodegeneration and Parkinson's disease**. Journal of neuroinflammation 2019; 16:153.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331333
ABSTRACT
This article describes pathogenic concepts and factors, in particular glycolipid abnormalities, that create cell dysfunction and synaptic loss in neurodegenerative diseases. By phenocopying lysosomal storage disorders, such as Gaucher disease and related disorders, age- and dose-dependent changes in glycolipid cell metabolism can lead to Parkinson's disease and related dementias. Recent results show that perturbation of sphingolipid metabolism can precede or is a part of abnormal protein handling in both genetic and idiopathic Parkinson's disease and Lewy body dementia. In aging and genetic predisposition with lipid disturbance, alpha-synuclein's normal vesicular and synaptic role may be detrimentally shifted toward accommodating and binding such lipids. Specific neuronal glycolipid, protein, and vesicular interactions create potential pathophysiology that is amplified by astroglial and microglial immune mechanisms resulting in neurodegeneration. This perspective provides a new logic for therapeutic interventions that do not focus on protein aggregation, but rather provides a guide to the complex biology and the common sequence of events that lead to age-dependent neurodegenerative disorders.

Literature update week 30 (2019)

[33] *Martinez E, Martorell J, Riambau V*. **Review of serum biomarkers in carotid atherosclerosis**. Journal of vascular surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31327598
ABSTRACT
BACKGROUND: Carotid artery atherosclerotic stenosis is a preventable major cause of stroke, but there is still a need for definition of high-risk plaque in asymptomatic patients who might benefit from interventional therapies. Several image markers are recommended to characterize unstable plaques. The measurement of serum biomarkers is a promising method to assist in decision making, but the lack of robust evidence in the carotid environment burdens their potential as a standard of care. The goal of this review was to offer an updated state-of-the-art study of available serum biomarkers with clinical implications, with focus on those that may predict carotid symptom development. METHODS: The Cochrane Library and MEDLINE databases were searched (all until September 2018) for studies on carotid plaque and serum biomarkers of atherosclerosis. Nonhuman, basic science, and histology studies were excluded, focusing on clinical studies. Selected abstracts were screened to include the most relevant articles on atherosclerotic plaque presence, progression, instability or symptom development. RESULTS: Some well-established biomarkers for coronary disease are not relevant to carotid atherosclerosis and other inflammatory biomarkers, lipids, interleukins, homocysteine, and adipokines may be useful in quantifying carotid disease-related risk. Some serum biomarkers combined with image features may assist vascular specialists in selecting patients at high risk for stroke and in need of intervention. CONCLUSIONS: Prospective studies applying a combination of biomarkers are essential to prove clinical usefulness.

[34] *Bittner V, Colantonio LD, Dai Y et al.* **Association of Region and Hospital and Patient Characteristics With Use of High-Intensity Statins After Myocardial Infarction Among Medicare Beneficiaries**. JAMA cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31339519
ABSTRACT
Importance: High-intensity statin use after myocardial infarction (MI) varies by patient characteristics, but little is known about differences in use by hospital or region. Objective: To explore the relative strength of associations of region and hospital and patient characteristics with high-intensity statin use after MI. Design, Setting, and Participants: This retrospective cohort analysis used Medicare administrative claims and enrollment data to evaluate fee-for-service Medicare beneficiaries 66 years or older who were hospitalized for MI from January 1, 2011, through June 30, 2015, with a statin prescription claim within 30 days of discharge. Data were analyzed from January 4, 2017, through May 12, 2019. Exposures: Beneficiary characteristics were abstracted from Medicare data. Hospital characteristics were obtained from the 2014 American Hospital Association Survey and Hospital Compare quality metrics. Nine regions were defined according to the US Census. Main Outcomes and Measures: Intensity of the first statin claim after discharge characterized as high (atorvastatin calcium, 40-80 mg, or rosuvastatin calcium, 20-40 mg/d) vs low to moderate (all other statin types and doses). Trends in high-intensity statins were examined from 2011 through 2015. Associations of region and beneficiary and hospital characteristics with high-intensity statin use from January 1, 2014, to June 15, 2015, were examined using Poisson distribution mixed models. Results: Among the

139 643 fee-for-service beneficiaries included (69 968 men [50.1%] and 69 675 women [49.9%]; mean [SD] age, 76.7 [7.5] years), high-intensity statin use overall increased from 23.4% in 2011 to 55.6% in 2015, but treatment gaps persisted across regions. In models considering region and beneficiary and hospital characteristics, region was the strongest correlate of high-intensity statin use, with 66% higher use in New England than in the West South Central region (risk ratio [RR], 1.66; 95% CI, 1.47-1.87). Hospital size of at least 500 beds (RR, 1.15; 95% CI, 1.07-1.23), medical school affiliation (RR, 1.11; 95% CI, 1.05-1.17), male sex (RR, 1.10; 95% CI, 1.07-1.13), and patient receipt of a stent (RR, 1.35; 95% CI, 1.31-1.39) were associated with greater high-intensity statin use. For-profit hospital ownership, patient age older than 75 years, prior coronary disease, and other comorbidities were associated with lower use. Conclusions and Relevance: This study's findings suggest that geographic region is the strongest correlate of high-intensity statin use after MI, leading to large treatment disparities.

[35] *Mizusaki N, Nomura K, Hosooka T et al.* **The Novel Lipid-Lowering Drug D-47 Ameliorates Hepatic Steatosis and Promotes Brown/Beige-Like Change of White Adipose Tissue in db/db Mice**. The Kobe journal of medical sciences 2019; 65:E36-e43.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31341155
ABSTRACT
D-47 is a newly developed solid dispersion of the arginine salt of (S)-(+)-4-[1-(4-tert-butylphenyl)-2-oxo-pyrrolidin-4-yl]methoxybenzoic acid (S-2E), which inhibits sterol and fatty acid synthesis. D-47 was recently shown to lower the serum level and hepatic content of both triglyceride and cholesterol in a rabbit model of familial hypercholesterolemia. We here investigated the effects of D-47 on dyslipidemia and hepatic steatosis in comparison with those of bezafibrate in the db/db mouse model of obesity. Treatment of db/db mice with D-47 or bezafibrate for 14 days lowered the serum triglyceride concentration without affecting that of cholesterol. D-47, but not bezafibrate, almost completely eliminated lipid droplets in hepatocytes and markedly lowered the triglyceride content of the liver in these mice. The two agents induced similar changes in the hepatic expression of genes including those related to beta-oxidation or fatty acid synthesis. D-47 however significantly reduced the mass of white adipose tissue and up-regulated the expression of genes related to energy expenditure, mitochondrial function, fatty acid oxidation or lipolysis in this tissue, indicating that D-47 induced the brown/beige adipocyte-like change in white adipose tissue, whereas bezafibrate had no such effects. Treatment of 3T3-L1 adipocytes with D-47 provoked the expression of genes related to mitochondrial function, fatty acid oxidation or lipolysis. Our data have thus shown that D-47 ameliorated hypertriglyceridemia and hepatic steatosis in an animal model of obesity, and they suggest that this latter effect might be mediated through the change of adipose tissue characteristics.

[36] *Kim YS, Cho BL, Kim WS et al.* **Frequency and Severity of Hypoglycemia in Type 2 Diabetes Mellitus Patients Treated with a Sulfonylurea-Based Regimen at University-Affiliated Hospitals in Korea: The Naturalistic Evaluation of Hypoglycemic Events in Diabetic Subjects Study**. Korean journal of family medicine 2019; 40:212-219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31344994
ABSTRACT

BACKGROUND: We assessed the frequency and severity of hypoglycemia in type 2 diabetes mellitus patients treated with sulfonylurea monotherapy or sulfonylurea+metformin. METHODS: We conducted a retrospective, observational, cross-sectional study in 2011 and 2012 including patients with type 2 diabetes mellitus aged >/=30 years who were treated with >/=6 months of sulfonylurea monotherapy or sulfonylurea+metformin at 20 university-affiliated hospitals in Korea. At enrollment, glycated hemoglobin (HbA1c) was assessed; participants completed self-reported questionnaires describing hypoglycemia incidents over the past 6 months. A review of medical records up to 12 months before enrollment provided data on demographics, disease history, comorbidities, laboratory results, and drug usage. RESULTS: Of 726 enrolled patients, 719 were included (55.6% male); 31.7% and 68.3% were on sulfonylurea monotherapy and sulfonylurea+metformin, respectively. Mean+/-standard deviation age was 65.9+/-10.0 years; mean HbA1c level was 7.0%+/-1.0%; 77.8% of patients had hypertension (89.4% used antihypertensive medication); 60.5% had lipid disorders (72.5% used lipid-lowering medication); and 52.0% had one or more micro- or macrovascular diseases. Among patients with A1c measurement (n=717), 56.4% achieved therapeutic goals (HbA1c <7.0%); 42.4% (305/719) experienced hypoglycemia within 6 months of enrollment; and 38.8%, 12.9%, 12.7%, and 3.9% of patients experienced mild, moderate, severe, and very severe hypoglycemia symptoms, respectively. Several reported hypoglycemia frequency as 1-2 times over the last 6 months. The mean number of very severe hypoglycemia episodes was 3.5+/-5.5. CONCLUSION: Among type 2 diabetes mellitus patients treated with sulfonylurea-based regimens, glycemic levels were relatively well controlled but hypoglycemia remained a prevalent side effect.

[37] *Zhao J, Chen F, Lu L et al.* **Effect of 106PEAR1 and 168PTGS1 genetic polymorphisms on recurrent ischemic stroke in Chinese patient**. Medicine (Baltimore) 2019; 98:e16457.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31335702

ABSTRACT

The impact of genetic polymorphisms on the occurrence of recurrent ischemic stroke (RIS) is not fully understood. This study was aimed to examine the relationships among the 106PEAR1 and 168PTGS1 polymorphisms and RIS.This was a single-center, retrospective, case-control study of patients seen in consultation between March 2016 and December 2016 at the Shandong Provincial Hospital. The 106PEAR1 (G>A) and 168PTGS1 (-842A>G) polymorphisms were determined by fluorescence in situ hybridization.There were 56 patients with RIS and 137 with initial stroke. Compared with the initial group, the RIS group showed lower LDL-C levels (P = .04). 168PTGS1 (-842A>G) did not meet the Hardy-Weinberg equilibrium. The AA genotype of the 106PEAR1 (G>A) polymorphism was more frequent in the RIS group (17.9% vs 5.8%, P = .009). The A allele also showed a higher frequency than the G allele in the RIS group (P = .02). The multivariable logistic regression analysis showed that 106PEAR1 (G>A) (OR = 3.24, 95%CI: 1.04-10.14, P = .04) and lipid-lowering agents (OR = 9.18, 95%CI: 4.48-18.84, P < .001) were independently associated with RIS.The polymorphism at 106PEAR1 (G>A) was independently associated with RIS in Chinese patients. The assessment of genetic polymorphisms in the prediction of RIS warrants further investigation in order to improve patient management and prognosis after a first ischemic stroke.

Literature update week 30 (2019)

[38] *Tatham LM, Liptrott NJ, Rannard SP, Owen A*. **Long-Acting Injectable Statins-Is It Time for a Paradigm Shift?** Molecules (Basel, Switzerland) 2019; 24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31344834
ABSTRACT
In recent years, advances in pharmaceutical processing technologies have resulted in development of medicines that provide therapeutic pharmacokinetic exposure for a period ranging from weeks to months following a single parenteral administration. Benefits for adherence, dose and patient satisfaction have been witnessed across a range of indications from contraception to schizophrenia, with a range of long-acting medicines also in development for infectious diseases such as HIV. Existing drugs that have successfully been formulated as long-acting injectable formulations have long pharmacokinetic half-lives, low target plasma exposures, and low aqueous solubility. Of the statins that are clinically used currently, atorvastatin, rosuvastatin, and pitavastatin may have compatibility with this approach. The case for development of long-acting injectable statins is set out within this manuscript for this important class of life-saving drugs. An overview of some of the potential development and implementation challenges is also presented.

[39] *Boulanger M, Li L, Lyons S et al.* **Effect of coexisting vascular disease on long-term risk of recurrent events after TIA or stroke**. Neurology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31337715
ABSTRACT
OBJECTIVE: To determine whether TIA or ischemic stroke patients with coexisting cardiovascular disease (i.e., history of coronary or peripheral artery disease) are still at high risk of recurrent ischemic events despite current secondary prevention guidelines. METHODS: In a population-based study in Oxfordshire, UK (Oxford Vascular Study), we studied consecutive patients with TIA or ischemic stroke for 2002-2014. Patients were treated according to current secondary prevention guidelines and we determined risks of coronary events, recurrent ischemic stroke, and major bleeding stratified by the presence of coexisting cardiovascular disease. RESULTS: Among 2,555 patients (9,148 patient-years of follow-up), those (n = 640; 25.0%) with coexisting cardiovascular disease (449 coronary only; 103 peripheral only; 88 both) were at higher 10-year risk of coronary events than those without (22.8%, 95% confidence interval 17.4-27.9; vs 7.1%, 5.3-8.8; p < 0.001; age- and sex-adjusted hazard ratio [HR] 3.07, 2.24-4.21) and of recurrent ischemic stroke (31.5%, 25.1-37.4; vs 23.4%, 20.5-26.2; p = 0.0049; age- and sex-adjusted HR 1.23, 0.99-1.53), despite similar rates of use of antithrombotic and lipid-lowering medication. However, in patients with noncardioembolic TIA/stroke, risk of extracranial bleeds was also higher in those with coexisting cardiovascular disease, particularly in patients aged <75 years (8.1%, 2.8-13.0; vs 3.4%, 1.6-5.3; p = 0.0050; age- and sex-adjusted HR 2.71, 1.16-6.30), although risk of intracerebral hemorrhage was not increased (age- and sex-adjusted HR 0.36, 0.04-2.99). CONCLUSIONS: As in older studies, TIA/stroke patients with coexisting cardiovascular disease remain at high risk of recurrent ischemic events despite current management. More intensive lipid-lowering might therefore be justified, but benefit from increased antithrombotic treatment might be offset by the higher risk of extracranial bleeding.

[40] *Gao J, Xiao H, Li J et al.* **N-3 Polyunsaturated Fatty Acids Decrease Long-Term Diabetic Risk of Offspring of Gestational Diabetes Rats by Postponing Shortening of Hepatic Telomeres and Modulating Liver Metabolism**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31340612
ABSTRACT
The long-term influence of gestational diabetes mellitus (GDM) on offspring and the effect of omega-3 polyunsaturated fatty acids (n-3 PUFA) on GDM offspring are poorly understood. We studied the long-term diabetic risk in GDM offspring and evaluated the effect of n-3 PUFA intervention. Healthy offspring rats were fed standard diet (soybean oil) after weaning. GDM offspring were divided into three groups: GDM offspring (soybean oil), n-3 PUFA adequate offspring (fish oil), and n-3 PUFA deficient offspring (safflower oil), fed up to 11 months old. The diabetic risk of GDM offspring gradually increased from no change at weaning to obvious impaired glucose and insulin tolerance at 11 months old. N-3 PUFA decreased oxidative stress and inflammation in the liver of older GDM offspring. There was a differential effect of n-3 PUFA and n-6 PUFA on hepatic telomere length in GDM offspring. Non-targeted metabolomics showed that n-3 PUFA played a modulating role in the liver, in which numerous metabolites and metabolic pathways were altered when GDM offspring grew to old age. Many metabolites were related to diabetes risk, such as alpha-linolenic acid, palmitic acid, ceramide, oxaloacetic acid, tocotrienol, tetrahydro-11-deoxycortisol, andniacinamide. In summary, GDM offspring exhibited obvious diabetes risk at old age, whereas n-3 PUFA decreased this risk.

[41] *Nishi H, Higashihara T, Inagi R*. **Lipotoxicity in Kidney, Heart, and Skeletal Muscle Dysfunction**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31330812
ABSTRACT
Dyslipidemia is a common nutritional and metabolic disorder in patients with chronic kidney disease. Accumulating evidence supports the hypothesis that prolonged metabolic imbalance of lipids leads to ectopic fat distribution in the peripheral organs (lipotoxicity), including the kidney, heart, and skeletal muscle, which accelerates peripheral inflammation and afflictions. Thus, lipotoxicity may partly explain progression of renal dysfunction and even extrarenal complications, including renal anemia, heart failure, and sarcopenia. Additionally, endoplasmic reticulum stress activated by the unfolded protein response pathway plays a pivotal role in lipotoxicity by modulating the expression of key enzymes in lipid synthesis and oxidation. Here, we review the molecular mechanisms underlying lipid deposition and resultant tissue damage in the kidney, heart, and skeletal muscle, with the goal of illuminating the nutritional aspects of these pathologies.

[42] *DiNicolantonio JJ, J OK*. **Dietary fats, blood pressure and artery health**. Open heart 2019; 6:e001035.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31328005
ABSTRACT

Literature update week 30 (2019)

[43] *Rochette E, Bourdier P, Pereira B et al.* **TNF blockade contributes to restore lipid oxidation during exercise in children with juvenile idiopathic arthritis**. Pediatric rheumatology online journal 2019; 17:47.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31331342
ABSTRACT
BACKGROUND: Children with juvenile idiopathic arthritis (JIA) have impaired physical abilities. TNF-alpha plays a crucial role in this pathogenesis, but it is also involved in the use of lipids and muscle health. Objective of this study was to explore substrate oxidation and impact of TNF blockade on energy metabolism in children with JIA as compared to healthy children. METHODS: Fifteen non-TNF-blockaded and 15 TNF-blockaded children with JIA and 15 healthy controls were matched by sex, age, and Tanner stage. Participants completed a submaximal incremental exercise test on ergocycle to determine fat and carbohydrate oxidation rates by indirect calorimetry. RESULTS: The maximal fat oxidation rate during exercise was lower in JIA children untreated by TNF blockade (134.3 +/- 45.2 mg.min(- 1)) when compared to the controls (225.3 +/- 92.9 mg.min(- 1), p = 0.007); but was higher in JIA children under TNF blockade (163.2 +/- 59.0 mg.min(- 1), p = 0.31) when compared to JIA children untreated by TNF blockade. At the same relative exercise intensities, there was no difference in carbohydrate oxidation rate between three groups. CONCLUSIONS: Lipid metabolism during exercise was found to be impaired in children with JIA. However, TNF treatment seems to improve the fat oxidation rate in this population. TRIAL REGISTRATION: In ClinicalTrials.gov, reference number NCT02977416 , registered on 30 November 2016.

[44] *Ramos MFP, Oliveira OB, de Barros A et al.* **Comparison of olive leaf, olive oil, palm oil, and omega-3 oil in acute kidney injury induced by sepsis in rats**. PeerJ 2019; 7:e7219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31333903
ABSTRACT
Background: Hypotension, increased production of reactive oxygen species, and inflammation are all observed in experimental models of sepsis induced by lipopolysaccharide (LPS). Purpose: The aim of this study was to evaluate the effects of an ethanolic extract of Brazilian olive leaf (Ex), Brazilian olive oil (Olv), Ex + Olv (ExOlv), and palm oil (Pal) in comparison to the effects of omega-3 fish oil (Omg) in a rat model of sepsis-induced acute kidney injury. Materials: Wistar rats were divided into seven groups (seven per group), which were either untreated (control) or treated with LPS, LPS + Ex, LPS + ExOlv, LPS + Olv, LPS + Omg, or LPS + Pal. Results: Lower values of creatinine clearance and blood pressure were observed in the LPS-treated group, and these values were not affected by Ex, Olv, ExOlv, Pal, or Omg treatment. Mortality rates were significantly lower in rats exposed to LPS when they were also treated with Ex, ExOlv, Olv, Pal, or Omg. These treatments also decreased oxidative stress and inflammation (Tumor necrosis factor alpha, interleukin-1 beta) and increased interleukin-10 levels and cell proliferation, which were associated with decreased apoptosis in kidney tissue. Conclusion: Ex and Pal treatments were beneficial in septic rats, since they increased survival rate and did not aggravate inflammation. However, the most effective treatments for septic rats were Olv in comparison to Omg. These natural food substances could enable the development of effective therapeutic interventions to sepsis.

Literature update week 30 (2019)

[45] *Pavanello C, Baragetti A, Branchi A et al.* **Treatment with fibrates is associated with higher LAL activity in dyslipidemic patients**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019:104362.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31330253
ABSTRACT
Lysosomal acid lipase (LAL) is responsible for the hydrolysis of cholesteryl esters (CE) and triglycerides (TG) within the lysosomes; generated cholesterol and free fatty acids (FFA) are released in the cytosol where they can regulate their own synthesis and metabolism. When LAL is not active, as in case of genetic mutations, CE and TG accumulate in the lysosomal compartment, while the lack of release of cholesterol and FFA in the cytosol leads to an upregulation of their synthesis. Thus, LAL plays a central role in the intracellular homeostasis of lipids. Since there are no indications about the effect of different lipid-lowering agents on LAL activity, aim of the study was to address the relationship between LAL activity and the type of lipid-lowering therapy in a cohort of dyslipidemic patients. LAL activity was measured on dried blood spot from 120 patients with hypercholesterolemia or mixed dyslipidemia and was negatively correlated to LDL-cholesterol levels. Among enrolled patients, ninety-one were taking one or more lipid-lowering drugs, as statins, fibrates, ezetimibe and omega-3 polyunsaturated fatty acids. When patients were stratified according to the type of lipid-lowering treatment, i.e. untreated, taking statins or taking fibrates, LAL activity was significantly higher in those with fibrates, even after adjustment for sex, age, BMI, lipid parameters, liver function, metabolic syndrome, diabetes and statin use. In a subset of patients tested after 3 months of treatment with micronized fenofibrate, LAL activity raised by 21%; the increase was negatively correlated with baseline LAL activity. Thus, the use of fibrates is independently associated with higher LAL activity in dyslipidemic patients, suggesting that the positive effects of PPAR-alpha activation on cellular and systemic lipid homeostasis can also include an improved LAL activity.

[46] *Lee Y, Hu S, Park YK, Lee JY*. **Health Benefits of Carotenoids: A Role of Carotenoids in the Prevention of Non-Alcoholic Fatty Liver Disease**. Preventive nutrition and food science 2019; 24:103-113.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31328113
ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases with a prevalence of ~25% worldwide. NAFLD includes simple hepatic steatosis, non-alcoholic steatohepatitis, fibrosis, and cirrhosis, which can further progress to hepatocellular carcinoma. Therefore, effective strategies for the prevention of NAFLD are needed. The pathogenesis of NAFLD is complicated due to diverse injury insults, such as fat accumulation, oxidative stress, inflammation, lipotoxicity, and apoptosis, which may act synergistically. Studies have shown that carotenoids, a natural group of isoprenoid pigments, prevent the development of NAFLD by exerting antioxidant, lipid-lowering, anti-inflammatory, anti-fibrotic, and insulin-sensitizing properties. This review summarizes the protective action of carotenoids, with primary focuses on astaxanthin, lycopene, beta-carotene, beta-cryptoxanthin, lutein, fucoxanthin, and crocetin, against the development and progression of NAFLD.

[47] *Yang S, Zhao L, Han Y et al.* **Corrigendum to "Probucol ameliorates renal injury in diabetic nephropathy by inhibiting the expression of the redox enzyme p66Shc" [Redox Biol. 13 (2017) 482-497]**. Redox biology 2019:101276.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31350214
ABSTRACT

[48] *Leung AKK, Genga KR, Topchiy E et al.* **Reduced Proprotein convertase subtilisin/kexin 9 (PCSK9) function increases lipoteichoic acid clearance and improves outcomes in Gram positive septic shock patients**. Scientific reports 2019; 9:10588.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31332258
ABSTRACT
Previous studies have shown lipopolysaccharide from Gram-negative bacteria is cleared from the circulation via LDL receptors on hepatocytes, which are downregulated by PCSK9. Whether clearance of Gram positive bacterial lipoteichoic acid (LTA) shows similar dependence on PCSK9, and whether this is clinically relevant in Gram positive human sepsis, is unknown. We examined survival data from three cohorts of patients who had Gram positive septic shock (n = 170, n = 130, and n = 59) and found that patients who carried a PCSK9 loss-of-function (LOF) allele had significantly higher 28-day survival (73.8%) than those with no LOF alleles (52.8%) ($p = 0.000038$). Plasma clearance of LTA was also found to be increased in PCSK9 knockout mice compared to wildtype control mice ($p = 0.002$). In addition, hepatocytes pre-treated with recombinant wildtype PCSK9 showed a dose-dependent decrease in uptake of fluorescently-labeled LTA ($p < 0.01$). In comparison to wildtype PCSK9, hepatocytes pre-treated with 3 different LOF variants of recombinant PCSK9 showed an increase in LTA uptake. This study shows the clearance of LTA follows a similar route as lipopolysaccharide, which is dependent on hepatic LDL receptors. This has important implications in health as strategies aimed at inhibiting PCSK9 function may be an effective treatment option for both Gram-positive and negative sepsis.

[49] *Kusminski CM, Scherer PE*. **Lowering ceramides to overcome diabetes**. Science 2019; 365:319-320.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31346052
ABSTRACT

[50] *Zarei L, Mahdavi Rad S, Abdollahzade Fard A*. **Co-administration of retinoic acid and atorvastatin mitigates high-fat diet induced renal damage in rats**. Veterinary research forum : an international quarterly journal 2019; 10:133-138.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31338146
ABSTRACT
Obesity causes many problems such as cardiovascular and chronic kidney diseases. The aim of this study was to evaluate the efficacy of retinoic acid and atorvastatin co-administration in kidneys protection against high-fat diet induced damage. Twenty-five male Wistar rats (200.00 +/- 20.00 g) were divided into five groups: 1) Control (standard diet), 2) High-fat diet (cholesterol 1.00%, 75 days), 3) High-fat diet + atorvastatin (20.00 mg kg(-1) per day, orally, on the 30(th) day, for 45 consecutive days), 4) High-fat diet + retinoic acid (5 mg kg(-1) per day,

orally, on the 30(th) day, for 45 consecutive days), and 5) High fat diet + atorvastatin and retinoic acid. At the end, blood and tissue samples were collected for biochemical and histological analyses. The results showed that atorvastatin and retinoic acid alone and in combination decreased cholesterol and low-density lipoprotein and increased high-density lipoprotein in high-fat diet. Also, atorvastatin - caused total antioxidant capacity increase and protein carbonyl content decrease the in the renal tissue. Atorvastatin also prevented high-fat diet-induced renal histological injury. Treatment with atorvastatin significantly mitigates high-fat diet-induced renal changes probably due to its potent antioxidant and lipid-lowering effects. The effect of retinoic acid in renal protection in a high-fat diet is far less than that of atorvastatin. The protective effect of the combination of these two agents in the high-fat diet on the kidneys seems to be due to the effect of atorvastatin.