Literature update week 24 (2019)

[1] *Farmakis I, Zafeiropoulos S, Kartas A et al.* **Treatment practices and lipid profile of patients with acute coronary syndrome: results from a tertiary care hospital**. Acta Cardiol 2019:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31219734

ABSTRACT
Background: Considering the increasing burden of cardiovascular risk factors and recent advances on the management of acute coronary syndromes (ACS), we studied the epidemiological characteristics and treatment strategies of patients presenting with ACS. We also evaluated the lipid profile and attainment of lipid goals in a 'real world' clinical setting. Methods: This was a substudy of IDEAL-LDL (Motivational interviewing to support low-density lipoprotein cholesterol (LDL-C) therapeutic goals and lipid-lowering therapy compliance in patients with acute coronary syndromes), a single-centre, prospective, randomised controlled trial. Baseline data from a total of 357 ACS patients were gathered using standardised methods. Results: Median age of patients was 60 years and 81.2% were males. Arterial hypertension and smoking were the most prevalent risk factors for coronary artery disease (CAD). Patients with ST-elevation myocardial infarction (STEMI) were heavier smokers, but were younger and exercised more compared to those with non-ST-elevation acute coronary syndrome (NSTE-ACS). Conversely, more NSTE-ACS patients had arterial hypertension, dyslipidaemia and diabetes mellitus. One-fifth of ACS patients was treated conservatively without a percutaneous coronary intervention (PCI). A combination of statin, dual antiplatelet therapy and beta-blockers were prescribed to 79.6% of patients upon discharge. A renin-angiotensin-aldosterone system inhibitor and a beta-blocker were prescribed to 67.3 and 91.8% of patients with LVEF </=40%, respectively. Of patients with prior history of CAD, 63.1%, 71.4% and 58.3% received regularly statins, antiplatelets and beta-blocker treatment, respectively. Only 22.3% of these CAD patients had an optimal LDL-C of <70 mg/dl at admission. Conclusions: In hospitalised patients with ACS, management practices differed by ACS type and discharge medication was, mostly, in line with the latest guidelines. However, medication adherence and lipid lowering goals of secondary CAD prevention were largely unachieved.

[2] *Antonazzo IC, Poluzzi E, Forcesi E et al.* **Myopathy with DPP-4 inhibitors and statins in the real world: investigating the likelihood of drug-drug interactions through the FDA adverse event reporting system**. Acta diabetologica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31203438

ABSTRACT
AIMS: To investigate the occurrence of myopathy with oral glucose-lowering drugs (OGLDs) and statins, with a focus on dipeptidyl peptidase-4 inhibitors (DPP4-is). METHODS: The FDA adverse event reporting system (FAERS) was queried (2004-2016) to compare the proportion of adverse events with OGLDs, alone and in combination with statins, using the reporting odds ratio (ROR) with relevant 95% confidence interval (95%CI), adjusted for sex, age and concomitant presence of other OGLDs/lipid-lowering drugs. Drug-drug interaction is claimed whenever the frequency of an event is enhanced by combination treatment. Consistency/robustness of findings was tested by applying additive/multiplicative models and accounting for competition bias (i.e., adverse events previously known to be associated with OGLDs were removed). RESULTS: Over a 13-year period, we retrieved 142,888 cases of myopathy. The use of DPP4-is alone was not associated with higher reporting of myopathy (no. of cases = 4898; adjusted ROR = 1.00; 95%CI

= 0.96-1.04), with the notable exclusion of vildagliptin (262; 1.64; 1.42-1.88). No increased occurrence emerged when used in combination with statins, with consistent findings from additive/multiplicative models for all DPP4-is. Likewise, no increased reporting was found for other OGLDs (28,964; 0.64; 0.62-0.67); data on the interaction with statins were consistent/robust across analyses only for sulfonylureas (the interaction is likely and biologically plausible) and sodium glucose cotransporter-2 inhibitors. CONCLUSIONS: Real-world FAERS data do not raise concern for muscular toxicity with DPP4-is in combination with statins, making a drug interaction very unlikely.

[3] *Sundfor TM, Svendsen M, Heggen E et al.* **BMI modifies the effect of dietary fat on atherogenic lipids: a randomized clinical trial**. The American journal of clinical nutrition 2019. **PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=31216575

ABSTRACT

BACKGROUND: SFA intake increases LDL cholesterol whereas PUFA intake lowers it. Whether the lipid response to dietary fat differs between normal-weight and obese persons is of relevance to dietary recommendations for obese populations. OBJECTIVES: We compared the effect of substituting unsaturated fat for saturated fat on LDL cholesterol and apoB concentrations in normal-weight (BMI </= 25 kg/m2) and obese (BMI: 30-45) subjects with elevated LDL cholesterol. METHODS: We randomly assigned 83 men and women (aged 21-70 y) stratified by BMI (normal: n = 44; obese: n = 39) and elevated LDL cholesterol (mean +/- SD, normal weight 4.6 +/- 0.9 mmol/L; obese 4.4 +/- 0.8 mmol/L) to either a PUFA diet enriched with oil-based margarine (n = 42) or an SFA diet enriched with butter (n = 41) for 6 wk. RESULTS: Seven-day dietary records showed differences of approximately 9 energy percent (E%) in SFA and approximately 4 E% in PUFA between the SFA and PUFA groups. In the total study population, the PUFA diet compared with the SFA diet lowered LDL cholesterol (-0.31 mmol/L; 95% CI: -0.47, -0.15 mmol/L, compared with 0.32 mmol/L; 95% CI: 0.18, 0.47 mmol/L; P < 0.001) and apoB (-0.08 g/L; 95% CI: -0.11, -0.05 g/L, compared with 0.07 g/L; 95% CI: 0.03, 0.10 g/L; P < 0.001). Tests of the BMI x diet interaction were significant for total cholesterol, LDL cholesterol, and apoB (P values </= 0.009). In normal-weight compared with obese participants post-hoc comparisons found that the respective changes in LDL cholesterol were 9.7% (95% CI: 5.3%, 14.2%) compared with 5.3% (95% CI: -0.7%, 11.2%), P = 0.206, in the SFA group, and -10.4% (95% CI: -15.2%, -5.7%) compared with -2.3% (95% CI: -7.4%, 2.8%), P = 0.020, in the PUFA group. ApoB changes were 7.5% (95% CI: 3.5%, 11.4%) compared with 3.0% (95% CI: -1.7%, 7.7%), P = 0.140, in the SFA group, and -8.9% (95% CI: -12.6%, -5.2%) compared with -3.8% (95% CI: -6.3%, -1.2%), P = 0.021, in the PUFA group. Responses to dietary fat were not associated with changes in polyprotein convertase subtisilin/kexin type 9 concentrations. CONCLUSIONS: BMI modifies the effect of PUFAs compared with SFAs, with smaller improvements in atherogenic lipid concentrations in obese than in normal-weight individuals, possibly supporting adjustment of dietary recommendations according to BMI. This trial was registered with www.clinicaltrials.gov as NCT02589769.

[4] *Rostamian S, de Haan S, van der Grond J et al.* **Cognitive Function in Dementia-Free Subjects and Survival in The Old Age: The PROSPER Study**. The American journal of medicine 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31228412

ABSTRACT

BACKGROUND: Impairment in domain-specific cognitive function is associated with the increased risk of mortality. We prospectively evaluated the association of executive function and memory with the risk of long-term mortality in dementia-free older subjects. Moreover, we investigated the role of structural brain abnormalities in this association. METHODS: We included 547 dementia-free participants (mean age 78years, 56.5% male) from the nested magnetic resonance imaging sub-study of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Cox proportional hazard models were used to model 10-year risk of all-cause, cardiovascular and non-cardiovascular mortality in relation to performance in executive function and memory. Moreover, we evaluated the role of total brain parenchymal volume, cerebral blood flow, white matter hyperintensity and the presence of microbleeds and infarcts in the link between cognitive function and mortality. RESULTS: In the multivariable model, lower performance in executive function was associated with greater risk of all-cause (hazard ratio [HR] 1.49, 95% confidence interval [CI] 1.31-1.70), cardiovascular (HR 1.69, 95%CI 1.36-2.11) and non-cardiovascular (HR 1.36, 95%CI 1.15-1.62) mortality. Similarly, poorer performance in memory tests associated with higher risk of all-cause (HR 1.47, 95%CI 1.29-1.68), cardiovascular (HR 1.45, 95%CI 1.15-1.83) and non-cardiovascular (HR 1.49, 95%CI 1.27-1.76) mortality. The associations were similar in subjects with various levels of brain structural abnormalities and cerebral blood flow (all p for interaction >0.05). CONCLUSIONS: Poorer performance in both executive function and memory tests associates with all-cause, cardiovascular and non-cardiovascular mortality in elderly individuals. This association is independent of cardiovascular risk factors and diseases, brain structural abnormalities and cerebral blood flow.

[5] *Sapey E, Patel JM, Greenwood H et al.* **Simvastatin Improves Neutrophil Function and Clinical Outcomes in Pneumonia: a Pilot Randomised Controlled Trial**. American journal of respiratory and critical care medicine 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31206313

ABSTRACT

RATIONALE: Population studies suggest improved sepsis outcomes with statins but randomized controlled trials in patients with sepsis and organ dysfunction in critical care settings have broadly been negative. In vitro data suggest statins modulate age-related neutrophil functions improving neutrophil responses to infection, but only in older patients and at high dose. OBJECTIVE: To determine if high dose simvastatin improved neutrophil functions and clinical outcomes in hospitalized older adults with community acquired pneumonia with sepsis (CAP+S) not admitted to critical care. METHODS: A randomized, double-blinded, placebo-controlled pilot study of simvastatin 80mg or placebo for 7 days for CAP+S patients aged >55 years admitted to a secondary care hospital. Day 4 primary endpoint was change in neutrophil NETosis. Day 4 secondary endpoints included neutrophil chemotaxis, safety and tolerability, Sequential Organ Failure Assessment(SOFA) score, mortality, readmission and markers of tissue degradation/inflammation. RESULTS: Four days of simvastatin adjuvant therapy in CAP+S was associated with improvements in systemic neutrophil function (NETosis and chemotaxis), a reduction in systemic neutrophil elastase burden and improved SOFA scores compared with

placebo. A post-hoc analysis demonstrated simvastatin therapy was associated with improved hospital-free survival compared to placebo. Simvastatin was well tolerated in this elderly and multi-morbid patient group with common co-prescription of macrolide antibiotics. CONCLUSION: This pilot study supports high-dose simvastatin as an adjuvant therapy in CAP+S in an older and milder disease cohort than assessed previously. A definitive multi-centred study is now warranted in this population to assess the likelihood of benefit and harm. Clinical trial registration available at clinicaltrialsregister.eu/ctr-search/search, ID: 2012-003343-29.

[6] *Wang XL, Qi J, Shi YQ et al.* **Atorvastatin plus therapeutic ultrasound improve postnatal neovascularization in response to hindlimb ischemia via the PI3K-Akt pathway**. American journal of translational research 2019; 11:2877-2886.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31217861
ABSTRACT
Statins and therapeutic ultrasound (TUS) have been shown to ameliorate angiogenesis on ischemic hindlimb animals and promote human umbilical vein endothelial cells (HUVECs) tube formation and proliferation. Here, we evaluate the therapeutic effect of TUS in combination with atorvastatin (Ator) therapy on angiogenesis in hindlimb ischemia and HUVECs. After subjecting excision of the left femoral artery, all mice were randomly distributed to one of four groups: Control; Ator treated mice (Ator); TUS treated mice (TUS); and Ator plus TUS treated mice (Ator+TUS). At day 14 post-surgery, the Ator plus TUS treatment cohort had the greatest blood perfusion, accompanied by elevated capillary density. In vitro, Ator plus TUS augmented tube formation, migration and proliferative capacities of HUVECs. Additionally, the united administration upregulated expression of angiogenic factors phosphorylated Akt (p-Akt), phosphorylated endothelial nitric oxide synthase (p-eNOS), as well as vascular endothelial growth factor (VEGF), both in vivo and in vitro. These benefits could be blocked by either phosphoinositide 3-kinase (PI3K) or eNOS inhibitor. Our data indicated that the united administration could significantly enhance ischemia-mediated angiogenesis and exert a protective effect against ischemic/hypoxia induced damage among HUVECs through up-regulating VEGF expression and activating the PI3K-Akt-eNOS pathway.

[7] *Pirazzi C, Hakansson L, Gustafsson C et al.* **High prevalence of genetic determined familial hypercholesterolemia in premature coronary artery disease**. The application of clinical genetics 2019; 12:71-78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31213876
ABSTRACT
Background: Premature coronary artery disease (CAD) is a major cause of mortality and morbidity. Increased low-density lipoprotein-cholesterol (LDL-C) level is a major risk factor for CAD and thus the main target for its prevention. Familial Hypercholesterolemia (FH) is a genetic inherited disorder characterized by high LDL-C, and subsequent premature CAD development. Early drug treatment with lipid-lowering medications in FH prevents cardiovascular disease onset. The FH prevalence in the Northern European general population is 0.3%, and it is estimated that it explains 20% of premature CAD cases in individuals with familial clustering. Despite the wide number of papers showing the prevalence of clinical FH in cardiovascular disease, the prevalence of genetic FH in individuals with premature CAD is not yet well known.

Here, we examined the prevalence of genetically determined FH in individuals with premature CAD. Patients and methods: 66 patients who underwent coronary angiography with suspected premature acute coronary syndrome (age <50 years for men and <55 years for women) underwent genetic screening to identify FH-causing mutations. All patients underwent physical and clinical examinations. Information about family and personal history, drug therapy and habits were also collected. Results: We found FH-causative mutations in 3/66 (4.5%) screened individuals with premature CAD. When considering individuals with confirmed CAD after coronary angiography, the FH mutation prevalence was 6.1% (3/49). After excluding individuals with classical risk factors for CAD other than hypercholesterolemia, the FH mutation prevalence raised to 15.8% (3/19). Conclusion: In conclusion, we found that individuals with premature CAD have a more than 15-fold increased prevalence of FH mutations compared to the general population.

[8] *Ewald B, Del Mar C, Hoffmann T*. **Quantifying the benefits and harms of various preventive health activities**. Australian journal of general practice 2018; 47:842-845.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31212401
ABSTRACT
Background and objective: It is helpful for general practitioners (GPs) and their patients to understand the amount of health benefit expected from different preventive activities to enable a thoughtful choice of which to adopt first. The aim of this article is to illustrate how it might be possible to quantify the mortality benefit for cancer screening, quitting smoking, losing weight and treating lipids, which are preventive activities from The Royal Australian College of General Practitioners' (RACGP's) Guidelines for preventive activities in general practice (Red Book). Methods: A sample of common preventive activities was taken, with an outcome for each selected for fair comparison, and benefits and harms were estimated. Results: For a man aged 50 years, the benefit in terms of reduced risk of dying is greatest for quitting smoking (at 24 fewer deaths/1000/decade), which is approximately 10 times the benefit of lowering lipids in a man with metabolic syndrome and about 50 times greater than from participating in regular colorectal cancer screening. Benefits for women are generally lower, as their baseline risk is lower. Discussion: It is feasible to quantify the benefits of some preventive activities, although estimating them is not straightforward and requires several assumptions. Nevertheless, extending estimates such as these to the items in the RACGP's Red Book would assist GPs and their patients' preventive activity prioritisation.

[9] *Holopainen M, Colas RA, Valkonen S et al.* **Polyunsaturated fatty acids modify the extracellular vesicle membranes and increase the production of proresolving lipid mediators of human mesenchymal stromal cells**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019; 1864:1350-1362.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31207356
ABSTRACT
Human mesenchymal stromal/stem cells (hMSCs) are used in experimental cell therapy to treat various immunological disorders, and the extracellular vesicles (hMSC-EVs) they produce have emerged as an option for cell-free therapeutics. The immunomodulatory function of hMSCs resembles the resolution of inflammation, in which proresolving lipid mediators (LMs) play key

roles. Multiple mechanisms underlying the hMSC immunosuppressive effect has been elucidated; however, the impact of LMs and EVs in the resolution is poorly understood. In this study, we supplemented hMSCs with polyunsaturated fatty acids (PUFAs); arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid, which serve as precursors for multiple LMs. We then determined the consequent compositional modifications in the fatty acid, phospholipid, and LM profiles. Mass spectrometric analyses revealed that the supplemented PUFAs were incorporated into the main membrane phospholipid classes with different dynamics, with phosphatidylcholine serving as the first acceptor. Most importantly, the PUFA modifications were transferred into hMSC-EVs, which are known to mediate hMSC immunomodulation. Furthermore, the membrane-incorporated PUFAs influenced the LM profile by increasing the production of downstream prostaglandin E2 and proresolving LMs, including Resolvin E2 and Resolvin D6. The production of LMs was further enhanced by a highly proinflammatory stimulus, which resulted in an increase in a number of mediators, most notably prostaglandins, while other stimulatory conditions had less a pronounced impact after a 48-h incubation. The current findings suggest that PUFA manipulations of hMSCs exert significant immunomodulatory effects via EVs and proresolving LMs, the composition of which can be modified to potentiate the therapeutic impact of hMSCs.

[10] *Winston-McPherson GN, Xie H, Yang K et al.* **Discovery of 2,3'-diindolylmethanes as a novel class of PCSK9 modulators**. Bioorganic & medicinal chemistry letters 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31227343
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the degradation of low density lipoprotein receptor (LDLR). Anti-PCSK9 agents have been approved for the treatment of hypercholesterolemia. We recently discovered a series of small-molecule PCSK9 modulators that contains a relatively small pharmacophore of 2,3'-diindolylmethane with molecular weights around only 250. These molecules can significantly lower the amount of PCSK9 protein in a cell-based phenotypic assay. Our SAR studies yielded compound 16 with a IC50-value of 200nM. No obvious cytotoxicity was observed at concentrations below 50microM.

[11] *Bekkering S, Stiekema LCA, Bernelot Moens S et al.* **Treatment with Statins Does Not Revert Trained Immunity in Patients with Familial Hypercholesterolemia**. Cell Metab 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31204280
ABSTRACT
Individuals with elevated LDL-cholesterol levels have an increased risk for cardiovascular disease. Despite lipid lowering strategies, however, a significant cardiovascular risk remains. Bekkering et al. show that monocytes from patients with familial hypercholesterolemia have a trained immunity phenotype and that lipid lowering with statins does not revert this pro-inflammatory phenotype.

[12] *Piqueras Ruiz S, Parra Virto A, Torres do Rego A et al.* **Transient ischaemic attack after spacing the dose of alirocumab: Is it advisable to reduce the doses of PCSK9 inhibitors with very low LDL-cholesterols?** Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221533

ABSTRACT

Inhibitors of the protein PCSK9, available since 2015, are capable of reducing the concentration of low density lipoprotein cholesterol by 40 to 70%, thus reducing the cardiovascular risk. The present case reports an adverse cardiovascular event that appeared when spacing out the administration of lipid-lowering treatment. A discussion will be presented on the importance of maintaining low cholesterol levels in order to achieve a greater benefit, according to the latest published clinical studies.

[13] *Kosuma P, Jedsadayanmata A*. **Prevalence and Predictors of Statin Treatment Among Patients With Chronic Heart Failure at a Tertiary-Care Center in Thailand**. Clinical Medicine Insights. Cardiology 2019; 13:1179546819855656.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31217695

ABSTRACT

Background: Statins play important roles in the prevention of atherosclerotic vascular diseases; however, their beneficial effects in patients with chronic heart failure (CHF) are uncertain. This study aimed to investigate the prevalence and predictors of treatment with statins to better understand their prescribing patterns in CHF patients. Methods: We conducted a cross-sectional study in patients with first-time diagnoses of CHF receiving care in the outpatient clinics affiliated with a tertiary-care teaching hospital in Thailand. Data were retrieved from electronic claims database. Multivariable logistic regression was used to identify independent predictors of treatment with statins. Results: A total of 3445 patients were included in this study. Among them, 1908 (55.4%) were prescribed statins, with most of them (89.7%) receiving simvastatin 20 mg daily. Factors independently associated with the statin treatment include the following: being male (odds ratio [OR] = 1.21, 95% confidence interval [CI] = 1.02-1.44, P = .03); diagnoses of dyslipidemia (OR = 4.88, 95% CI = 3.88-6.14, P < .001), ischemic heart disease (OR = 2.71, 95% CI = 2.18-3.36, P < .001), diabetes (OR = 1.95, 95% CI = 1.55-2.46, P < .001), or cerebrovascular disease (OR = 1.64, 95% CI = 1.12-2.40, P = .01); and receipt of angiotensin-converting enzyme inhibitors (OR = 3.44, 95% CI = 2.87-4.13, P < .001), aspirin (OR = 2.79, 95% CI = 2.30-3.40, P < .001), non-dihydropyridine calcium channel blockers (OR = 2.35, 95% CI = 1.30-4.24, P = .004), organic nitrates (OR = 2.04, 95% CI = 1.16-3.58, P = .01), beta-blockers (OR = 1.51, 95% CI = 1.23-1.84, P < .001), and digoxin (OR = 0.65, 95% CI = 0.50-0.86, P = .002). Conclusions: Statins were prescribed to more than half of the newly diagnosed CHF patients. Independent predictors of statin treatments include hypercholesterolemia and comorbidities indicative of high atherosclerotic vascular risk as well as drugs recommended as cardiovascular protective therapy for CHF patients.

[14] *Dalgic Y, Abaci O, Kocas C et al.* **The relationship between protein convertase subtilisin kexin type-9 levels and extent of coronary artery disease in patients with non-ST-elevation myocardial infarction**. Coronary artery disease 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31206403

ABSTRACT

BACKGROUND: Cardiovascular disease is one of the leading causes of death worldwide. According to the results of various studies, protein convertase subtilisin kexin type-9 (PCSK9)

was determined as a novel risk factor for stable coronary artery disease. Few studies have investigated the relationship between PCSK9 levels and the severity of coronary artery disease in patients with acute coronary syndrome; thus, we herein aimed to investigate this relationship in patients with non-ST-elevation myocardial infarction (NSTEMI) who underwent coronary angiography. PATIENTS AND METHODS: Herein, 168 patients with NSTEMI were prospectively enrolled, and severity of atherosclerotic lesions was determined using SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX), Gensini and Jeopardy scores. Plasma PCSK9 levels, lipid parameters and C-reactive protein levels were measured after a 12-h fasting period. The relationship of PCSK9 levels and clinical and laboratory parameters of patients with their SYNTAX, Gensini and Jeopardy scores was investigated. RESULTS: Pearson correlation analysis showed a strong positive correlation between PCSK9 and the three scores ($P<0.001$, $r>0.5$ for all). In ROC analysis, a mid-high SYNTAX score of at least 25 was predicted with a sensitivity of 81% and a specificity of 63% when the PCSK9 level was higher than 52.8 ng/ml (area under a curve 0.76, $P<0.001$). Multivariate linear regression analysis revealed that PCSK9, low-density lipoprotein cholesterol and creatinine levels were independent predictors of a high SYNTAX score. CONCLUSION: Taken together, high PCSK9 levels may be a risk factor for adverse events in patients with NSTEMI. Aggressive lipid-lowering therapies may benefit this group of patients.

[15] *Rogers AJ, Guan J, Trtchounian A et al.* **Association of Elevated Plasma Interleukin 18 Level With Increased Mortality in a Clinical Trial of Statin Treatment for Acute Respiratory Distress Syndrome**. Critical care medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31206358
ABSTRACT
OBJECTIVE: A high plasma level of inflammasome mediator interleukin-18 was associated with mortality in observational acute respiratory distress syndrome cohorts. Statin exposure increases both inflammasome activation and lung injury in mouse models. We tested whether randomization to statin therapy correlated with increased interleukin-18 in the ARDS Network Statins for Acutely Injured Lungs from Sepsis trial. DESIGN: Retrospective analysis of randomized controlled clinical trial. SETTING: Multicenter North American clinical trial, the ARDS Network Statins for Acutely Injured Lungs from Sepsis. PATIENTS: Six hundred eighty-three subjects with infection-related acute respiratory distress syndrome, representing 92% of the original trial population. INTERVENTIONS: Random assignment of rosuvastatin or placebo for up to 28 days or 3 days after ICU discharge. MEASUREMENTS AND MAIN RESULTS: We measured plasma interleukin-18 levels in all Statins for Acutely Injured Lungs from Sepsis patients with sample available at day 0 (baseline, n = 683) and day 3 (after randomization, n = 588). We tested the association among interleukin-18 level at baseline, rising interleukin-18, and the impact of statin therapy on 60-day mortality, adjusting for severity of illness. Baseline plasma interleukin-18 level greater than or equal to 800 pg/mL was highly associated with 60-day mortality, with a hazard of death of 2.3 (95% CI, 1.7-3.1). Rising plasma interleukin-18 was also associated with increased mortality. For each unit increase in log2 (interleukin-18) at day 3 compared with baseline, the hazard of death increased by 2.3 (95% CI, 1.5-3.5). Subjects randomized to statin were significantly more likely to experience a rise in plasma interleukin-18 levels. Subjects with acute kidney injury, shock, low baseline interleukin-18, and those not

receiving systemic corticosteroids were more likely to experience rising interleukin-18. Randomization to statin therapy was associated with rising in interleukin-18 in all of those subsets, however. CONCLUSIONS: Elevated baseline plasma interleukin-18 was associated with higher mortality in sepsis-induced acute respiratory distress syndrome. A rise in plasma interleukin-18 was also associated with increased mortality and was more common in subjects randomized to statin therapy in this clinical trial.

[16] *Miyoshi T, Osawa K, Ichikawa K et al.* **Emerging Role of Coronary Computed Tomography Angiography in Lipid-Lowering Therapy: a Bridge to Image-Guided Personalized Medicine**. Current cardiology reports 2019; 21:72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31228004
ABSTRACT
PURPOSE OF REVIEW: To summarize the current status of coronary computed tomography angiography (CTA) in the assessment of coronary plaques and discuss the ability of serial coronary CTA to quantitatively measure changes in the plaque burden in response to lipid-lowering therapy. RECENT FINDINGS: Recent advances in coronary CTA have allowed identification of high-risk coronary features in acute coronary syndrome and measurement of changes in the coronary plaque burden with good reproducibility. Statin therapy may delay plaque progression and change some plaque features. However, the clinical relevance of quantitative changes in coronary plaques and the optimal methods to reduce the plaque burden remain unclear. Despite guideline-directed lipid-lowering therapy, adverse events still occur in substantial numbers of patients receiving statins. Coronary CTA is noninvasive and has high diagnostic performance in patients with coronary artery disease, making change in the plaque burden an applicable biomarker for individualized assessment of future risk.

[17] *Stein R, Ferrari F, Scolari F*. **Genetics, Dyslipidemia, and Cardiovascular Disease: New Insights**. Current cardiology reports 2019; 21:68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31227920
ABSTRACT
PURPOSE OF REVIEW: The cardiovascular (CV) risk related to lipid disorders is well established and is based on a robust body of evidence from well-designed randomized clinical trials, as well as prospective observational studies. In the last two decades, significant advances have been made in understanding the genetic basis of dyslipidemias. The present review is intended as a comprehensive discussion of current knowledge about the genetics and pathophysiology of disorders that predispose to dyslipidemia. We also focus on issues related to statins and the proprotein convertase subtilisin/kexin type 9 (PCSK9) and some of its polymorphisms, as well as new cholesterol-lowering medications, including PCSK9 inhibitors. RECENT FINDING: Cholesterol is essential for the proper functioning of several body systems. However, dyslipidemia-especially elevated low-density lipoprotein (LDL-c) and triglyceride levels, as well as reduced lipoprotein lipase activity-is associated with an increased risk of coronary artery disease (CAD). High-density lipoprotein (HDL-c), however, seems to play a role as a risk marker rather than as a causal factor of the disease, as suggested by Mendelian randomization studies. Several polymorphisms in the lipoprotein lipase locus have been described and are associated with variations in the activity of this enzyme, producing high concentrations of triglycerides and

increased risk of CAD. Dyslipidemia, especially increased LDL-c and triglyceride levels, continues to play a significant role in CV risk. The combination of genetic testing and counseling is important in the management of patients with dyslipidemia of genetic etiology. Strategies focused on primary prevention can offer an opportunity to reduce CV events.

[18] *van den Hoogen IJ, van Rosendael AR, Lin FY et al.* **Coronary Computed Tomography Angiography as a Gatekeeper to Coronary Revascularization: Emphasizing Atherosclerosis Findings Beyond Stenosis**. Current cardiovascular imaging reports 2019; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31217835
ABSTRACT
Purpose of Review: Coronary computed tomography angiography (CCTA) is the optimal non-invasive test to rule out coronary artery disease (CAD). Decisions to perform coronary revascularization have traditionally been based upon ischemia testing. This review summarizes the latest observations and trials evaluating the suitability of CCTA to select patients for invasive coronary angiography (ICA) and subsequent revascularization. Recent Findings: Recent data shows that beyond stenosis, whole-heart quantification and characterization of coronary atherosclerotic plaque improves the estimation of myocardial ischemia. This comprehensive evaluation of the coronary artery tree has greater diagnostic accuracy for invasive fractional flow reserve (FFR) than conventional stress tests. Further, clinical trials have demonstrated that the performance of CCTA in patients with a clinical indication for ICA results in more effective patient care and significantly lower costs. Summary: Besides the excellent ability to rule out CAD, recent data shows that quantification and characterization of the coronary artery tree results in high accuracy for ischemia and that CCTA-guided care to select patients for ICA and revascularization is effective. Trials evaluating revascularization based on CCTA findings may be needed.

[19] *Abbaspour N, Roberts T, Hooshmand S et al.* **Effect of Mixed Nut Consumption on Cardiovascular Disease Risk Factors in Overweight and Obese Adults (OR19-05-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31224278
ABSTRACT
Objectives: Emerging research indicates that nuts are a source of compounds that promote cardioprotective benefits. However, most studies have assessed the effect of single nuts rather than a mixture containing a variety of nuts. Therefore, the objective of this study is to examine the effect of mixed nuts on cardiovascular disease risk factors including inflammation, glucose, insulin, antioxidant capacity, and liver function. Methods: In an 8-week randomized controlled trial, 48 participants (19 female and 29 male, 18-54 years) were equally divided into groups that consumed isocaloric (250 kcal) amounts of pretzels (69g) or mixed nuts (42.5g) for 8 weeks. Serum lipids, inflammatory biomarkers, oxidative stress, antioxidant capacity, antioxidant enzymes, and markers of liver function were measured at baseline and 4 weeks and 8 weeks after intervention. Results: Significant decreases were detected for body weight (P = 0.013) and BMI (P = 0.022), but only within the nut group. Nut consumption reduced glucose (P = 0.040) and insulin (P = 0.032) concentrations after 4 and 8 weeks, respectively; whereas, pretzel intake increased triglycerides (P = 0.048) between week 4 to week 8. While total cholesterol did not

change, HDL-C (P = 0.044) dropped and LDL-C (P = 0.038) increased from baseline to week 4 of pretzel consumption with no significant changes in the nut group. Among liver function biomarkers, alkaline phosphatase exhibited a reducing trend from baseline to week 8 of nut ingestion and lactate dehydrogenase decreased significantly from baseline and week 4 to week 8 (P < 0.01), while it increased within the pretzel group at week 8 compared to baseline (P = 0.018). Conclusions: Our results suggest that the incorporation of mixed-nuts into the diet improves body weight, some liver and cardiac functions, and maintains total cholesterol, triglyceride, HDL-C, and LDL-C levels in comparison to a refined snack food. Future research should determine whether nuts impact cardiovascular disease outcomes. Funding Sources: American Heart Association (16GRNT31360007).

[20] *Gadowski A, Nanayakkara N, Heritier S et al.* **Association Between Dietary Intake and Lipid-lowering Therapy: Prospective Analysis Using a Quantile Regression Approach (OR22-03-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31224960
ABSTRACT
Objectives: Lipid-lowering therapy (LLT) is ideally accompanied by dietary guidance for cardiovascular risk reduction, however current evidence suggests sub optimal dietary behaviours in those on pharmacological interventions. This study examines associations between daily intake of major food groups (vegetable, fruit, cereal, protein and dairy) and LLT use in Australian adults. Methods: Data were analysed from 5895 participants of the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) aged >/= 25 years. Medical history and dietary intake was obtained at baseline (1999-00) and follow up (2004-05). LLT use was categorised as: LLT users, commenced LLT, ceased LLT, and non-users. The association between dietary intake and LLT use was examined using quantile regression, at the 25th, 50th and 75th quantile of dietary intake. Analysis was adjusted for known risk factors. Results: A total of 446 participants remained on LLT from baseline to follow up; 565 participants commenced LLT; 71 participants ceased LLT and 4813 were non-users. Less than 1% of the cohort met recommended intakes of all food groups at baseline and follow up, with no difference by LLT status. Median daily dietary intake at follow up among LLT users was 2.2 serves of vegetables, 1.4 serves of fruit, 2.8 serves of cereal, 2.0 serves of protein and 1.4 serves of dairy. Dietary intake was similar across all LLT groups. LLT use was not significantly associated with dietary intake at the 25th, 50th and 75th quantile. Conclusions: Adjusted quantile regression analysis showed no differences in median daily intake of key food groups in LLT users, compared to non-users. The dietary behaviours observed suggest that all adults, regardless of their medication regimen, need additional education on improving their dietary intake. These findings emphasise the importance of addressing adherence to dietary guidelines, for people with chronic disease, with special focus on people requiring LLT. Funding Sources: Nil. Supporting Tables Images and/or Graphs:

[21] *Hoong JSY, Chew WS, Torta F et al.* **Plasma Sphingolipids and Subclinical Atherosclerosis - Novel Associations Uncovered by a Large-scale Lipidomic Analysis (P18-129-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31223704
ABSTRACT

Objectives: Sphingolipids (SP) are a diverse class of heterogenous lipids that includes ceramides, sphingomyelins, and glycosphingolipids. Many SPs have diverse roles in cell functions including cell growth, inflammation and angiogenesis, and previous studies suggest that SPs may also be involved in the pathogenesis of cardiovascular diseases. We aimed to identify plasma SPs and subsequently evaluate associations between plasma SPs and subclinical atherosclerosis in a subset of the Multiethnic Cohort of Singapore with the goal of uncovering novel biomarkers predictive of heart disease. Methods: We conducted a lipidomics evaluation of 103 molecularly-distinct SPs in the plasma of 559 Singaporeans aged 50 years and above using electrospray ionization mass spectrometry coupled with liquid chromatography. All participants did not have a history of diabetes, heart disease, stroke or cancer at baseline, and completed a detailed health screening that evaluated risk factors for cardiovascular disease including computed tomography scans of the abdomen and coronary arteries. Multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between SPs and subclinical atherosclerosis (defined as coronary artery calcium score >/= 100). Results: Ceramides (Cer), particularly those with a d16:1 or d18:1 backbone, were directly associated with higher risk of subclinical atherosclerosis whereas a small number of monohexosylceramides (MHCer), dihexosylceramides (DHCer) and sphingomyelins (SM) with a d18:2 sphingoid backbone were inversely associated. However most associations were attenuated after adjusting for conventional cardiovascular risk factors, including blood lipid (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) concentrations and glycemic markers, suggesting that the associations may be mediated by these risk factors. Conclusions: High-throughput lipidomics may uncover novel sphingolipids predictive of heart disease. Characterization of these lipid species could provide insights into disease etiology. Funding Sources: This work was supported by the National University Health System and the National Research Foundation Investigatorship grant. Supporting Tables Images and/or Graphs:

[22] *Ma C, Gurol ME, Huang Z et al.* **Low-density Lipoprotein Cholesterol and Risk of Intracerebral Hemorrhage: A Prospective Study, Systematic Review, and Meta-analysis (P18-029-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31225126
ABSTRACT
Objectives: To prospectively examine the association between low density lipoprotein cholesterol (LDL-C) concentrations and intracerebral hemorrhage (ICH) risk, and test the association in a meta-analysis combining the present data with previous studies. Methods: The current cohort study included 96,043 participants (mean age 51.3 y), free of stroke, myocardial infarction, and cancer at baseline (2006). Serum LDL-C concentrations were assessed in 2006, 2008, 2010 and 2012. Cumulative average LDL-C concentrations were calculated from all available LDL-C data during that period. Incident ICH was confirmed by review of medical records. Results: We identified 753 incident ICH cases during 9 years of follow-up. The ICH risk was similar among participants with LDL concentrations of 70-99 mg/dL and those with LDL-C concentrations >/=100 mg/dL. In contrast, participants with LDL-C concentrations less than 70 mg/dL had a significantly higher risk of developing ICH than those with LDL-C concentrations of 70-99 mg/dL -adjusted HR 1.65 (95%CI, 1.32 to 2.05) for LDL-C concentrations of 50-69 mg/dL

and 2.69 (95%CI, 2.03 to 3.57) for LDL-C concentrations of <50 mg/dL. In the meta-analysis of 11 prospective studies, the pooled HRs of hemorrhagic stroke for per 10 mg/dL decrement in LDL-C was 1.03 (95% CI, 1.01 to 1.06). Conclusions: We observed a significant association between lower LDL-C and higher risk of ICH when LDL-C concentrations <70 mg/dL, and the risk decreased to a non-significance level and stabilized when LDL-C >/=70 mg/dL. These data can help determination of ideal LDL range in patients who are at increased risk of both atherosclerotic disease and hemorrhagic stroke and also guide planning of future lipid lowering studies. Funding Sources: Supported by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. Supporting Tables Images and/or Graphs:

[23] *Meng L, Wang Y, Li T, Szeto IM*. **"Vegetable, Fruit and Cereal" Dietary Pattern in Chinese Children Aged 3-12 Years Old: Is It Associated with Dietary Protein and Micronutrient Inadequacy? (P18-104-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31225159
ABSTRACT
Objectives: To identify the dietary pattern and to investigate the association between dietary pattern with dietary protein and micronutrient inadequacy among Chinese children, using a national representative data. Methods: A total of 1484 children aged 3-12 years from the 2011 China Health and Nutrition Survey (CHNS) were included for analysis. Dietary nutrients intake were assessed based on three 24-h recall periods. Overall micronutrient inadequacy (OMI) was defined as having a mean adequacy ratio (MAR) below 0.75, where MAR was calculated as the sum of each nutrient adequacy ratio divided by the number of involved nutrients. Nutrient inadequacy was defined as the proportion of individuals whose nutrient intake was less than the estimated average requirement. Dietary patterns were derived using factor analysis with a principal component method. The logistic regression model was employed to explore the association of nutrient inadequacy with tertile categories of standardized dietary pattern score. Results: A "vegetable, fruit and cereal" (VFC) dietary pattern, characterized by high consumption of vegetables, fruits and cereals, was identified. With VFC dietary pattern score increasing, the prevalence of inadequacy of protein, vitamin A, thiamine, riboflavin, vitamin C, niacin, calcium, iron, zinc, selenium, phosphorus, magnesium and OMI was decreasing ($P < 0.01$). After adjustment confounders of age, gender, urbanization level and daily energy intake, the VFC pattern was significantly negatively associated with involved dietary nutrient inadequacy except calcium, with the odds ratio (OR) ranging from 0.10 to 0.36 for the medium tertile and 0.02 to 0.18 for the upper tertile, with the lower tertile as the reference group. Conclusions: This study indicates that a "vegetable, fruit and cereal" dietary pattern are negatively associated with inadequacy of protein and micronutrients in Chinese children. Funding Sources: This research received no external funding. The datasets we used are based on the online resources, which are open to the public for free. Supporting Tables Images and/or Graphs:

[24] *Qiao T, Duan N, Cheng G*. **Development of a Dietary Index to Assess Overall Diet Quality for Chinese Adults: The Chinese Adults Dietary Index (P18-089-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31224628

ABSTRACT
Objectives: To develop a Chinese Adults Dietary Index (CADI) based on current Chinese dietary guideline (2016), Chinese dietary reference intakes (2013) and existing scientific evidence and to apply it to assess the overall dietary among Chinese adults. Methods: Dietary data were obtained using 24-hour dietary recalls among 932 adults aged 18 to 70 years between 2013 and 2014. Potential confounders were also collected. The Chinese Adults Dietary Index included 17 components, which incorporated foods/food groups (grains, red meat, white meat, nuts, vegetables, fruits, dairy and dairy products, soybeans, drinking water, alcohol, SSBs, dietary variety) nutrients (dietary fiber, fatty acids, calcium, magnesium) and energy balance. The Chinese Adults Dietary Index was designed as a continuous scoring system and the range of possible CADI score was 0 to 170, with a higher score indicating better diet quality. The Pearson or Spearman correlation were used to assess the correlations between the total CADI score and age, body mass index (BMI) and nutrient adequacy ratios to test the association between CADI scores and significant indicators of diet quality. A stepwise multiple regression analysis of the data was performed to explored that if socioeconomic factors were correlated with the CADI scores. Results: The means, 25th and 75th percentiles of CADI score was 91.0, 78.5 and 102.6 points, respectively. Scores for red meat, white meat, nuts, dairy and dairy products and soybeans were much lower (<3 points), reflecting excessive consumption of red meat and insufficient consumption of white meat, nuts, dairy and dairy products and soybeans. The CADI score of women was higher than that of men ($P < 0.0001$). Significant and positive correlations of CADI with the majority of nutrient adequacy ratios (energy, protein, vitamin A, vitamin C, vitamin E, thiamin, riboflavin, niacin, potassium, iron, zinc, phosphorous, copper, selenium) were observed (Pearson or Spearman correlation coefficients ranging from 0.11 to 0.56). which indicated increasing CADI scores reflected higher overall diet quality. Age, educational level and smoking status were correlated with Chinese Adults Dietary Index. Conclusions: The findings indicate that the Chinese Adults Dietary Index is capable of recognizing differences in Chinese diet, therefore, it can be used to assess overall diet quality among Chinese adults. Diet quality needs to be improved among Chinese adults. Funding Sources: This study was supported by a research grant from the National Natural Science Foundation of China (81,673,158). Supporting Tables Images and/or Graphs:

[25] *So J, Wu D, Lichtenstein A, Lamon-Fava S*. **Docosahexaenoic Acid and Eicosapentaenoic Acid Supplementation Differentially Modulate Pro- and Anti-inflammatory Cytokines in Subjects with Chronic Inflammation (OR29-02-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31225033

ABSTRACT
Objectives: Despite extensive works on the cardioprotective effects of fish oil containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the distinct mechanisms by which DHA and EPA modulate inflammation and plasma lipids are not well characterized. We compared the effects of DHA and EPA supplementation on serum cytokines and blood monocyte inflammatory response and on blood lipids in subjects with chronic inflammation. Methods: Twenty-one subjects (9 men and 12 women, 50-75 y) with chronic inflammation (CRP > 2 microg/mL) were enrolled in a randomized, controlled crossover trial consisting of a 4-week lead-in control phase (high oleic sunflower oil, 3 g/d) followed by two sequential 10-week

supplementation phases with pure DHA or EPA (3 g/d each) with a 10-week washout in between. Serum concentrations of cytokines were determined by electrochemiluminescence (ECL) assay. Following lipopolysaccharides (LPS) stimulation of blood monocytes, gene expression and secretion of cytokines were assessed by qPCR and ECL. Plasma lipid concentrations were measured by enzymatic assays. Results: Relative to the control phase, DHA reduced the LPS-induced gene expression of pro-inflammatory TNFA (median % change: -45%, $P < 0.001$), IL6 (-51%, $P < 0.05$), MCP1 (-28%, $P < 0.04$) as well as anti-inflammatory IL10 (-33%, $P < 0.02$) and the secretion of TNF-alpha (-41%, $P < 0.02$), MCP-1 (-29%, $P < 0.01$), and IL-10 (-47%, $P < 0.05$) in monocytes. On the other hand, EPA increased serum concentrations of IL-10 (+14%, $P < 0.05$) and lowered only TNFAexpression (-20%, $P < 0.03$) in monocytes. When compared to EPA supplementation, DHA decreased serum concentrations of MCP-1 ($P < 0.03$), and monocyte MCP-1 secretion ($P < 0.05$) and IL10 expression ($P < 0.04$). Regarding plasma concentrations of lipids, relative to the control phase, both DHA (-16%, $P < 0.001$) and EPA decreased triglycerides (-22%, $P < 0.001$) while only DHA increased LDL-cholesterol (+7%, $P < 0.02$). Conclusions: DHA and EPA differently modulate the balance between pro- and anti-inflammatory cytokines in serum and blood monocytes in subjects with chronic inflammation. While DHA inhibits a broad range of pro- and anti-inflammatory cytokines, EPA has a relatively minor role in lowering pro-inflammatory cytokines but preserves the anti-inflammatory IL-10. DHA, but not EPA, increases LDL-cholesterol. Funding Sources: Funded by USDA/NIFA.

[26] *Solano-Aguilar G, Shao J, Urban J, Jr. et al.* **Dietary Patterns Differentially Affect Microbiome Composition and Function in a Porcine Model of Obesity-related Metabolic Disorder (OR23-04-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31223764

ABSTRACT

Objectives: To determine the impact of two isocaloric diets containing (38% ,15% and 47% energy from fat, protein and carbohydrate, respectively): Western diet (WD) rich in saturated fat, refined carbohydrate, low in fiber and high in cholesterol, and a heart healthy diet (HHD) rich in unsaturated fat, unrefined carbohydrate, fruits/vegetables, high in fiber and low in cholesterol, on the composition and function of the gut microbiome. Methods: Thirty-Ossabaw pigs were fed WD or HHD diets with half within each group therapeutically treated with statin (atorvastatin [Lipitor]). The fecal microbiome was analyzed one and six months after dietary intervention by 16S rRNA sequencing and metagenomic function was empirically inferred. Results: Genus diversity was transiently affected with a reduced Shannon Diversity index one month after feeding the WD or HHD (FDR $P < 0.05$) with no change between groups at 6 months. Bacterial communities were clustered and separated by diet independent of gender and separated by treatment with statin in the HHD only. Verrucomicrobiaceae (Akkermansia) and Methanobacteriales (Methanobrevibacter) were increased in pigs as early as one month after feeding the HHD, as was Clostridiales and Bifidobacterium (associated with optimal intestinal health). There was an enrichment of Proteobacteria (Succinivibrionaceae, Desulfovibrionaceae) in pigs fed the WD. Additional members of the Firmicutes phylum were detected. Diet-dependent associations (all $P < 0.05$) were identified between Lachnospiraceae members and early host dyslipidemia, inflammation, and atheromatous lesions in the left anterior descending proximal (LAD) and LAD/Left circumflex (LCX) bifurcation six months post-

intervention. Conclusions: These data document for the first time a distinctive bacterial profile in Ossabaw pigs with a diet-induced dyslipidemia and early stage atherosclerosis. Taken together these results represent a new model to examine mechanistic pathways of dietary patterns and/or drug interactions and its effect on modulating microbiome in developing atherosclerosis. Funding Sources: USDA project 8040-51530-056-00 and Inter Agency USDA Agreement 588-1950-9-001 between BHNRC and Jean Mayer USDA-HNRCA.

[27] *Tyagi S, Toteja GS, Bhatia N*. **Maternal Dietary Intake During Pregnancy and Its Association with Size of Offspring at Birth and One Year of Age (P11-031-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31224136
ABSTRACT
Objectives: In resource poor countries like India pregnant women are prone to inadequate dietary intake which causes macronutrient and micronutrient deficiencies and consequently leads to low-birth weight infants with higher risks of morbidity and mortality. Present study was planned with the following objectives: To assess dietary intake of pregnant women during third trimester.To correlate maternal dietary intake with size of infants at birth and at one year of age. Methods: This longitudinal study was carried out among slum population of Delhi. Dietary intake data was obtained from 144 pregnant women during pregnancy (gestational age > 28 weeks) using 24 hr recall and Food Frequency Questionnaire (FFQ) method. Pregnant women were followed upto delivery and birth size (weight, length, head circumference and MUAC) of infants was measured within 72 hours of birth. Infants were followed quarterly upto one year of age for anthropometric measurements. For statistical analysis One Way ANOVA and Pearson correlation coefficient methods were used. Results: Food consumption data revealed that average consumption of all food groups was lower than the Recommended Dietary Intake (RDI) and percentage adequacy was poor for cereals (96.25%), pulses (51.3%), green leafy vegetables (24.4%), other vegetables (42.5%), fruits (34.8%) and milk and milk products (36.9%).Median intake for all the nutrients was also found lower than Recommended Dietary Allowances (RDA). Percentage adequacy was alsopoor for energy (70.4%), protein (61.0%), thiamine (70.8%), riboflavin (28.6%), niacin (54.9%), B6 (41.6%), folates (35.1%), ascorbic acid (99.4%), retinol (16.2%), calcium (33.6%), iron (28.6%), magnesium (90.1%), and zinc (57.8%).Maternal food group intake and nutrient intake during pregnancy were found significantly correlated with weight, length and MUAC of infants at birth but not at 12 months of age. Even though birth weight and weight at 12 months increased consistently with increase in maternal energy and protein adequacy, this association was not significant at 12 months of age. Conclusions: Dietary intake of pregnant women was lower than the recommended dietary intake among slum population of Delhi. Maternal dietary intake was found significantly associated with size of infants at birth. Funding Sources: Indian Council Of Medical Research, New Delhi, India.

[28] *Walker M, Xanthakis V, Ma J et al.* **A Mediterranean Style Diet Is Favorably Associated with Concentrations of Circulating Ceramides and Ceramide Ratios in the Framingham Offspring Cohort (P18-048-19)**. Current developments in nutrition 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31224021
ABSTRACT

Literature update week 24 (2019)

Objectives: A Mediterranean style diet may impact cardiometabolic health by modifying concentrations of circulating lipid species. Distinct circulating ceramide species are positively associated with cardiometabolic risk; whereas, ratios of very-long to long-chain ceramides demonstrate an inverse association. We evaluated the relation between consuming a Mediterranean-style diet with concentrations of three circulating ceramides and ceramide ratios. Methods: Participants of the Framingham Offspring cohort who attended exam cycle 8 (n = 2174, mean age 67 years, 55% women) were categorized according to quartile of a Mediterranean-style diet score (MDS). The MDS consisted of 9 components (vegetables, fruits, nuts, legumes, whole grains, fish, red meat, monounsaturated to saturated fat ratio, and alcohol). For each component, scores in each exam cycle were based on sex-specific consumption quartiles. A higher score represents greater conformity, with a maximum score of 25. We determined the cumulative MDS, reflective of usual intake over 14 years (mean of exam cycles 5 and 8). Plasma ceramide concentrations (ug/mL) were assayed at exam 8 using a validated LC-MS/MS protocol. Multivariable linear regression was used to relate the MDS to circulating ceramide concentrations (C16:0, C22:0, and C24:0), and to ceramide ratios (C22:0/C16:0 and C24:0/C16:0) adjusting for age, sex, smoking status, lipid-lowering medications, total energy intake, physical activity, and BMI. Results: The median (IQR) MDS within each quartile was Q1: 7.5 (2.0), Q2: 11.0 (1.5), Q3: 13.5 (1), and Q4: 17.0 (3.0). A higher cumulative MDS was inversely associated with concentrations of the C16:0 (LS mean [95% CI] microg/mL; Q1: 0.169 [0.166, 0.172], Q4: 0.158 [0.155, 0.161]) and C22:0 (Q1: 0.628 [0.612, 0.643], Q4: 0.594 [0.579, 0.610]) ceramides (both Ptrend < 0.05, across quartiles). In contrast, a higher cumulative MDS was positively associated with the C24:0/C16:0 ratio (Q1: 13.41 [13.13, 13.70], Q4: 14.60 [14.33, 14.88]; Ptrend < 0.05). Associations between the MDS score and concentrations of the C24:0 ceramide and the C22:0/C16:0 ratio were not statistically significant. Conclusions: This cross-sectional study provides insight into how a Mediterranean style diet may favorably influence distinct ceramide species and ceramide ratios. Funding Sources: NIH Multidisciplinary Training Program in Cardiovascular Epidemiology, NIH National Heart Lung and Blood Institute (NHLBI) Framingham Heart Study, and the U.S. Department of Agriculture, Agricultural Research Service. Supporting Tables Images and/or Graphs:

[29] *Aznaouridis K, Masoura C, Vlachopoulos C, Tousoulis D*. **Statins in stroke**. Curr Med Chem 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31218948
ABSTRACT
A narrative review of current evidence regarding the effect of statins in stroke management. Electronic searches of MEDLINE, EMBASE and Cochrane Databases was performed. Results: In primary prevention of stroke in patients with risk factors but no established cardiovascular disease, potent statins such as atorvastatin and rosuvastatin have shown some benefit, but the clinical relevance of this effect is questionable. In populations at higher risk of stroke, such as patients with established coronary heart disease, the majority of relevant studies have shown a beneficial effect of statins in preventing stroke. Similarly, in patients with a previous cerebrovascular event, there is a clear benefit of statins for prevention of recurrent events. Use of statins is not associated with an increased risk of intracranial bleeding in primary prevention studies. There may be an increased incidence of non-fatal hemorrhagic stroke with high dose

statins in patients with a previous cerebrovascular event. Patients who experience a stroke while on statins should clearly not discontinue statins. In addition, statins are associated with better survival and improved functional outcome when administered during the acute phase of stroke in statin-naive patients. In contrast, statins do not confer any benefit in patients with acute ischemic stroke who receive thrombolysis. Conclusion: Treatment with statins prevents ischemic stroke, especially in patients with high cardiovascular risk and established atherosclerotic disease. It seems that both lipid lowering and pleiotropic effects contribute to these effects.

[30] *Soran H, Ho JH, Adam S, Durrington PN*. **Non-HDL cholesterol should not generally replace LDL cholesterol in the management of hyperlipidaemia**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31219837
ABSTRACT
PURPOSE OF REVIEW: Non-HDL cholesterol was originally conceived as a therapeutic target for statin treatment in hypertriglyceridaemia when apolipoprotein B100 assays were not widely available. Recently non-HDL cholesterol has been recommended to replace LDL cholesterol in the clinical management of dyslipidaemia routinely in general medical practice. This is misguided. RECENT FINDINGS: Non-HDL cholesterol is heterogeneous, constituting a mixture of triglyceride-rich VLDL, intermediate density lipoprotein and LDL in which small dense LDL is poorly represented and to which VLDL cholesterol contributes increasingly as triglyceride levels rise. This makes it unsuitable as a goal of lipid-lowering treatment or as an arbiter of who should receive such treatment. Results of trials designed to lower LDL cholesterol are not easily translated to non-HDL cholesterol. Fasting is no longer thought essential for screening the general population for raised LDL cholesterol. ApoB100 measurement also does not require fasting even in rarer more extreme lipoprotein disorders encountered in the Lipid Clinic, provides greater precision and specificity and overcomes the problems posed by LDL and non-HDL cholesterol. It is more easily interpreted both in diagnosis and as a therapeutic goal and it includes SD-LDL. SUMMARY: If we are to discourage use of LDL cholesterol, it should be in favour of apoB100 not non-HDL cholesterol.

[31] *Milajerdi A, Larijani B, Esmaillzadeh A*. **Statins influence biomarkers of low grade inflammation in apparently healthy people or patients with chronic diseases: A systematic review and meta-analysis of randomized clinical trials**. Cytokine 2019; 123:154752.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31228727
ABSTRACT
BACKGROUND: No earlier study summarized findings on the effect of statins on inflammatory biomarkers in apparently healthy individuals or those with chronic diseases. This study was done to systematically review earlier publications on the effect of statins on serum concentrations of C-reactive protein (CRP) and Interleukin-6 (IL-6) in apparently healthy individuals or those with chronic diseases. METHODS: We searched relevant publications published up to December 2018 in PubMed, MEDLINE, SCOPUS, EMBASE, and Google Scholar databases. For this purpose, suitable MESH and non-MESH keywords were used. Randomized placebo-controlled clinical trials that examined the effect of statins on serum concentrations of CRP and IL-6 in apparently healthy adults or those with chronic diseases were included.

RESULTS: Overall, 18 studies with 23 effect sizes, that enrolled 32,156 individuals (38% female and 62% male; mean age: 44.79years) were included. When we combined 21 effect sizes from 16 studies, we observed a significant reduction in circulating levels of CRP following administration of statins [Weighted Mean Difference (WMD): -0.80; 95% CI: -1.05, -0.56]. Combining 12 effect sizes from 11 studies, a significant reduction was found in serum CRP concentrations following administration of Atorvastatin (WMD: -0.57; 95% CI: -0.78, -0.35). Pooling 5 effect sizes from 2 studies, we found a significant reduction in serum concentrations of CRP following administration of Simvastatin (WMD: -0.29; 95% CI: -0.49, -0.10; I(2)=88.5%). Combining 6 effect sizes from 5 studies, we found a significant reduction in serum IL-6 concentrations after Atorvastatin therapy (WMD: -2.13; 95% CI: -3.96, -0.30; I(2)=98.6%). CONCLUSIONS: In conclusion, we found that statins administration in apparently healthy people or those with chronic diseases help reducing serum CRP concentrations. In addition, Atorvastatin administration resulted in reduced serum IL-6 concentrations in these people.

[32] *Hilvo M, Meikle PJ, Pedersen ER et al.* **Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31209498
ABSTRACT
AIMS: Distinct ceramide lipids have been shown to predict the risk for cardiovascular disease (CVD) events, especially cardiovascular death. As phospholipids have also been linked with CVD risk, we investigated whether the combination of ceramides with phosphatidylcholines (PCs) would be synergistic in the prediction of CVD events in patients with atherosclerotic coronary heart disease in three independent cohort studies. METHODS AND RESULTS: Ceramides and PCs were analysed using liquid chromatography-mass spectrometry (LC-MS) in three studies: WECAC (The Western Norway Coronary Angiography Cohort) (N = 3789), LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) trial (N = 5991), and KAROLA (Langzeiterfolge der KARdiOLogischen Anschlussheilbehandlung) (N = 1023). A simple risk score, based on the ceramides and PCs showing the best prognostic features, was developed in the WECAC study and validated in the two other cohorts. This score was highly significant in predicting CVD mortality [multiadjusted hazard ratios (HRs; 95% confidence interval) per standard deviation were 1.44 (1.28-1.63) in WECAC, 1.47 (1.34-1.61) in the LIPID trial, and 1.69 (1.31-2.17) in KAROLA]. In addition, a combination of the risk score with high-sensitivity troponin T increased the HRs to 1.63 (1.44-1.85) and 2.04 (1.57-2.64) in WECAC and KAROLA cohorts, respectively. The C-statistics in WECAC for the risk score combined with sex and age was 0.76 for CVD death. The ceramide-phospholipid risk score showed comparable and synergistic predictive performance with previously published CVD risk models for secondary prevention. CONCLUSION: A simple ceramide- and phospholipid-based risk score can efficiently predict residual CVD event risk in patients with coronary artery disease.

[33] *Bank PCD, Swen JJ, Schaap RD et al.* **A pilot study of the implementation of pharmacogenomic pharmacist initiated pre-emptive testing in primary care**. Eur J Hum Genet 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31227807

ABSTRACT
Despite the nationwide availability of pharmacogenomic (PGx) guidelines in electronic medication surveillance systems in The Netherlands, PGx guided prescribing is still uncommon in primary care. We set out to investigate the adoption of pharmacist initiated PGx testing in primary care. Community pharmacists were offered a free PGx test covering 40 variants in 8 genes to test patients receiving an incident prescription (IRx) of a selection of 10 drugs. Results of the PGx test along with predicted phenotypes and a therapeutic recommendation based on the Dutch Pharmacogenetics Working Group (DPWG) guidelines were transferred to the pharmacist and physician. Adoption was defined as the percentage of eligible patients that received genotyping. From November 2014-July 2016, 200 patients were included with an adoption of 18.0%. Of the included patients 57.5% received an IRx for atorvastatin, 14.5% started with simvastatin and 28.0% received an IRx for amitriptyline, (es)citalopram, nortriptyline, or venlafaxine. 90% of the patients carried at least one actionable PGx test result in the selected PGx-panel. In 31.0% of the incident prescriptions a combination between a drug with a known gene-drug interaction and an actionable genotype was present and a therapeutic recommendation was provided. The provided recommendations were accepted by the clinicians in 88.7% of the patients. Pharmacist initiated implementation of PGx in primary care is feasible, and the frequency of actionable gene-drug interactions for the selected drugs is high.

[34] *Welsh J, Korda RJ, Joshy G, Banks E*. **Primary Absolute Cardiovascular Disease Risk and Prevention in Relation to Psychological Distress in the Australian Population: A Nationally Representative Cross-Sectional Study**. Frontiers in public health 2019; 7:126.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31214558

ABSTRACT
People who experience psychological distress have an elevated risk of incident cardiovascular disease (CVD). However, the extent to which traditional CVD prevention strategies could be used to reduce the CVD burden in this group is unclear because population-level data on CVD risk profiles and appropriate management of risk in relation to distress are currently not available. The aim of this study was to use nationally representative data to quantify variation in CVD risk and appropriate management of risk according to level of psychological distress in the Australian population. Data were from 2,618 participants aged 45-74 years without prior CVD who participated in the 2011-12 Australian Health Survey, a cross-sectional and nationally representative study of Australian adults. Age-and sex-adjusted prevalence of 5-year absolute risk of primary CVD (low <10%, moderate 10-15%, or high >15%), CVD risk factors, blood-pressure, and cholesterol assessments, and appropriate treatment (combined blood pressure- and lipid-lowering medication) if at high primary risk, were estimated. Prevalence ratios (PR) quantified variation in these outcomes in relation to low (Kessler-10 score: 10-<12), mild (12-<16), moderate (16-<22) and high (22-50) psychological distress, after adjusting for sociodemographic characteristics. The prevalence of high absolute risk of primary CVD for low, mild, moderate and high distress was 10.9, 12.3, 11.4, and 18.6%, respectively, and was significantly higher among participants with high compared to low distress (adjusted PR:1.62, 95%CI:1.04-2.52). The prevalence of CVD risk factors was generally higher in those with higher psychological distress. Blood pressure and cholesterol assessments were reported by the

majority of participants (>85%) but treatment of high absolute risk was low (<30%), and neither were related to psychological distress. Our findings confirm the importance of recognizing people who experience psychological distress as a high risk group and suggest that at least part of the excess burden of primary CVD events among people with high psychological distress could be reduced with an absolute risk approach to assessment and improved management of high primary CVD risk.

[35] *Schumacher JD, Kong B, Wu J et al.* **Direct and Indirect Effects of FGF15 and FGF19 on Liver Fibrosis Development**. Hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31206730
ABSTRACT
Farnesoid X receptor (FXR) induces fibroblast growth factor 15 (FGF15, human ortholog FGF19) in the gut to potently inhibit bile acid (BA) synthesis in the liver. FXR activation in hepatic stellate cells (HSCs) reduces liver fibrosis. Fgf15(-/-) mice develop attenuated liver fibrosis but the underlying mechanisms for this protection are unclear. We hypothesized that FGF15/19 functions as a profibrotic mediator or mitogen to HSCs and increased BAs in Fgf15(-/-) mice leads to enhanced FXR activation in HSCs, subsequently reducing fibrogenesis. In this study, complimentary in-vivo and in-vitro approaches were used: 1) carbon tetrachloride (CCl4)-induced liver fibrosis model in wild type (WT), Fgf15(-/-) , and Fgf15 transgenic (TG) mice with BAs levels modulated by feeding cholestyramine- or cholic acid-containing diets, 2) analysis of primary HSCs isolated from WT and Fgf15(-/-) mice, and 3) treatment of a human HSC line, LX-2, with FXR activators and/or recombinant FGF19 protein. The results showed that Fgf15(-/-) mice had lower basal collagen expression, which was increased by BA sequestration. CCl4 -induced fibrosis with similar severity in all genotypes, however, cholestyramine increased fibrosis severity only in Fgf15(-/-) mice. HSCs from Fgf15(-/-) mice showed increased FXR activity and reduced expression of profibrotic mediators. In LX-2 cells, FXR activation increased PPARgamma activity and reduced proliferation. FGF19 activated both STAT3 and JNK pathways, and reduced NFkappaB signaling without increasing fibrogenic gene expression or cell proliferation. Conclusion: FGF15/19 does not act as a direct profibrotic mediator or mitogen to HSCs in our models, and the protection against fibrosis by FGF15 deficiency may be mediated through increased BA activation of FXR in HSCs.

[36] *Pugliese G, Muscogiuri G, Barrea L et al.* **Irritable bowel syndrome: a new therapeutic target when treating obesity?** Hormones (Athens, Greece) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31228102
ABSTRACT
There is accumulating evidence showing that obesity is due not merely to increased food intake, but could have a more complex pathophysiology possibly originating from the gut. Due to its microbiological, hormonal, and nutritional aspects, the gut could represent a starting point for the treatment of weight excess. Obesity is associated with a change of microbiota composition that not only could increase the calorie extraction from food but also could create a functional derangement resulting in irritable bowel syndrome (IBS). Several mechanisms have been postulated to explain this association, such as specific foods that are poorly absorbed, i.e., carbohydrates and lipids, as well as conditions of psychological stress which could stimulate

colonic hypersensitivity giving rise to IBS symptoms. Another factor involved in this link could be the subclinical inflammation typical of obesity, characterized by the release of inflammatory mediators that can irritate intestinal nerve endings. The change of levels of some anorexigenic hormones, as well as the alterations of the gut microbiota with the reduction of the bacteroides/Firmicutes ratio, could also contribute to the pathogenesis of IBS related to obesity. Thus, the aim of this manuscript is to review the current evidence on the association between obesity and IBS while providing physiopathological hypotheses that may explain this link. Further, we will report the effect of weight loss on IBS symptoms, highlighting the importance of an accurate assessment of gut function in obese patients.

[37] *Tirronen A, Hokkanen K, Vuorio T, Yla-Herttuala S*. **Recent advances in novel therapies for lipid disorders**. Human molecular genetics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31227825
ABSTRACT
The prevalence of lipid disorders is alarmingly increasing in the Western world. They are the result of either primary causes, such as unhealthy lifestyle choices or inherited risk factors, or secondary causes like other diseases or medication. Atypical changes in the synthesis, processing and catabolism of lipoprotein particles may lead to severe hypercholesterolemia, hypertriglyceridemia or elevated Lp(a). Although cholesterol-lowering drugs are the most prescribed medications, not all patients achieve guideline recommended cholesterol levels with the current treatment options, emphasising the need for new therapies. Also, some lipid disorders do not have any treatment options but rely only on stringent dietary restriction. Patients with untreated lipid disorders carry a severe risk of cardiovascular disease, diabetes, non-alcoholic fatty liver disease and pancreatitis among others. To achieve better treatment outcome, novel selective gene expression and epigenetic targeting therapies are constantly being developed. Therapeutic innovations employing targeted RNA technology utilise small interfering RNAs, antisense oligonucleotides, long non-coding RNAs and microRNAs to regulate target protein production whereas viral gene therapy provides functional therapeutic genes and CRISPR/Cas technology relies on gene editing and transcriptional regulation. In this brief review, we will discuss the latest advances in clinical trials for novel lipid-lowering therapies and potential new targets in pre-clinical phase.

[38] *Kachroo P, Kelly RS, Mirzakhani H et al.* **Fish oil supplementation during pregnancy is protective against asthma/wheeze in offspring**. The journal of allergy and clinical immunology. In practice 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31226448
ABSTRACT

[39] *Benn M, Tybjaerg-Hansen A, Nordestgaard BG*. **Low LDL Cholesterol by PCSK9 Variation Reduces Cardiovascular Mortality**. Journal of the American College of Cardiology 2019; 73:3102-3114.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221259
ABSTRACT

BACKGROUND: Reduced low-density lipoprotein (LDL) cholesterol due to inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) reduces cardiovascular events and may therefore also reduce cardiovascular and all-cause mortality. OBJECTIVES: This study tested the hypothesis that genetically low LDL cholesterol due to PCSK9 variation is causally associated with low cardiovascular and all-cause mortality in the general population. METHODS: A total of 109,566 individuals from the Copenhagen General Population Study and the Copenhagen City Heart Study were genotyped for PCSK9 R46L (rs11591147), R237W (rs148195424), I474V (rs562556), and E670G (rs505151). During a median follow-up of 10 years (range 0 to 42 years) and 1,247,225 person-years, there were 3,828 cardiovascular deaths and 16,373 deaths from any cause. Results were validated using data on 431,043 individuals from the UK Biobank. RESULTS: An increasing number of weighted PCSK9 alleles were associated with stepwise lower LDL cholesterol of up to 0.61 mmol/l (24 mg/dl; 18.2%; p for trend <0.001) and with lower cardiovascular mortality (p = 0.001), but not with lower all-cause mortality (p = 0.11). In causal, genetic analyses, a 0.5-mmol/l (19.4-mg/dl) lower LDL cholesterol was associated with risk ratios for cardiovascular and all-cause mortality of 0.79 (95% confidence interval [CI]: 0.63 to 0.99; p = 0.04) and 1.02 (95% CI: 0.94 to 1.12; p = 0.63) in the Copenhagen studies, 0.79 (95% CI: 0.58 to 1.08; p = 0.14) and 0.98 (95% CI: 0.87 to 1.10; p = 0.75) in the UK Biobank, and of 0.79 (95% CI: 0.65 to 0.95; p = 0.01) and 1.01 (95% CI: 0.94 to 1.08; p = 0.85), respectively, in studies combined. CONCLUSIONS: Genetically low LDL cholesterol due to PCSK9 variation was causally associated with low risk of cardiovascular mortality, but not with low all-cause mortality in the general population.

[40] *Schwartz GG, Taylor MRG*. **PCSK9 Function and Cardiovascular Death: The Knot Tightens**. Journal of the American College of Cardiology 2019; 73:3115-3117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221260
ABSTRACT

[41] *Shekari A, Forouzannia SK, Davarpasand T et al.* **Comparison of the effect of 80 vs 40 mg atorvastatin in patients with isolated coronary artery bypass graft surgery: A randomized clinical trial**. Journal of cardiac surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31212365
ABSTRACT
OBJECTIVES: Atorvastatin can decrease cardiac injury after coronary artery bypass graft (CABG) surgery. We compared the effects of 80 and 40 mg of atorvastatin per day on the levels of cardiac troponin T (cTnT) and creatine kinase-MB (CK-MB) after an isolated CABG. METHODS: This randomized single-blind parallel clinical trial enrolled 125 patients (mean age = 60.59 +/- 8.37 years) who were candidates for elective isolated CABG at the Tehran Heart Center between May 2017 and December 2017. Patients were randomly allocated into two groups to receive either 80 mg (n = 62) or 40 mg of atorvastatin (n = 63) per day, 5 days before surgery. The levels of cTnT and CK-MB, used as myocardial injury markers, were measured at baseline and then at 8 and 24 hours after CABG. RESULTS: The levels of CK-MB and cTnT at baseline and at 8 and 24 hours following CABG were not significantly different between the two groups. Our repeated measures analysis of variance showed that the levels of CK-MB and cTnT increased significantly over time (P < .001). No significant interaction was observed between time and the

atorvastatin dosage on the levels of either CK-MB (P = .159) or cTnT (P = .646). In addition, the between-group effects were not significant for CK-MB (P = .632) and cTnT (P = .126). CONCLUSION: The higher dose of atorvastatin (80 mg) did not exert a more protective effect than the standard dose of atorvastatin (40 mg) after CABG surgery.

[42] *Lalwani ND, Hanselman JC, MacDougal DE et al.* **Complementary low-density lipoprotein-cholesterol lowering and pharmacokinetics of adding bempedoic acid (ETC-1002) to high-dose atorvastatin background therapy in hypercholesterolemic patients: A randomized placebo-controlled trial**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31202641
ABSTRACT
BACKGROUND: Bempedoic acid is an oral, once-daily, first-in-class medication being developed to treat hypercholesterolemia. OBJECTIVE: The aim of the study was to assess the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of bempedoic acid added to stable high-intensity atorvastatin background therapy and multiple-dose plasma pharmacokinetics of atorvastatin alone and combined with steady-state bempedoic acid. METHODS: This was a phase 2 study in patients with hypercholesterolemia (NCT02659397). Patients received once-daily open-label atorvastatin 80 mg for 4 weeks then were randomized 2:1 at baseline to receive double-blind bempedoic acid 180 mg (n = 45) or placebo (n = 23) plus open-label atorvastatin 80 mg for 4 weeks. Efficacy was assessed 4 weeks after randomization. Atorvastatin and metabolites' steady-state levels were analyzed before first dosing with bempedoic acid and after 2 weeks of treatment. RESULTS: The 4-week stabilization phase with 80 mg atorvastatin resulted in approximately 40% lowering of LDL-C values from screening. The placebo-adjusted least squares mean lowering of LDL-C from baseline to Day 29 with bempedoic acid was 22% (P = .003). Placebo-adjusted reductions from baseline with bempedoic acid also were significant for total cholesterol (-10%; P = .014), non-high-density lipoprotein cholesterol (-13%; P = .015), apolipoprotein B (-15%; P = .004), and high-sensitivity C-reactive protein (-44%; P = .002). Point estimates of bempedoic acid effects on steady-state atorvastatin and ortho-hydroxy atorvastatin area under the curve were <30% and not clinically meaningful. CONCLUSIONS: Bempedoic acid 180 mg added to stable high-dose atorvastatin therapy effectively lowers LDL-C in patients with hypercholesterolemia without causing clinically important increases in atorvastatin exposure.

[43] *Barclay J, McCollum B, Schoretsanitis G, de Leon J*. **Gemfibrozil May Decrease Norclozapine Elimination: A Case Report**. Journal of clinical psychopharmacology 2019; 39:405-407.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31205191
ABSTRACT

[44] *Jena PK, Sheng L, McNeil K et al.* **Long-term Western diet intake leads to dysregulated bile acid signaling and dermatitis with Th2 and Th17 pathway features in mice**. Journal of dermatological science 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31213388
ABSTRACT

BACKGROUND: Dietary interventions are implicated in the development of atopic dermatitis, psoriasis, and acne. OBJECTIVE: To investigate the effect of diet and the bile acid (BA) receptors, such as TGR5 (Takeda G protein receptor 5) and S1PR2 (sphingosine-1-phosphate receptor 2) in the development of dermatitis. METHODS: C57BL/6 mice were fed a control diet (CD) or Western diet (WD) since weaning until they were 10 months old followed by analyzing histology, gene expression, and BA profiling. RESULTS: Mice developed dermatitis as they aged and the incidence was higher in females than males. Additionally, WD intake substantially increased the incidence of dermatitis. Cutaneous antimicrobial peptide genesS100A8, S100A9, and Defb4 were reduced in WD-fed mice, but increased when mice developed skin lesions. In addition, Tgr5 and TGR5-regulated Dio2 and Nos3 were reduced in WD intake but induced in dermatitic lesions. Trpa1 and Trpv1, which mediate itch, were also increased in dermatitic lesions. The expression of S1pr2 and genes encoding sphingosine kinases, S1P phosphatases, binding protein, and transporter were all reduced by WD intake but elevated in dermatitic lesions. Furthermore, dermatitis development increased total cutaneous BA with an altered profile, which may change TGR5 and S1PR2 activity. Moreover, supplementation with BA sequestrant cholestyramine reduced epidermal thickening as well as cutaneous inflammatory cytokines. CONCLUSION: In summary, activation of TGR5 and S1PR2, which regulate itch, keratinocyte proliferation, metabolism, and inflammation, may contribute to WD-exacerbated dermatitis with Th2 and Th17 features. In addition, elevated total BA play a significant role in inducing dermatitis and cutaneous inflammation.

[45] *Karatug Kacar A, Yildirim M, Bolkent S, Oztay F*. **The effects of atorvastatin on the kidney injury in mice with pulmonary fibrosis**. The Journal of pharmacy and pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31215034
ABSTRACT
OBJECTIVES: The present study investigated the effects of atorvastatin on kidney injury in mice with pulmonary fibrosis (PF). METHODS: Adult mice were divided into four groups: mice treated with intratracheal bleomycin (I) and their controls (II), and mice treated with atorvastatin for 10 days after 7 days from bleomycin treatment (III) and their controls (IV). Mice were dissected on the 21st day. KEY FINDINGS: Mononuclear cell infiltrations, injured proximal tubule epithelium and p-c-Jun level increased, while cell proliferation and the levels of p-SMAD2, ELK1, p-ELK1, p-ATF2 and c-Jun decreased in the kidney tissue of mice with PF. The atorvastatin treatments to mice with PF resulted in significant increases at the TGF-beta activation, cell proliferation and kidney damage and decreases in the levels of p-SMAD2, p-ELK1, p-ATF2 and p-c-Jun, but not change the p-SMAD3, ELK1 and ATF2 in kidneys. CONCLUSIONS: The depletion of MAPK signals, rather than SMAD signalling, is effective in kidney damage of mice with PF. Atorvastatin did not regress kidney damage in these mice, whereas it increases the kidney injury. The c-Jun-mediated JNK signals could help kidney repair through cell proliferation. The treatment time and doses of atorvastatin should be optimized for regression of kidney damage.

[46] *Akhmedzhanov NM, Vezikova NN, Voevoda MI et al.* **[Improvement of outcomes in patients with recent acute coronary syndrome: the place of PCSK9 inhibitors. The Resolution of National Advisory Board]**. Kardiologiia 2019; 59:58-64.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221076

ABSTRACT
On April 9, 2018, the national advisory board "Improvement of outcomes in patients with recent ACS: the place of PCSK9 inhibitors" was held in Moscow. Leading Russian experts in the field of atherosclerosis and lipid-lowering treatment attended the board. The purpose of the Board was to determine the place of PCSK9 inhibitors in the improvement of outcomes in patients with recent (less than 1 year) acute coronary syndrome (ACS). During the Board, three major aspects of lipid-lowering treatment were discussed: 1) issues in reaching the target levels of LDL cholesterol in real clinical practice among patients with recent ACS; 2) the results of ODYSSEY OUTCOMES study and their role in the improvement of outcomes in patients with recent ACS; 3) treatment with PCSK9 inhibitors in the management of patients with recent (less than 1 year) ACS in everyday clinical practice, the role of lipid centers.

[47] *Dyadyk AI, Kugler TE, Zborowskyy SR, Suliman YV*. **[Statin-associated muscle symptoms: epidemiology, risk factors, mechanisms and treatment]**. Kardiologiia 2019; 59:4-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221071

ABSTRACT
Statins are widely prescribed and the risk of adverse drug reactions of lipid-lowering therapy is actively discussed, including muscle symptoms. This review synthesizes the knowledge about the clinical aspects of statin-associated muscle symptoms, which is important for the practitioner. Potential mechanisms of their development, risk factors, clinical manifestations, treatment and prevention are described. Timely detection the side effects of statins makes it possible to diagnose and eliminate, which is crucial for conducting lipid-lowering therapy for patients with atherosclerotic cardiovascular diseases. Management of statin-associated muscle symptoms requires altering (reduced dosages, use of another statin or alternative lipid-lowering drugs) or discontinuing the statin treatment.

[48] *Kobalava JD, Gurevich VS, Galyavich AM et al.* **[Possibilities of clinical use of ezetimibe Otrio (JSC "AKRIKHIN", Russia) in patients with high and very high cardiovascular risk who have not reached the target values of lipid metabolism. Conclusion of the Board of experts]**. Kardiologiia 2019; 59:47-57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221075

ABSTRACT
This Conclusion of the Board of experts is devoted to the analysis of the evidence base, the position in modern clinical guidelines, the efficacy and safety analysis as well as the options of combined therapy with statins and ezetimibe (Otrio, JSC "AKRIKHIN") in various categories of patients in routine clinical practice in theRussian Federation. Cardiovascular diseases (CVD) continue to lead in the structure of morbidity and mortality inRussia. Hypercholesterolemia is one of the main modifiable risk factors for CVD. Administration of HMGCo-A-reductase inhibitors (statins) remains the basis for the prevention and treatment of the main complications of atherosclerosis, but the achievement of target levels of LDL-C on of statin monotherapy in Russian practice among different categories of risk does not exceed 50%. Proportion of patients (up to 12%) does not tolerate statin therapy, which requires the search for alternative therapies. To optimize the control of the level of LDL-C, combination therapy with statins and ezetimibe is used. Ezetimibe is an effective lipid-lowering drug, an inhibitor of

intestinal absorption of cholesterol, which was investigated in many international and Russian studies, the results of which have demonstrated good tolerability, safety and efficacy (reduction of LDL-C levels by 18% in monotherapy). It was noted that the combined therapy with low/medium doses of statins and ezetimibe effectively reduces the level of LDL-C by 44-53%, which is comparable to the effect of high doses of statins and reduces CV risk in patients with CKD and ACS. Otrio (INN Ezetimib) tablets 10 mg (JSC "AKRIKHIN",Russia) has demonstrated bioequivalence to the original drug Ezetrol tablets 10 mg (Schering-plough Labo N. V,Belgium). Broad use of a new generic product Otrio in combination with different statins will significantly increase the frequency of achievement of target lipid levels in patients with high and very high CV risk, including patients with chronic renal failure, type 2 diabetes and in patients with high hypercholesterolemia (LDL-C > 5 mmol/l) and, ultimately, reduce the burden of CV disease and mortality in Russia.

[49] *Zykov MV*. **[The problem of safety of lipid-lowering therapy]**. Kardiologiia 2019; 59:13-26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31221072

ABSTRACT

This study focused on analysis of current publications evaluating safety of lipid-lowering therapy. Search for literature was performed on websites of cardiological societies and online databases, including PubMed, EMBASE, and eLibrary by the following key words: statins, statin intolerance, lipid-lowering therapy, statin safety, and statin small a, Cyrillicdverse effects. The focus is on statins, in view of the fact that they are the most commonly prescribed, highly effective and safe drugs for primary and secondary cardiovascular prophylaxis. This review consistently summarized information about myopathies, hepatic and renal dysfunction, potentiation of DM, and other possible adverse effects of lipid-lowering therapy. The author concluded that despite the high safety of statins acknowledged by all international cardiological societies, practicing doctors still continue unreasonably cancel statins, exposing the patient under even greater danger. Information about the corresponding author.

[50] *Liu X, Men P, Wang B et al.* **Effect of dipeptidyl-peptidase-4 inhibitors on C-reactive protein in patients with type 2 diabetes: a systematic review and meta-analysis**. Lipids in health and disease 2019; 18:144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31208420

ABSTRACT

BACKGROUND: Dipeptidyl peptidase-4 inhibitors (DPP-4i) are emerging glucose-lowering agents through interacting with DPP-4 substrate, impact of which on systemic inflammation in type 2 diabetes mellitus (T2DM) remains unknown. This study aimed to evaluate the effect of DPP-4i on modulating serum levels of C-reactive protein (CRP) in T2DM. METHODS: PubMed, Cochrane library and Embase databases were searched. Randomized controlled trials (RCTs) with comparators were selected. A random-effects model was used for quantitative data analysis. Heterogeneity was evaluated with I(2) index. Sensitivity analysis was performed using the one-study remove approach. RESULTS: Sixteen trials with 1607 patients with T2DM were included. Pooled analysis of DPP-4i demonstrated a significant decrease in serum CRP concentrations (-0.86 mg/L, 95% CI, - 1.36 to - 0.36). No significant difference was found between DPP-4i and active comparators on serum CRP concentrations (0.64 mg/L, 95% CI, - 0.10 to 1.37). Pooled

analysis proved to be stable and credible by sensitivity analysis. In subgroup analysis, changes in serum concentrations of CRP were significantly associated with short diabetes duration (- 0.23 mg/L, 95% CI, - 0.41 to - 0.05). CONCLUSIONS: DDP-4i effectively reduced serum CRP levels and showed no stronger effect than traditional oral antidiabetic agents. International Prospective Register for Systematic Review (PROSPERO) number: CRD42017076838.

[51] *Tziomalos K, Katrini K, Papagianni M et al.* **Impaired antioxidative activity of high-density lipoprotein is associated with more severe acute ischemic stroke**. Metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31202834
ABSTRACT
BACKGROUND/AIMS: High-density lipoprotein (HDL) has important anti-atherogenic functions, including antioxidant effects. However, it is unclear whether the antioxidative activity of HDL is associated with the severity and outcome of acute ischemic stroke. We aimed to evaluate this association. METHODS: We prospectively studied 199 consecutive patients admitted with acute ischemic stroke and followed them up until discharge. We measured HDL antioxidant capacity, HDL-associated paraoxonase-1 (PON1) activity and HDL-associated myeloperoxidase (MPO) levels. Severe stroke was defined as National Institutes of Health Stroke Scale (NIHSS) at admission >/=5. Dependency was defined as modified Rankin scale at discharge between 2 and 5. RESULTS: Patients with severe stroke had lower HDL antioxidant capacity, higher MPO levels and higher MPO/PON1 ratio. Independent risk factors for severe stroke were female gender (RR 2.80, 95% CI 1.37-5.70, p=0.005), glucose levels (RR 1.01, 95% CI 1.0-1.02, p<0.01) and HDL antioxidant capacity (RR 1.03, 95% CI 1.01-1.06, p<0.05). Patients who were dependent at discharge had lower HDL antioxidant capacity, higher MPO levels and higher MPO/PON1 ratio. Independent predictors of dependency at discharge were lack of lipid-lowering treatment (RR 6.86, 95% CI 1.83-25.67, p<0.005) and NIHSS (RR 1.56, 95% CI 1.29-1.88, p<0.0001). The HDL antioxidant capacity did not differ between patients who died during hospitalization and those who were discharged. The only independent predictor of in-hospital mortality was NIHSS (RR 1.16, 95% CI 1.06-1.27, p<0.005). CONCLUSIONS: Impaired antioxidative activity of HDL is associated with more severe acute ischemic stroke and might also predict a worse functional outcome in these patients.

[52] *Hackl MT, Furnsinn C, Schuh CM et al.* **Brain leptin reduces liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis**. Nature communications 2019; 10:2717.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31222048
ABSTRACT
Hepatic steatosis develops when lipid influx and production exceed the liver's ability to utilize/export triglycerides. Obesity promotes steatosis and is characterized by leptin resistance. A role of leptin in hepatic lipid handling is highlighted by the observation that recombinant leptin reverses steatosis of hypoleptinemic patients with lipodystrophy by an unknown mechanism. Since leptin mainly functions via CNS signaling, we here examine in rats whether leptin regulates hepatic lipid flux via the brain in a series of stereotaxic infusion experiments. We demonstrate that brain leptin protects from steatosis by promoting hepatic triglyceride export and decreasing de novo lipogenesis independently of caloric intake. Leptin's anti-

steatotic effects are generated in the dorsal vagal complex, require hepatic vagal innervation, and are preserved in high-fat-diet-fed rats when the blood brain barrier is bypassed. Thus, CNS leptin protects from ectopic lipid accumulation via a brain-vagus-liver axis and may be a therapeutic strategy to ameliorate obesity-related steatosis.

[53] *Todorovska B, Caloska-Ivanova V, Dimitrova-Genadieva M et al.* **Atorvastatin in Combination with Pegylated Interferon and Ribavirin Provided High Rate of Sustained Virological Response in Patients with Genotype 3 Hepatitis C Virus**. Open access Macedonian journal of medical sciences 2019; 7:1641-1648.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31210815
ABSTRACT
BACKGROUND: Chronic hepatitis C virus infection represents a more frequent cause of liver cirrhosis and hepatocellular carcinoma. Statins, inhibit HCV replication in vitro, enhance the antiviral effect of the already known antiviral drugs and reduce their resistance. AIM: To determine the impact of additional therapy (treatment with Atorvastatin 20 mg) to the standard antiviral therapy (pegylated interferon alpha-peg-IFN alpha and ribavirin) on achieving sustained virological response (SVR). MATERIAL AND METHODS: In the study which is comparative, open-label, prospective-retrospective, 70 patients diagnosed with chronic hepatitis C virus infection who met criteria for treatment with standard antiviral therapy combined with anti-lipemic therapy (Atorvastatin 20 mg) were included. Patients in the study were divided into two groups: one group of 35 patients receiving combination therapy (Atorvastatin + peg-IFN alpha + Ribavirin) and another group of 35 patients received only standard antiviral therapy. Those parameters were followed in all patients: genotyping, quantification of the virus, histological assessment of liver inflammation and fibrosis degree (before starting treatment), the presence of steatosis, laboratory analysis: hematology, liver, lipid and carbohydrate status, insulin blood level (the calculation of HOMA-IR) and body mass index (BMI) calculation. The overall treatment of the patients depends from the virus genotype, thus, patients with genotype 1 and 4 received 48 weeks standard antiviral therapy, but patients with genotypes 2 and 3 received 24 weeks of antiviral therapy. SVR was considered an undetectable level of HCV RNA levels 24 weeks after completion of antiviral therapy. The results were statistically analysed, and all results for $p < 0.05$ were considered statistically significant. RESULTS: Combination therapy leads to a slightly higher percentage of SVR (85.71%) in patients with chronic hepatitis C versus standard therapy (74.29%), but in a group of patients with genotype 3 this rate of SVR amounting to 95.83%. Combination therapy leads to significant improvement of lipid and glucose status after treatment, and in terms of side effects, there was no appearance of serious adverse events that would be a reason for discontinuation of the therapy. CONCLUSION: Combination therapy Atorvastatin + pegylated interferon alpha + Ribavirin leads to high rate of SVR of 95.83% in patients with chronic hepatitis C, genotype 3. Statins can be used safely in patients with chronic hepatitis C.

[54] *DiNicolantonio JJ, J OK*. **Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis**. Open heart 2019; 6:e001011.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31218005
ABSTRACT

[55] *Cutler RL, Torres-Robles A, Wiecek E et al.* **Pharmacist-led medication non-adherence intervention: reducing the economic burden placed on the Australian health care system**. Patient preference and adherence 2019; 13:853-862.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31213779

ABSTRACT

Background: Scarcity of prospective medication non-adherence cost measurements for the Australian population with no directly measured estimates makes determining the burden medication non-adherence places on the Australian health care system difficult. This study aims to indirectly estimate the national cost of medication non-adherence in Australia comparing the cost prior to and following a community pharmacy-led intervention. Methods: Retrospective observational study. A de-identified database of dispensing data from 20,335 patients (n=11,257 on rosuvastatin, n=6,797 on irbesartan and n=2,281 on desvenlafaxine) was analyzed and average adherence rate determined through calculation of PDC. Included patients received a pharmacist-led medication adherence intervention and had twelve months dispensing records; six months before and six months after the intervention. The national cost estimate of medication non-adherence in hypertension, dyslipidemia and depression pre- and post-intervention was determined through utilization of disease prevalence and comorbidity, non-adherence rates and per patient disease-specific adherence-related costs. Results: The total national cost of medication non-adherence across three prevalent conditions, hypertension, dyslipidemia and depression was $10.4 billion equating to $517 per adult. Following enrollment in the pharmacist-led intervention medication non-adherence costs per adult decreased $95 saving the Australian health care system and patients $1.9 billion annually. Conclusion: In the absence of a directly measured national cost of medication non-adherence, this estimate demonstrates that pharmacists are ideally placed to improve patient adherence and reduce financial burden placed on the health care system due to non-adherence. Funding of medication adherence programs should be considered by policy and decision makers to ease the current burden and improve patient health outcomes moving forward.

[56] *Elsayed I, El-Dahmy RM, Elshafeey AH et al.* **Tripling the Bioavailability of Rosuvastatin Calcium Through Development and Optimization of an In-Situ Forming Nanovesicular System**. Pharmaceutics 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31212660

ABSTRACT

In situ forming nanovesicular systems (IFNs) were prepared and optimized to improve Rosuvastatin calcium (RC) oral bioavailability through increasing its solubility and dissolution rate. The IFN was composed of Tween((R)) 80 (T80), cetyl alcohol (CA), in addition to mannitol or Aerosil 200. A single simple step was adopted for preparation, then the prepared formulations were investigated by analyzing their particle size (PS), polydispersity index (PDI), Zeta potential (ZP), entrapment efficiency (EE), and flowability properties. D-optimal design was applied to choose the optimized formulations. The maximum desirability values were 0.754 and 0.478 for the optimized formulations containing 0.05 g CA, 0.18 g T80, and 0.5 g mannitol (OFM) or Aerosil (OFA), respectively. In vitro drug release from the optimized formulations showed a significantly faster dissolution rate when compared to the market product. In vivo

performance of the optimized formulations in rabbits was investigated after filling them into enteric-coated capsules. Ultimately, OFA formulation achieved a 3 times increase in RC oral bioavailability in comparison with the market product, supporting the hypothesis of considering IFNs as promising nanocarriers able to boost the bioavailability of BCS class II drugs.

[57] *Herrera-Gomez F, Chimeno MM, Martin-Garcia D et al.* **Cholesterol-Lowering Treatment in Chronic Kidney Disease: Multistage Pairwise and Network Meta-Analyses**. Scientific reports 2019; 9:8951.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31222137
ABSTRACT
Pairwise and network meta-analyses on the relationship between the efficacy of the use of statins with or without ezetimibe and reductions in low-density lipoprotein cholesterol (LDLc) and C-reactive protein (CRP) in patients with chronic kidney disease (CKD) are presented. In the pairwise meta-analysis, statins with or without ezetimibe were shown to be efficacious in reducing major adverse cardiovascular events (MACE) in patients with CKD and an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m(2), in the context of both primary prevention [odds ratio (OR)/95% confidence interval (95% CI)/I(2)/number of studies (n): 0.50/0.40-0.64/0%/6] and primary/secondary prevention (0.66/0.57-0.76/57%/18). However, in the Bayesian network meta-analysis, compared to the placebo, only atorvastatin 80 mg daily and atorvastatin and rosuvastatin at doses equivalent to simvastatin 20 mg daily reduced the odds of MACEs in this patient population. The network meta-analysis for LDLc and CRP treatment objectives also showed that, regardless of eGFR and excluding dialysis patients, the number of MACEs decreased in patients with CKD, with reductions in both LDLc and CRP of less than 50% (surface under the cumulative ranking (SUCRA)/heterogeneity (vague)/n: 0.77/0.14/3). The evaluation of the benefits of drugs may lead to individualized therapy for CKD patients: Cholesterol-lowering treatment for CKD patients with high levels of both LDLc and CRP is suggested.

[58] *Seshadri S, Rapaka N, Prajapati B et al.* **Statins exacerbate glucose intolerance and hyperglycemia in a high sucrose fed rodent model**. Scientific reports 2019; 9:8825.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31217552
ABSTRACT
Statins are first-line therapy drugs for cholesterol lowering. While they are highly effective at lowering cholesterol, they have propensity to induce hyperglycemia in patients. Only limited studies have been reported which studied the impact of statins on (a) whether they can worsen glucose tolerance in a high sucrose fed animal model and (b) if so, what could be the molecular mechanism. We designed studies using high sucrose fed animals to explore the above questions. The high sucrose fed animals were treated with atorvastatin and simvastatin, the two most prescribed statins. We examined the effects of statins on hyperglycemia, glucose tolerance, fatty acid accumulation and insulin signaling. We found that chronic treatment with atorvastatin made the animals hyperglycemic and glucose intolerant in comparison with diet alone. Treatment with both statins lead to fatty acid accumulation and inhibition of insulin signaling in the muscle tissue at multiple points in the pathway.

[59] *Dressel A, Schmidt B, Schmidt N et al.* **Cost effectiveness of lifelong therapy with PCSK9 inhibitors for lowering cardiovascular events in patients with stable coronary artery disease: Insights from the Ludwigshafen Risk and Cardiovascular Health cohort**. Vascular pharmacology 2019:106566.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31207358

ABSTRACT
Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) reduce cardiovascular events in coronary artery disease (CAD). Their costs exceed that of established oral lipid-lowering agents. Previous cost-effectiveness assessments have been inconsistent. Markov cohort state transitions models for stable CAD patients were calculated using information from 1530 participants of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) with known causes of deaths. Non-fatal to fatal event rates, drug prices, direct treatment costs, and utility weights were from public sources. At an assumed relative risk reduction of 32.5% and an annual drug price of 8500 Euros, QALYs gained were 1.23 and 1.20, savings were 2390 and 2410 Euros, and ICERs were 112,530 and 108,660 Euros in women and men, respectively. When the annual cost of this medication was set at 1600 Euros, corresponding ICERs were 21,180 and 20,450 Euros. PCSK9i treatment is cost-effective in stable CAD at a threshold of 150,000 Euro and annual costs of 8500 Euros. As the broad use of PCSK9i therapy in CAD would have a disruptive impact on the healthcare budget, treatment should be focused on very high risk patients (>/=3 comorbidities, annual risk of 10%); alternatively, and for lower risk, significant cost reductions would be needed.