Literature update week 17 (2019)

[1] *Farajzadeh MA, Yadeghari A, Abbaspour M*. **Dispersive Solid Phase Extraction Using Magnetic Nanoparticles Performed in a Narrow-Bored Tube for Extraction of Atorvastatin, Losartan, and Valsartan in Plasma**. Advanced pharmaceutical bulletin 2019; 9:138-146.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31011568

ABSTRACT

Purpose: In this investigation, a new version of magnetic solid phase extraction (MSPE) performed in a narrow-bore tube has been proposed. In this study, hydrophobic octyl (C8) functionalized Fe3O4 magnetic nanoparticles (MNPs) stabilized by SiOH groups (Fe3O4@SiO2@C8) are used as magnetic nano-sorbents for the extraction of cardiovascular drugs from human plasma prior to their determination by high performance liquid chromatography-photodiode array detection. Methods: After precipitation of the plasma proteins, the supernatant is diluted with deionized water and filled into the narrow-bore tube. Then mg-level of the sorbent is added into the tube. The sorbent is dispersed and moved down through the solution instead of passing the solution from the cartridge. Using an external magnet, the collected nano-sorbents at the bottom of the tube are transferred on top of the solution and released to move down through the solution for three times to increase the extraction efficiency. Results: The linearity of the assay was ranging from 0.4-500 mg mL(-1). The limits of detection and quantification of the method were obtained in the ranges of 0.05-0.07 and 0.16-0.24 mg L(-1), respectively. The extraction recoveries were obtained in the range of 31-49%. Intra- and inter-day precisions were calculated and obtained in the ranges of 5-8 and 7%-9% for 0.5 mg L(-1) of each analyte, and 5-6 and 6%-8% for 2 mg L(-1) of each analyte, respectively. Conclusion: The proposed method was successfully used in determination of the studied drugs in patient's plasmas.

[2] *Miao H, Yang Y, Wang H et al.* **Intensive Lipid-Lowering Therapy Ameliorates Asymptomatic Intracranial Atherosclerosis**. Aging and disease 2019; 10:258-266.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31011477

ABSTRACT

Statins have proven to exert protective effects in patients with symptomatic intracranial atherosclerotic stenosis (SICAS). It is unclear whether intensive lipid-lowering therapy (ILLT) can ameliorate atherosclerosis in asymptomatic ICAS (AICAS). A single-center, prospective cohort study was performed in 71 AICAS patients with lipid-lowering therapy. Vascular stenoses were evaluated with transcranial color-coded sonography (TCCS) before and after statin treatment. With target therapeutic level of low-density lipoprotein cholesterol (LDL-C) </= 1.8 mmol/L or >/= 50% reduction from baseline after the two years of follow-up, patients were divided into intensive statin treatment (IST) group and standard statin treatment (SST) group. A total of 104 stenotic intracranial arteries were detected in 51 patients belonging to the IST group and 47 arteries in 20 patients of the SST group. In the first year, LDL-C levels were significantly decreased in the IST compared with SST groups (1.48 +/- 0.26 vs. 2.20 +/- 0.58, P=0.000). However, the ratio of regressed ICAS in IST was not significantly higher than that in SST (26.3% vs. 5.9%, P=0.052). Forty-nine branches in 25 patients of the IST group and 16 branches in 7 patients of the SST group were followed up for two years. The LDL-C level was decreased in the IST compared with SST groups (1.55 +/- 0.29 vs. 2.36 +/- 0.77, P=0.048). The ratio of regressed ICAS in the IST group was significantly higher than that in SST group (34.7% vs. 6.3%, P=0.017).

We concluded that the degree of stenosis in AICAS can be ameliorated with intensive lipid-lowering therapy within two years; target LDL-C level can be reached by moderate-intensity statin treatment for Chinese AICAS patients.

[3] *Ostermann AI, West AL, Schoenfeld K et al.* **Plasma oxylipins respond in a linear dose-response manner with increased intake of EPA and DHA: results from a randomized controlled trial in healthy humans**. The American journal of clinical nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006007
ABSTRACT
BACKGROUND: The health effects of long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) are partly mediated by their oxidized metabolites, i.e., eicosanoids and other oxylipins. Some intervention studies have demonstrated that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) increase systemic concentrations of n-3 PUFA-derived oxylipins and moderately decrease arachidonic acid-derived oxylipins. There is no information on the dose-response of oxylipin concentrations after n-3 PUFA intake. OBJECTIVE: The aim of this study was to quantify oxylipins in human plasma samples from an intervention study in which participants were randomly assigned to different daily intakes of EPA and DHA for 12 mo. METHODS: Healthy adult men and women with low habitual fish consumption (n = 121) were randomly assigned to receive capsules providing doses of n-3 PUFAs reflecting 3 patterns of consumption of oily fish [1, 2, or 4 portions/wk with 3.27 g EPA + DHA (1:1.2, wt:wt) per portion] or placebo. Oxylipins were quantified in plasma after 3 and 12 mo. Relative and absolute changes of individual oxylipins were calculated and concentrations were correlated with the dose and the content of EPA and DHA in blood lipid pools. RESULTS: Seventy-three oxylipins, mostly hydroxy-, dihydroxy-, and epoxy-PUFAs, were quantified in the plasma samples. After 3 and 12 mo a linear increase with dose was observed for all EPA- and DHA-derived oxylipins. Cytochrome-P450-derived anti-inflammatory and cardioprotective epoxy-PUFAs increased linearly with n-3 PUFA dose and showed low interindividual variance ($r^2 > 0.95$). Similarly, 5, 12-, and 15-lipoxygenase-derived hydroxy-PUFAs as well as those formed autoxidatively increased linearly. These include the precursors of so-called specialized pro-resolving lipid mediators (SPMs), e.g., 17-hydroxy-DHA and 18-hydroxy-EPA. CONCLUSIONS: Plasma concentrations of biologically active oxylipins derived from n-3 PUFAs, including epoxy-PUFAs and SPM-precursors, increase linearly with elevated intake of EPA and DHA. Interindividual differences in resulting plasma concentrations are low. This trial was registered at controlled-trials.com as ISRCTN48398526.

[4] *Zhang Y, Zhang X, Zeng C et al.* **Targeted delivery of atorvastatin via asialoglycoprotein receptor (ASGPR)**. Bioorganic & medicinal chemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31005367
ABSTRACT
Targeted drug delivery platforms can increase the concentration of drugs in specific cell populations, reduce adverse effects, and hence improve the therapeutic effect of drugs. Herein, we designed two conjugates by installing the targeting ligand GalNAc (N-acetylgalactosamine) onto atorvastatin (AT). Compared to the parent drug, these two conjugates, termed G2-AT and G2-K-AT, showed increased hepatic cellular uptake. Moreover, both conjugates were able to

release atorvastatin, and consequently showed dramatic inhibition of beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA) reductase and increased LDL receptors on cell surface.

[5] *Malik VS, Vasudevan S, Wedick NM et al.* **Substituting brown rice for white rice on diabetes risk factors in India: A randomized controlled trial**. The British journal of nutrition 2019:1-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006420
ABSTRACT
ABSTRACTIndia has the second largest number of people with type 2 diabetes (T2D) globally. Epidemiological evidence indicates that consumption of white rice is positively associated with T2D risk, while intake of brown rice is inversely associated. Thus, we explored the effect of substituting brown rice for white rice on T2D risk factors among adults in urban South India. A total of 166 overweight (BMI >/= 23kg/m2) adults aged 25-65 years were enrolled in a randomized cross-over trial in Chennai, India. Interventions were a parboiled brown rice or white rice regimen providing 2 ad libitum meals/day, 6 days/week for 3 months with a 2-week wash-out. Primary outcomes were blood glucose, insulin, HbA1c, insulin resistance (HOMA-IR) and lipids. High-sensitivity C-reactive protein (hs-CRP) was a secondary outcome. We did not observe significant between-group differences for primary outcomes among all participants. However, a significant reduction in HbA1c was observed in the brown rice group among participants with metabolic syndrome (-0.18 (0.08) %) relative to those without metabolic syndrome (0.05 (0.05) %) (p-for-heterogeneity = 0.02). Improvements in HbA1c, total and LDL cholesterol were observed in the brown rice group among participants with a BMI >/= 25 compared to those with a BMI < 25 (p-for- heterogeneity < 0.05). We observed a smaller increase in hs-CRP in the brown (0.03 (2.12) mg/L) compared to white rice group (0.63 (2.35) mg/L) (p = 0.04). In conclusion, substituting brown rice for white rice showed a potential benefit on HbA1c among participants with metabolic syndrome and an elevated BMI. A small benefit on inflammation was also observed.

[6] *Liptak B, Knezl V, Gasparova Z*. **Anti-arrhythmic and cardio-protective effects of atorvastatin and a potent pyridoindole derivative on isolated hearts from rats with metabolic syndrome**. Bratislavske lekarske listy 2019; 120:200-206.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31023038
ABSTRACT
OBJECTIVES: Aims of this study were to investigate the anti-arrhythmic and cardio-protective effect of atorvastatin and of a new pyridoindole derivative (SMe1EC2) on isolated and perfused hearts while following the Langendorff principles. BACKGROUND: Metabolic syndrome is a widely distributed condition progressing to cardiovascular disease. Many of the metabolic syndrome patients take (HMG)-co-enzyme A (CoA) reductase inhibitors with potential cardio-protective effects. SMe1EC2 is a promising new drug, exerting many positive effects in experimental settings. METHODS: Rats with induced metabolic syndrome were treated with atorvastatin (25 mg/kg) and SMe1EC2 (25 mg/kg and 0.5 mg/kg, respectively) daily for 3 weeks. After the treatment, the hearts were isolated and perfused according to Langendorff. RESULTS: Both atorvastatin and SMe1EC2 improved cardiac function by elevating the left ventricular developed pressure (VLDP) and cardiac contractility. Both SMe1EC2-treated groups improved LVDP during reperfusion, significantly increased dP/dt, and moderately elevated +dP/dt values.

The treatment with both atorvastatin and SMe1EC2 (25 mg/kg) significantly reduced malignant arrhythmia in comparison to control group and group treated with SMe1EC2 0.5 mg/kg. CONCLUSIONS: Owing to its anti-arrhythmic and cardio-protective effects, atorvastatin and SMe1EC2 could be of benefit to patients suffering from metabolic syndrome (Tab. 3, Fig. 3, Ref. 41).

[7] *Lang W, Frishman WH*. **Angiopoietin-like 3 Protein Inhibition: A New Frontier in Lipid Lowering Treatment**. Cardiology in review 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31008773
ABSTRACT
Angiopoietin-like 3 protein (ANGPTL3) is an inhibitor of both lipoprotein lipase and endothelial lipase in humans. Population studies indicate a relationship between loss of function mutations in ANGPTL3 and favorable reductions in triglycerides and non-HDL cholesterol. In addition, loss of function mutations are associated with a reduced risk of coronary artery disease. While ANGPTL3's role in human lipid metabolism has yet to be fully clarified, it is unlikely that ANGPTL3 impacts cholesterol uptake via the LDL-receptor, unlike the proprotein convertase subtilisin/kexin9 inhibitors. In contrast to other forms of lipid-lowering therapy, ANGPTL3 inhibition may improve insulin sensitivity. The promise of this new therapy, particularly its independence from the LDL-receptor, has prompted the creation of a monoclonal antibody inhibitor; evinacumab. Evinacumab has shown favorable lipid-lowering action in both human and mouse models. Efficacy trials are currently ongoing and will be completed in the near future. In addition, ANGPTL3 inhibition via an antisense oligonucleotide was performed in healthy human subjects, which resulted in a dose-dependent reduction in circulating ANGPTL3 levels and an anti-atherogenic lipid profile. When tested in mouse models, administration of the antisense oligonucleotide caused a reduction in progression of atherosclerosis. Further investigation is required to evaluate the efficacy, safety and net benefit of clinical ANGPTL3 inhibition before it can be accepted into clinical practice.

[8] *Ishikawa M, Muramatsu T, Nanasato M et al.* **Associations of coronary plaque characteristics by integrated backscatter intravascular ultrasound with detectability of vessel external elastic lamina using optical frequency domain imaging in human coronary arteries: A sub-analysis of the MISTIC-1 trial**. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31025511
ABSTRACT
OBJECTIVES: We sought to examine associations between plaque characteristics by intravascular ultrasound (IVUS) and detectability of external elastic lamina (EEL) by optical frequency domain imaging (OFDI) in human coronary arteries. BACKGROUND: It is often challenging to detect EEL which represents vessel size by light-based imaging modalities due to light intensity attenuation through atherosclerotic plaque. METHODS: IVUS and OFDI prior to stent implantation were sequentially investigated per protocol. We identified corresponding cross-sections by minimum lumen area (MLA) or just distally to side branches as anatomical landmarks. Plaque characterization was determined by integrated backscatter IVUS analysis. We categorized detectable EEL arc by OFDI into four groups: 0</= and <1 quadrant (group 1),

1</= and <2 quadrants (group 2), 2</= and <3 quadrants (group 3), or 3</= and <4 quadrants (group 4). RESULTS: We prospectively studied 103 vessels in 93 patients with stable coronary artery disease. Corresponding 711 cross-sections were analyzed. Cross-sections with detectable EEL arc <2 quadrants (group 1 or 2) were observed in 86.1% of MLA sites but only in 29.3% of non-MLA sites (p < .05). Percentage plaque area (%PA) appeared to be the strongest predictor to detect EEL arc <2 quadrants with the cut-off of 60.3% (AUC 0.90; sensitivity 79.8%, specificity 85.5%). Lipid pool and calcification remained statistically significant in predicting detectable EEL arc <2 quadrants after adjustment with %PA. CONCLUSIONS: Presence of large plaque burden, lipid pool, and calcification significantly predicts the detectability of EEL by OFDI assessment. Locations with detectable EEL arc <2 quadrants should thus be avoided for optimal stent landing zone.

[9] *Wang S, Xiu J, Liao W et al.* **Relative Effect of Current Intensive Lipid-Lowering Drugs on Cardiovascular Outcomes in Secondary Prevention- A Meta-Analysis of 12 Randomized Trials**. Circulation journal : official journal of the Japanese Circulation Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006730
ABSTRACT
BACKGROUND: We aimed to investigate the comparative cardiovascular benefits of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin treatments in secondary prevention patients.Methods and Results:We selected 12 randomized controlled trials (n=131,978 patients) using PubMed and Embase (inception-June 1, 2018). Subgroup differences were explored by meta-regression and Cochran Q test. The relative effects of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin on major cardiovascular events (MACE), and revascularization were varied and decreased gradually, of which high-dose statin resulted in lower risk of MACE and revascularization than PCSK9 inhibitor-statin per 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-C): risk ratio (RR) for MACE, 0.86 (95% confidence interval (CI), 0.81-0.90) for high-dose statin, 0.90 (95% CI, 0.83-0.96) for ezetimibe-statin, and 0.94 (95% CI, 0.92-0.96) for PCSK9 inhibitor-statin; RR for revascularization, 0.84 (95% CI, 0.77-0.90) for high-dose statin, 0.91 (95% CI, 0.81-1.00) for ezetimibe-statin, and 0.94 (95% CI, 0.90-0.97) for PCSK9 inhibitor-statin. Similar relative effects of intensive lipid-lowering treatment were also observed in analyses of myocardial infarction and stroke, although no significant difference between groups was identified. CONCLUSIONS: In secondary prevention patients, the relative benefits of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin treatments were varied and decreased gradually, of which high-dose statin was significantly superior to PCSK9 inhibitor-statin for improving MACE and revascularization per 1 mmol/L reduction of LDL-C.

[10] *Parikh R, Bates JHT, Poynter ME et al.* **Pharmacokinetics of omega-3 fatty acids in patients with severe sepsis compared with healthy volunteers: A prospective cohort study**. Clinical nutrition (Edinburgh, Scotland) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31005335
ABSTRACT
BACKGROUND: Pharmacokinetics (PK) of pharmaceuticals and pharmaconutrients are poorly understood in critically ill patients, and dosing is often based on healthy subject data. This

might be particularly problematic with enteral medications due to metabolic abnormalities and impaired gastrointestinal tract absorption common in critically ill patients. Utilizing enteral fish oil, this study was undertaken to better understand and define PK of enteral omega-3 fatty acids (eicospentaenoic acid [EPA] and docosahexaenoic acid [DHA]) in critically ill patients with severe sepsis. MATERIALS AND METHODS: Healthy volunteers (n = 15) and mechanically ventilated (MV) adults with severe sepsis (n = 10) were recruited and received 9.75 g EPA and 6.75 g DHA daily in two divided enteral doses of fish oil for 7 days. Volunteers continued their normal diet without other sources of fish oil, and sepsis patients received standard enteral feeding. Blood was collected at frequent intervals during the 14-day study period. Peripheral blood mononuclear cells (PMBCs) and neutrophils were isolated and analyzed for membrane fatty acid (FA) content. Mixed linear models and t-tests were used to analyze changes in FA levels over time and FA levels at individual time points, respectively. PK parameters were obtained based on single compartment models of EPA and DHA kinetics. RESULTS: Healthy volunteers were 41.1 +/- 10.3 years; 67% were women. In patients with severe sepsis (55.6 +/- 13.4 years, 50% women), acute physiologic and chronic health evaluation (APACHE) II score was 27.2 +/- 8.8 at ICU admission and median MV duration was 10.5 days. Serum EPA and DHA were significantly lower in sepsis vs. healthy subjects over time. PBMC EPA concentrations were generally not different between groups over time, while PBMC DHA was higher in sepsis patients. Neutrophil EPA and DHA concentrations were similar between groups. The half-life of EPA in serum and neutrophils was significantly shorter in sepsis patients, whereas other half-life parameters did not vary significantly between healthy volunteers and sepsis patients. CONCLUSIONS: While incorporation of n-3 FAs into PBMC and neutrophil membranes was relatively similar between healthy volunteers and sepsis patients receiving identical high doses of fish oil for one week, serum EPA and DHA were significantly lower in sepsis patients. These findings imply that serum concentrations and EPA and DHA may not be the dominant driver of leukocyte membrane incorporation of EPA and DHA. Furthermore, lower serum EPA and DHA concentrations suggest that either these n-3 FAs were being metabolized rapidly in sepsis patients or that absorption of enteral medications and pharmaconutrients, including fish oil, may be impaired in sepsis patients. If enteral absorption is impaired, doses of enteral medications administered to critically ill patients may be suboptimal.

[11] *Sharifi M, Futema M, Nair D, Humphries SE*. **Polygenic Hypercholesterolemia and Cardiovascular Disease Risk**. Current cardiology reports 2019; 21:43.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31011892
ABSTRACT
PURPOSE OF THE REVIEW: Identification of loci and common single-nucleotide polymorphisms (SNPs) that have modest effects on plasma lipids have been used to confirm or refute the causal role of lipid traits in the development of coronary heart disease (CHD), and as tools to identify individuals with polygenic hypercholesterolemia. RECENT FINDINGS: Several groups have reported on the use of SNP scores in distinguishing individuals with a clinical diagnosis of familial hypercholesterolemia (FH) with a monogenic or polygenic etiology. We review evidence that those with monogenic FH have worse prognosis and discuss the possible mechanisms for this and their management. Individuals with a clinical phenotype of FH and a monogenic cause are at greater risk of CHD than those where no causative mutation can be found. The patients

with polygenic hypercholesterolemia would not require elaborate cascade screening or secondary care input for their management.

[12] *Bisgaard LS, Christoffersen C*. **Apolipoprotein M/sphingosine-1-phosphate: novel effects on lipids, inflammation and kidney biology**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31008738
ABSTRACT
PURPOSE OF REVIEW: In 2011, the crystal structure of apolipoprotein M (apoM) and its capacity to bind sphingosine-1-phosphate (S1P) was characterized. Since then, a variety of studies has increased our knowledge on apoM biology and functionality. From being an unknown and hardly significant player in overall metabolism, apoM has gained significant interest. RECENT FINDINGS: Key discoveries in the last 2 years have indicated that the apoM/S1P complex has important roles in lipid metabolism (affecting triglyceride turnover), inflammation (a marker of severe sepsis and potentially providing anti-inflammatory signaling) and kidney biology (potential to protect against immunoglobulin A nephropathy). SUMMARY: Several studies suggest a potential for apoM/S1P as biomarkers for inflammation, sepsis and nephropathy. Also, a novel chaperone is characterized and could have potential as a drug for treatment in inflammation and nephropathy.

[13] *Henriksbo BD, Tamrakar AK, Xu J et al.* **Statins Promote IL-1beta-Dependent Adipocyte Insulin Resistance via Lower Prenylation not Cholesterol**. Diabetes 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31010959
ABSTRACT
Statins lower cholesterol and adverse cardiovascular outcomes, but this drug class increases diabetes risk. Statins are generally anti-inflammatory. However, statins can promote inflammasome-mediated adipose tissue inflammation and insulin resistance through an unidentified immune effector. Statins lower mevalonate pathway intermediates beyond cholesterol, but it is unknown if lower cholesterol underpins statin-mediated insulin resistance. We sought to define the mevalonate pathway metabolites and immune effectors that propagate statin-induced adipose insulin resistance. We found that LDL-cholesterol lowering was dispensable, but statin-induced lowering of isoprenoids required for protein prenylation triggered NLRP3/Caspase-1 inflammasome activation and IL-1beta-dependent insulin resistance in adipose tissue. Multiple statins impaired insulin action at the level of Akt/PKB signaling in mouse adipose tissue. Providing geranylgeranyl isoprenoids or inhibiting caspase-1 prevented statin-induced defects in insulin signaling. Atorvastatin (Lipitor(TM)) impaired insulin signaling in adipose tissue from WT and IL-18(-/-) mice, but not IL-1beta(-/-) mice. Atorvastatin decreased cell-autonomous insulin-stimulated lipogenesis, but did not alter lipolysis or glucose uptake in 3T3-L1 adipocytes. Our results show that statin lowering of prenylation isoprenoids activate caspase-1/IL-1beta inflammasome responses that impair endocrine control of adipocyte lipogenesis. This may allow targeting of cholesterol-independent statin side-effects on adipose lipid handling without compromising the blood lipid/cholesterol lowering effects of statins.

Literature update week 17 (2019)

[14] *Ilhan ZE, Laniewski P, Thomas N et al.* **Deciphering the complex interplay between microbiota, HPV, inflammation and cancer through cervicovaginal metabolic profiling**. EBioMedicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31027917
ABSTRACT
BACKGROUND: Dysbiotic vaginal microbiota have been implicated as contributors to persistent HPV-mediated cervical carcinogenesis and genital inflammation with mechanisms unknown. Given that cancer is a metabolic disease, metabolic profiling of the cervicovaginal microenvironment has the potential to reveal the functional interplay between the host and microbes in HPV persistence and progression to cancer. METHODS: Our study design included HPV-negative/positive controls, women with low-grade and high-grade cervical dysplasia, or cervical cancer (n=78). Metabolic fingerprints were profiled using liquid chromatography-mass spectrometry. Vaginal microbiota and genital inflammation were analysed using 16S rRNA gene sequencing and immunoassays, respectively. We used an integrative bioinformatic pipeline to reveal host and microbe contributions to the metabolome and to comprehensively assess the link between HPV, microbiota, inflammation and cervical disease. FINDINGS: Metabolic analysis yielded 475 metabolites with known identities. Unique metabolic fingerprints discriminated patient groups from healthy controls. Three-hydroxybutyrate, eicosenoate, and oleate/vaccenate discriminated (with excellent capacity) between cancer patients versus the healthy participants. Sphingolipids, plasmalogens, and linoleate positively correlated with genital inflammation. Non-Lactobacillus dominant communities, particularly in high-grade dysplasia, perturbed amino acid and nucleotide metabolisms. Adenosine and cytosine correlated positively with Lactobacillus abundance and negatively with genital inflammation. Glycochenodeoxycholate and carnitine metabolisms connected non-Lactobacillus dominance to genital inflammation. INTERPRETATION: Cervicovaginal metabolic profiles were driven by cancer followed by genital inflammation, HPV infection, and vaginal microbiota. This study provides evidence for metabolite-driven complex host-microbe interactions as hallmarks of cervical cancer with future translational potential. FUND: Flinn Foundation (#1974), Banner Foundation Obstetrics/Gynecology, and NIH NCI (P30-CA023074).

[15] *De Cock E, Hannon H, Moerman V, Schurgers M*. **Statin-induced myopathy: a case report**. European heart journal. Case reports 2018; 2:yty130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31020206
ABSTRACT
Background: Statins are one of the most frequently used drug groups among patients with cardiovascular disease. Muscle pain is very frequent among patients using statins. It is important to distinguish patients with benign muscle pain without significant biochemical correlates from patients with serious myopathies. Case summary: We present the case of a 68-year-old woman taking atorvastatin in the past 8 months after a coronary bypass grafting, presenting with proximal muscle weakness and pain. Biochemical analysis showed a markedly elevated creatine kinase (CK) (24,159 U/L). Despite discontinuation of the statin and therapy for rhabdomyolysis (IV fluid, mannitol, and sodium bicarbonate), CK levels did not drop as much as expected. Muscle biopsy showed mild inflammatory changes and few necrotic muscle fibres, suggestive for an immune-mediated necrotizing myopathy (IMNM). Serology showed a high

anti-HMG-CoA reductase antibody (anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody) titre, diagnostic for an IMNM induced by statins. The patient was treated with corticosteroids and methotrexate. Creatine kinase levels, muscle weakness, and pain gradually improved over the following months. Discussion: IMNM induced by statins is a relatively new entity. It is important to be recognized because it is not a self-limiting adverse effect such as the frequent benign muscle pains caused by statins. Beside discontinuation of the causative statin, aggressive immunosuppressive therapy is mandatory in IMNM. Therefore, it is important to test for anti-HMGCR antibodies and if necessary perform a muscle biopsy in patients taking statins, presenting with muscle weakness, and CK elevations not improving after discontinuation of the statin.

[16] *van Broekhoven A, Krijnen PAJ, Fuijkschot WW et al.* **Short-term LPS induces Aortic Valve thickening in ApoE*3Leiden mice**. European journal of clinical investigation 2019:e13121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31013351
ABSTRACT
BACKGROUND: Recently, it was shown that 12 weeks of lipopolysacharide (LPS) administration to non-atherosclerotic mice induced thickening of the aortic heart valve (AV). Whether such effects may also occur even earlier is unknown. As most patients with AV stenosis also have atherosclerosis, we studied the short-term effect of LPS on the AVs in an atherosclerotic mouse model. METHODS: ApoE*3Leiden mice, on an atherogenic diet, were injected intra-peritoneally with either LPS or phosphate buffered saline (PBS), and sacrificed 2 or 15 days later. AVs were assessed for size, fibrosis, glycosaminoglycans (GAGs), lipids, calcium deposits, iron deposits and inflammatory cells. RESULTS: LPS-injection caused an increase in maximal leaflet thickness at 2 days (128.4 mum) compared to PBS-injected mice (67.8 mum; p=0.007), whereas at 15 days this was not significantly different. LPS-injection did not significantly affect average AV thickness on day 2 (37.8 mum), but did significantly increase average AV thickness at day 15 (41.6 mum; p=0.038) compared to PBS-injected mice (31.7 mum and 32.3 mum respectively). LPS-injection did not affect AV fibrosis, GAGs and lipid content. Furthermore, no calcium deposits were found. Iron deposits, indicative for valve hemorrhage, were observed in one AV of the PBS-injected group (a day 2 mouse; 9.1%) and in five AVs of the LPS-injected group (both day 2- and 15 mice; 29.4%). No significant differences in inflammatory cell infiltration were observed upon LPS-injection. CONCLUSION: Short-term LPS apparently has the potential to increase AV thickening and hemorrhage. These results suggest that systemic inflammation can acutely compromise AV structure.

[17] *Wang Y, Yan BP, Tomlinson B, Lee VW*. **Is lipid goal one-size-fits-all: A review of evidence for recommended low-density lipoprotein treatment targets in Asian patients**. European journal of preventive cardiology 2019:2047487319843077.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31023098
ABSTRACT
The international guideline recommendations for low-density lipoprotein cholesterol (LDL-C) lowering were made based on the results of randomized controlled trials (RCTs), meta-analyses, and observational studies mostly in the White population. It was not clear whether these LDL-C targets could be applicable to other ethnic groups, for example, Asian patients. This review

aimed to address major aspects related to the lipid goal and statin therapy in Asia, including the epidemiology of cardiovascular disease, the LDL-C profiles, the lipid goals from localized guidelines, genetics and lifestyles, and the efficacy and safety of statins. Owing to the geographic, ethnic, genetic, and cultural diversity in this region, we observed a geographic pattern of diversity in cardiovascular epidemiology and statin response in Central Asia, East Asia (particularly for Asia-Pacific region), and South Asia. The rapidly growing literature from Asian countries questioning "lower is better" hypothesis was noticed. However, owing to the nature of these dominantly observational data, the conclusion was hardly confirmative. Despite the rapid expansion of the current literature in this region, efforts should be made to ensure an adequate sample size to assess the significance of a given lipid parameter on overall cardiovascular outcomes in this Asian population.

[18] *Matsumoto H, Watanabe S, Kyo E et al.* **Standardized volumetric plaque quantification and characterization from coronary CT angiography: a head-to-head comparison with invasive intravascular ultrasound**. European radiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31028446
ABSTRACT
OBJECTIVES: We sought to evaluate the accuracy of standardized total plaque volume (TPV) measurement and low-density non-calcified plaque (LDNCP) assessment from coronary CT angiography (CTA) in comparison with intravascular ultrasound (IVUS). METHODS: We analyzed 118 plaques without extensive calcifications from 77 consecutive patients who underwent CTA prior to IVUS. CTA TPV was measured with semi-automated software comparing both scan-specific (automatically derived from scan) and fixed attenuation thresholds. From CTA, %LDNCP was calculated voxels below multiple LDNCP thresholds (30, 45, 60, 75, and 90 Hounsfield units [HU]) within the plaque. On IVUS, the lipid-rich component was identified by echo attenuation, and its size was measured using attenuation score (summed score analysis length) based on attenuation arc (1 = < 90 degrees ; 2 = 90-180 degrees ; 3 = 180-270 degrees ; 4 = 270-360 degrees) every 1 mm. RESULTS: TPV was highly correlated between CTA using scan-specific thresholds and IVUS ($r = 0.943$, $p < 0.001$), with no significant difference (2.6 mm(3), $p = 0.270$). These relationships persisted for calcification patterns (maximal IVUS calcium arc of 0 degrees , < 90 degrees , or >/= 90 degrees). The fixed thresholds underestimated TPV (- 22.0 mm(3), $p < 0.001$) and had an inferior correlation with IVUS ($p < 0.001$) compared with scan-specific thresholds. A 45-HU cutoff yielded the best diagnostic performance for identification of lipid-rich component, with an area under the curve of 0.878 vs. 0.840 for < 30 HU ($p = 0.023$), and corresponding %LDNCP resulted in the strongest correlation with the lipid-rich component size ($r = 0.691$, $p < 0.001$). CONCLUSIONS: Standardized noninvasive plaque quantification from CTA using scan-specific thresholds correlates highly with IVUS. Use of a < 45-HU threshold for LDNCP quantification improves lipid-rich plaque assessment from CTA. KEY POINTS: * Standardized scan-specific threshold-based plaque quantification from coronary CT angiography provides an accurate total plaque volume measurement compared with intravascular ultrasound. * Attenuation histogram-based low-density non-calcified plaque quantification can improve lipid-rich plaque assessment from coronary CT angiography.

[19] *Martinet W, Coornaert I, Puylaert P, De Meyer GRY*. **Macrophage Death as a Pharmacological Target in Atherosclerosis**. Frontiers in pharmacology 2019; 10:306.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31019462

ABSTRACT

Atherosclerosis is a chronic inflammatory disorder characterized by the gradual build-up of plaques within the vessel wall of middle-sized and large arteries. Over the past decades, treatment of atherosclerosis mainly focused on lowering lipid levels, which can be accomplished by the use of statins. However, some patients do not respond sufficiently to statin therapy and therefore still have a residual cardiovascular risk. This issue highlights the need for novel therapeutic strategies. As macrophages are implicated in all stages of atherosclerotic lesion development, they represent an important alternative drug target. A variety of anti-inflammatory strategies have recently emerged to treat or prevent atherosclerosis. Here, we review the canonical mechanisms of macrophage death and their impact on atherogenesis and plaque stability. Macrophage death is a prominent feature of advanced plaques and is a major contributor to necrotic core formation and plaque destabilization. Mechanisms of macrophage death in atherosclerosis include apoptosis, passive or accidental necrosis as well as secondary necrosis, a type of death that typically occurs when apoptotic cells are insufficiently cleared by neighboring cells via a phagocytic process termed efferocytosis. In addition, less-well characterized types of regulated necrosis in macrophages such as necroptosis, pyroptosis, ferroptosis, and parthanatos may occur in advanced plaques and are also discussed. Autophagy in plaque macrophages is an important survival pathway that protects against cell death, yet massive stimulation of autophagy promotes another type of death, usually referred to as autosis. Multiple lines of evidence indicate that a better insight into the different mechanisms of macrophage death, and how they mutually interact, will provide novel pharmacological strategies to resolve atherosclerosis and stabilize vulnerable, rupture-prone plaques.

[20] *Buddhari W, Uerojanaungkul P, Sriratanasathavorn C et al.* **Low-Density Lipoprotein Cholesterol Target Attainment in Patients Surviving an Acute Coronary Syndrome in Thailand: Results From the Dyslipidemia International Study (DYSIS) II**. Heart, lung & circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006593

ABSTRACT

BACKGROUND: Patients suffering an acute coronary syndrome (ACS) are at increased risk for future cardiovascular events. Effective management of hyperlipidaemia in such patients is essential. We aimed to document the use of lipid-lowering therapy (LLT) and low-density lipoprotein cholesterol (LDL-C) target achievement in patients hospitalised with an ACS in Thailand. METHODS: The Dyslipidemia International Study (DYSIS) II was a multinational, observational study that enrolled patients over 18 years of age who were hospitalised with an ACS in 2013-2014 and survived until discharge. Patients were analysed according to whether or not they were treated with LLT prior to hospital admission. A lipid profile was carried forward from blood taken within the first 24 hours after admission, and attainment of the LDL-C target of <70 mg/dL (1.8 mmol/L) for very high-risk subjects was reported. Details of LLTs were collected. Lipid levels, LLT use and cardiovascular events since discharge were collected at a follow-up interview 4 months later. RESULTS: A total of 320 ACS patients were enrolled from

seven sites across Thailand, 188 (58.8%) of whom were being treated with LLT prior to the acute event. The mean LDL-C levels of the LLT and no LLT patients were 106.2 +/- 39.4 mg/dL (2.75 +/- 1.02 mmol/L) and 139.8 +/- 46.6 mg/dL (3.62 +/- 1.21), respectively, with 15.4% and 4.5% having an LDL-C level below 70 mg/dL (1.8 mmol/L). Lipid-lowering therapy consisted mainly of statins, with an atorvastatin-equivalent daily dosage of 17 +/- 13 mg/day. At the 4-month follow-up, LDL-C target attainment remained low at 26.7% for the initial LLT group and 24.1% for the no LLT group. Although most patients were being treated with LLT at this point, the dosage was still low (28 +/- 16 mg/day) and there was little use of combination therapy. CONCLUSION: In this cohort of Thai ACS patients, LDL-C levels were highly elevated, placing them at extreme risk of recurrent adverse cardiovascular events. Lipid-lowering therapy was widely used after the ACS; however, treatment was rarely optimised. Huge improvements are required in the management of hyperlipidaemia in Thailand.

[21] *Yu PL, Wang C, Li W, Zhang FX*. **Visfatin Level and The Risk of Hypertension and Cerebrovascular Accident: A Systematic Review and Meta-Analysis**. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2019; 51:220-229.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31022738

ABSTRACT

High blood pressure is related with increased cerebrovascular accident. High visfatin / NAMPT(nicotinamide phosphoribosyltransferase) plasma levels may promote vascular inflammation and atherosclerotic plaque destabilization and have been evaluated as a marker for identifying stages of essential hypertension. However, its role in the pathogenesis of hypertension and cerebrovascular accident (CVA) is still uncertain. In order to review and meta-analyze observational studies investigating visfatin concentration and the risk for hypertension or CVA, a systematic search of PubMed, ovid EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) until December 07, 2016 was performed. After data extraction and quality assessment, a meta-analysis was performed using RevMan 5.3 and STATA 14.0. A total of 1693 adults from 8 studies for hypertension (974 with hypertension) and 1696 adults from 7 CVA studies (957 with CVA) were enrolled in the current meta-analysis. Cochran's Q-statistic and I(2) test were applied to estimate the heterogeneity of the studies. The fixed-effects were used to compute the weighted mean difference in visfatin levels. Plasma visfatin concentration was much higher in hypertension and CVA patients than in healthy individuals. These evidences suggested the association of hypertension and CVA with higher plasma visfatin level.

[22] *Borna H, Hosseini Qale Noe SH, Harchegani AB et al.* **A review on proteomics analysis to reveal biological pathways and predictive proteins in sulfur mustard exposed patients: roles of inflammation and oxidative stress**. Inhalation toxicology 2019; 31:3-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31010353

ABSTRACT

Sulfur mustard (SM) is a mutagenic compound that targets various organs. Although it causes a wide range of abnormalities, cellular and molecular mechanisms of its action are not-well-understood. Oxidation of DNA, proteins, lipids, as well as depletion of cellular nicotinamide adenine dinucleotide (NAD), antioxidants and increase of intracellular calcium are the hypothesized mechanisms of its action at the acute phase of injury. In this review, the

proteome analysis of SM toxicity has been considered. We selected articles that considered proteomics analysis of SM toxicity with two-dimensional gel electrophoresis (2DE) followed by mass spectrometry. Our search yielded nine related articles, four original in vitro and five human studies. The results of these studies have revealed a change in expression pattern of various proteins such as haptoglobin, amyloid A1, surfactant proteins, S100 proteins, apolipoprotein, Vit D binding protein, transferrin, alpha 1 antitrypsin, protein disulfide isomerase and antioxidant enzymes in patients who were exposed to SM about 30 years ago. Most of these proteins are up- or down-regulated in response to excessive production of reactive oxygen species (ROS) and oxidative stress (OS). There is a tight link between the expression pattern of these proteins with accumulation of leukocytes, inflammatory conditions, antioxidant depletion, mitochondrial deficiency, as well as increased expression or activity of several proteases such as caspases and matrix metalloproteinases (MMPs). Therefore, excessive production of ROS and OS along with chronic inflammatory may be the long-term toxic effects of SM following acute exposure.

[23] *Janic M, Lunder M, Novakovic S et al.* **Expression of Longevity Genes Induced by a Low-Dose Fluvastatin and Valsartan Combination with the Potential to Prevent/Treat "Aging-Related Disorders"**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31013989

ABSTRACT

The incidence of aging-related disorders may be decreased through strategies influencing the expression of longevity genes. Although numerous approaches have been suggested, no effective, safe, and easily applicable approach is yet available. Efficacy of low-dose fluvastatin and valsartan, separately or in combination, on the expression of the longevity genes in middle-aged males, was assessed. Stored blood samples from 130 apparently healthy middle-aged males treated with fluvastatin (10 mg daily), valsartan (20 mg daily), fluvastatin-valsartan combination (10 and 20 mg, respectively), and placebo (control) were analyzed. They were taken before and after 30 days of treatment and, additionally, five months after treatment discontinuation. The expression of the following longevity genes was assessed: SIRT1, PRKAA, KLOTHO, NFE2L2, mTOR, and NF-kappaB. Treatment with fluvastatin and valsartan in combination significantly increased the expression of SIRT1 (1.8-fold; $p < 0.0001$), PRKAA (1.5-fold; $p = 0.262$) and KLOTHO (1.7-fold; $p < 0.0001$), but not NFE2L2, mTOR and NF-kappaB. Both fluvastatin and valsartan alone significantly, but to a lesser extent, increased the expression of SIRT1, and did not influence the expression of other genes. Five months after treatment discontinuation, genes expression decreased to the basal levels. In addition, analysis with previously obtained results revealed significant correlation between SIRT1 and both increased telomerase activity and improved arterial wall characteristics. We showed that low-dose fluvastatin and valsartan, separately and in combination, substantially increase expression of SIRT1, PRKAA, and KLOTHO genes, which may be attributed to their so far unreported pleiotropic beneficial effects. This approach could be used for prevention of ageing (and longevity genes)-related disorders.

[24] *Morillo-Hernandez C, Lee JJ, English JC, 3rd*. **Research letter: Retrospective outcome analysis of 25 alopecia areata patients treated with simvastatin/ezetimibe**. Journal of the American Academy of Dermatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31015012
ABSTRACT

[25] *Lin Z, Chen R, Jiang Y et al.* **Cardiovascular Benefits of Fish-Oil Supplementation Against Fine Particulate Air Pollution in China**. Journal of the American College of Cardiology 2019; 73:2076-2085.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31023432
ABSTRACT
BACKGROUND: Few studies have evaluated the health benefits of omega-3 fatty acid supplementation against fine particulate matter (aerodynamic diameter <2.5 mum [PM2.5]) exposure in highly polluted areas. OBJECTIVES: The authors sought to evaluate whether dietary fish-oil supplementation protects cardiovascular health against PM2.5 exposure in China. METHODS: This is a randomized, double-blinded, and placebo-controlled trial among 65 healthy college students in Shanghai, China. Participants were randomly assigned to either the placebo group or the intervention group with dietary fish-oil supplementation of 2.5 g/day from September 2017 to January 2018, and received 4 rounds of health examinations in the last 2 months of treatments. Fixed-site PM2.5 concentrations on campus were measured in real time. The authors measured blood pressure and 18 biomarkers of systematic inflammation, coagulation, endothelial function, oxidative stress, antioxidant activity, cardiometabolism, and neuroendocrine stress response. Acute effects of PM2.5 on these outcomes were evaluated within each group using linear mixed-effect models. RESULTS: The average PM2.5 level was 38 mug/m(3) during the study period. Compared with the placebo group, the fish-oil group showed relatively stable levels of most biomarkers in response to changes in PM2.5 exposure. Between-group differences associated with PM2.5 exposure varied by biomarkers and by lags of exposure. The authors observed beneficial effects of fish-oil supplementation on 5 biomarkers of blood inflammation, coagulation, endothelial function, oxidative stress, and neuroendocrine stress response in the fish-oil group at a false discovery rate of <0.05. CONCLUSIONS: This trial shows that omega-3 fatty acid supplementation is associated with short-term subclinical cardiovascular benefits against PM2.5 exposure among healthy young adults in China. (Effect of Dietary Supplemental Fish Oil in Alleviating Health Hazards Associated With Air Pollution; NCT03255187).

[26] *Rajagopalan S, Brook RD*. **Fishin' Mission on Emissions**. Journal of the American College of Cardiology 2019; 73:2086-2088.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31023433
ABSTRACT

[27] *Chamberlain AM, Gong Y, Shaw KM et al.* **PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network**. Journal of the American Heart Association 2019; 8:e011246.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31020929

ABSTRACT
Background PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors effectively lower LDL (low-density lipoprotein) cholesterol and have been shown to reduce cardiovascular outcomes in high-risk patients. We used real-world electronic health record data to characterize use of PCSK9 inhibitors, in addition to standard therapies, according to cardiovascular risk status. Methods and Results Data were obtained from 18 health systems with data marts within the National Patient-Centered Clinical Research Network (PCORnet) using a common data model. Participating sites identified >17.5 million adults, of whom 3.6 million met study criteria. Patients were categorized into 3 groups: (1) dyslipidemia, (2) untreated LDL >/=130 mg/dL, and (3) coronary artery disease or coronary heart disease. Demographics, comorbidities, estimated 10-year atherosclerotic cardiovascular disease risk, and lipid-lowering pharmacotherapies were summarized for each group. Participants' average age was 62 years, 50% were female, and 11% were black. LDL cholesterol ranged from 85 to 151 mg/dL. Among patients in groups 1 and 3, 54% received standard lipid-lowering therapies and a PCSK9 inhibitor was prescribed in <1%. PCSK9 inhibitor prescribing was greatest for patients with coronary artery disease or coronary heart disease and, although prescribing increased during the study period, overall PCSK9 inhibitor prescribing was low. Conclusions We successfully used electronic health record data from 18 PCORnet data marts to identify >3.6 million patients meeting criteria for 3 patient groups. Approximately half of patients had been prescribed lipid-lowering medication, but <1% were prescribed PCSK9 inhibitors. PCSK9 inhibitor prescribing increased over time for patients with coronary artery disease or coronary heart disease but not for those with dyslipidemia.

[28] *Neeland IJ, Boone SC, Mook-Kanamori DO et al.* **Metabolomics Profiling of Visceral Adipose Tissue: Results From MESA and the NEO Study**. Journal of the American Heart Association 2019; 8:e010810.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31017036

ABSTRACT
Background Identifying associations between serum metabolites and visceral adipose tissue (VAT) could provide novel biomarkers of VAT and insights into the pathogenesis of obesity-related diseases. We aimed to discover and replicate metabolites reflecting pathways related to VAT . Methods and Results Associations between fasting serum metabolites and VAT area (by computed tomography or magnetic resonance imaging) were assessed with cross-sectional linear regression of individual-level data from participants in MESA (Multi-Ethnic Study of Atherosclerosis; discovery, N=1103) and the NEO (Netherlands Epidemiology of Obesity) study (replication, N=2537). Untargeted (1)H nuclear magnetic resonance metabolomics profiling of serum was performed in MESA, and metabolites were replicated in the NEO study using targeted (1)H nuclear magnetic resonance spectroscopy. A total of 30 590 metabolomic spectral variables were evaluated. After adjustment for age, sex, race/ethnicity, socioeconomic status, smoking, physical activity, glucose/lipid-lowering medication, and body mass index, 2104 variables representing 24 nonlipid and 49 lipid/lipoprotein subclass metabolites remained significantly associated with VAT (P=4.88x10(-20)-1.16x10(-3)). These included conventional metabolites, amino acids, acetylglycoproteins, intermediates of glucose and hepatic metabolism, organic acids, and subclasses of apolipoproteins, cholesterol, phospholipids, and

triglycerides. Metabolites mapped to 31 biochemical pathways, including amino acid substrate use/metabolism and glycolysis/gluconeogenesis. In the replication cohort, acetylglycoproteins, branched-chain amino acids, lactate, glutamine (inversely), and atherogenic lipids remained associated with VAT (P=1.90x10(-35)-8.46x10(-7)), with most associations remaining after additional adjustment for surrogates of VAT (glucose level, waist circumference, and serum triglycerides), reflecting novel independent associations. Conclusions We identified and replicated a metabolite panel associated with VAT in 2 community-based cohorts. These findings persisted after adjustment for body mass index and appear to define a metabolic signature of visceral adiposity.

[29] *Prasad M, Sara J, Widmer RJ et al.* **Triglyceride and Triglyceride/ HDL (High Density Lipoprotein) Ratio Predict Major Adverse Cardiovascular Outcomes in Women With Non-Obstructive Coronary Artery Disease**. Journal of the American Heart Association 2019; 8:e009442.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31014162
ABSTRACT
Background Women with non-obstructive coronary artery disease have increased cardiovascular morbidity. The role of risk factors in this population has yet to be established. We aimed to study the predictive effect of triglycerides and the triglyceride/high-density lipoprotein ratio on major adverse cardiovascular events (MACE) in patients with non-obstructive coronary artery disease, and to explore the role of lipid lowering therapy in modifying this risk. Methods and Results This is a prospective cohort study enrolling patients with anginal symptoms referred to the cardiac catheterization laboratory for suspected ischemia, who were subsequently diagnosed with non-obstructive coronary artery disease, defined as no stenosis >20% on angiography. All patients had baseline laboratory testing and were followed for 7.8+/-4.3 years for the development of major adverse cardiovascular events. We performed Cox proportional hazard testing to determine the effect of triglycerides on risk of major adverse cardiovascular events among men and women by baseline statin use. A total of 462 patients were included. Median age was 53 (Q1, Q3: 45, 62) years. In a Cox proportional hazard model stratified by statin use adjusting for confounders, among those not on baseline statins, triglycerides were independently predictive of major adverse cardiovascular events in women (per 50 mg/dL risk ratio: hazard ratio 1.25 [95% CI : 1.06, 1.47]; P=0.01). This was not true among men. The interaction between triglycerides and sex, and triglycerides and statin was statistically significant. Conclusions Triglyceride levels may play a key role in predicting cardiovascular-specific risk in women, and statin use may be protective. Further investigation is necessary to better delineate the role of statin use in preventing cardiovascular risk.

[30] *Vogt L, Bangalore S, Fayyad R et al.* **Atorvastatin Has a Dose-Dependent Beneficial Effect on Kidney Function and Associated Cardiovascular Outcomes: Post Hoc Analysis of 6 Double-Blind Randomized Controlled Trials**. Journal of the American Heart Association 2019; 8:e010827.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31020900
ABSTRACT

Literature update week 17 (2019)

Background Kidney function decreases during the lifetime, and this decline is a powerful predictor of both kidney and cardiovascular outcomes. Statins lower cardiovascular risk, which may relate to beneficial effects on kidney function. We studied whether atorvastatin influences kidney function decline and assessed the association between individual kidney function slopes and cardiovascular outcome. Methods and Results Data were collected from 6 large atorvastatin cardiovascular outcome trials conducted in patients not selected for having kidney disease. Slopes of serum creatinine reciprocals representing measures of kidney function change ([mg/dL](-1)/y), were analyzed in 30 621 patients. Based on treatment arms, patients were categorized into 3 groups: placebo (n=10 057), atorvastatin 10 mg daily (n=12 763), and 80 mg daily (n=7801). To assess slopes, mixed-model analyses were performed for each treatment separately, including time in years and adjustment for study. These slopes displayed linear improvement over time in all 3 groups. Slope estimates for patients randomized to placebo or atorvastatin 10 mg and 80 mg were 0.009 (0.0008), 0.011 (0.0006), and 0.014 (0.0006) (mg/dL)(-1)/y, respectively. A head-to-head comparison of atorvastatin 10 and 80 mg based on data from 1 study (TNT [Treating to New Targets]; n=10 001) showed a statistically significant difference in slope between the 2 doses (P=0.0009). From a Cox proportional hazards model using slope as a predictor, a significant (P<0.0001) negative association between kidney function and cardiovascular outcomes was found. Conclusions In patients at risk of or with cardiovascular disease, atorvastatin improved kidney function over time in a dose-dependent manner. In the 3 treatment groups, kidney function improvement was strongly associated with lower cardiovascular risk. Clinical Trial Registration URL : http://www.clinicaltrials.gov . Unique identifiers: NCT00327418; NCT00147602; NCT00327691.

[31] *Cai YY, Zhang HB, Fan CX et al.* **Renoprotective effects of brown adipose tissue activation in diabetic mice**. Journal of diabetes 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31020790
ABSTRACT
BACKGROUND: Brown adipose tissue (BAT) has been regarded as a potential target organ to combat obesity and related metabolic disorders. However, the effect of BAT activation on the development of diabetic kidney disease (DKD) remains unclear. METHODS: Diabetic mice were induced by streptozotocin (STZ) combined with high-fat diet. CL316,243, a beta3-adrenergic receptor agonist to activate BAT, was administered intraperitoneally (ip.,1mg/kg/day) to mice for 4 weeks. Blood glucose, serum lipids, adipokines, 24h-urinary albumin and 8-OH-dG, circulating microRNAs (miRNAs) and renal pathology were analyzed. We observed renal histological changes, fibrosis, inflammation and oxidative stress related genes expression. FGF21/ beta-klotho/ FGF receptor1c (FGFR1c) and AMPK/ SIRT1/PGC1alpha signaling pathway in the kidney were also analyzed. RESULTS: Treatment with CL316,243 reduced blood glucose non-significantly (20.58+/-3.55 vs 23.6+/-3.87mmol/L) but decreased TG, LDL-c and increased HDL-c level significantly. Simultaneously, activation of BAT led to significantly decreased 24h urinary albumin (34.21+/-6.28 vs 70.46+/-15.81mug/24h; P<0.05) and 8-OH-dG, improved renal fibrosis, inflammation, and oxidative stress, and ameliorated renal morphological abnormalities. In addition to obviously enhanced BAT activity, CL316,243 significantly increased serum adiponectin level and renal FGF21 sensitivity, and then reactivated renal AMPK-SIRT1-PGC1alpha signaling pathway. Furthermore, the CL316,243 treatment also increased some

circulating miRNAs and down-regulated their renal related target genes. CONCLUSIONS: Activating BAT could improve the kidney injury in diabetic mice via metabolic improvement and renal AMPK activation by beneficial adipokines and miRNAs.

[32] *Bermudez-Millan A, Wagner JA, Feinn RS et al.* **Inflammation and Stress Biomarkers Mediate the Association between Household Food Insecurity and Insulin Resistance among Latinos with Type 2 Diabetes**. The Journal of nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006809
ABSTRACT
BACKGROUND: Household food insecurity (HFI) is a stressor that is associated with type 2 diabetes (T2D). However, little is known about HFI and the insulin resistance (IR) underlying T2D, and the mechanisms involved. OBJECTIVE: We examined the cross-sectional association between HFI and IR among low-income Latinos with T2D and tested whether inflammation and stress hormones mediated this association. METHODS: HFI was measured with the 6-item US Household Food Security Survey module. IR was calculated from fasting plasma blood glucose and serum insulin. Inflammation was indicated by high-sensitivity C-reactive protein (hsCRP), and stress hormones included urinary cortisol, metanephrine, and normetanephrine. To test for an indirect effect of HFI on homeostasis model assessment of IR, a parallel multiple mediation model was run with biological markers that significantly differed between food security status-entered as mediators in the model. We used 95% bias-corrected bootstrap CIs, with 10,000 bootstrap samples, to assess the significance of the indirect effects. RESULTS: The 121 participants with T2D were primarily Puerto Rican (85.8%), aged mean = 60.7 y, and 74% were female. Eighty-two (68%) were classified as food insecure. Compared with food-secure individuals, food-insecure individuals had a significantly higher IR [mean difference (Delta) = 7.21, P = 0.001], insulin (Delta = 9.7, P = 0.019), glucose (Delta = 41, P < 0.001), hsCRP (Delta = 0.8, P = 0.008), cortisol (Delta = 21, P = 0.045), and total cholesterol (Delta = 29, P = 0.004). Groups did not differ on other lipids, metanephrine, normetanephrine, or A1c. The mediation model showed a significant direct effect of HFI on hsCRP (P = 0.020) and on cortisol (P = 0.011). There was a direct effect of cortisol (P = 0.013), hsCRP (P = 0.044), and HFI on IR (P = 0.015). The total combined indirect effect of HFI through cortisol and hsCRP indicated partial mediation. CONCLUSIONS: Among Latinos with T2D, HFI is associated with IR partially through inflammation and stress hormones. Interventions to ameliorate HFI and mitigate its effects on inflammation, stress, and IR are warranted. This trial was registered at clinicaltrials.gov as NCT01578096.

[33] *Blanco Mejia S, Messina M, Li SS et al.* **A Meta-Analysis of 46 Studies Identified by the FDA Demonstrates that Soy Protein Decreases Circulating LDL and Total Cholesterol Concentrations in Adults**. The Journal of nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006811
ABSTRACT
BACKGROUND: Certain plant foods (nuts and soy protein) and food components (viscous fibers and plant sterols) have been permitted by the FDA to carry a heart health claim based on their cholesterol-lowering ability. The FDA is currently considering revoking the heart health claim for soy protein due to a perceived lack of consistent LDL cholesterol reduction in randomized

controlled trials. OBJECTIVE: We performed a meta-analysis of the 46 controlled trials on which the FDA will base its decision to revoke the heart health claim for soy protein. METHODS: We included the 46 trials on adult men and women, with baseline circulating LDL cholesterol concentrations ranging from 110 to 201 mg/dL, as identified by the FDA, that studied the effects of soy protein on LDL cholesterol and total cholesterol (TC) compared with non-soy protein. Two independent reviewers extracted relevant data. Data were pooled by the generic inverse variance method with a random effects model and expressed as mean differences with 95% CI. Heterogeneity was assessed and quantified. RESULTS: Of the 46 trials identified by the FDA, 43 provided data for meta-analyses. Of these, 41 provided data for LDL cholesterol, and all 43 provided data for TC. Soy protein at a median dose of 25 g/d during a median follow-up of 6 wk decreased LDL cholesterol by 4.76 mg/dL (95% CI: -6.71, -2.80 mg/dL, P < 0.0001; I2 = 55%, P < 0.0001) and decreased TC by 6.41 mg/dL (95% CI: -9.30, -3.52 mg/dL, P < 0.0001; I2 = 74%, P < 0.0001) compared with non-soy protein controls. There was no dose-response effect or evidence of publication bias for either outcome. Inspection of the individual trial estimates indicated most trials (approximately 75%) showed a reduction in LDL cholesterol (range: -0.77 to -58.60 mg/dL), although only a minority of these were individually statistically significant. CONCLUSIONS: Soy protein significantly reduced LDL cholesterol by approximately 3-4% in adults. Our data support the advice given to the general public internationally to increase plant protein intake. This trial was registered at clinicaltrials.gov as NCT03468127.

[34] *Zhang Y, Koradia A, Kamato D et al.* **Treatment of atherosclerotic plaque: perspectives on theranostics**. The Journal of pharmacy and pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31025381
ABSTRACT
OBJECTIVES: Atherosclerosis, a progressive condition characterised by the build-up of plaque due to the accumulation of low-density lipoprotein and fibrous substances in the damaged arteries, is the major underlying pathology of most cardiovascular diseases. Despite the evidence of the efficacy of the present treatments for atherosclerosis, the complex and poorly understood underlying mechanisms of atherosclerosis development and progression have prevented them from reaching their full potential. Novel alternative treatments like usage of nanomedicines and theranostics are gaining attention of the researchers worldwide. This review will briefly discuss the current medications for the disease and explore potential future developments based on theranostics nanomaterials that may help resolve atherosclerotic cardiovascular disease. KEY FINDINGS: Various drugs can slow the effects of atherosclerosis. They include hyperlipidaemia medications, anti-platelet drugs, hypertension and hyperglycaemia medications. Most of the theranostic agents developed for atherosclerosis have shown the feasibility of rapid and noninvasive diagnosis, as well as effective and specific treatment in animal models. However, there are still some limitation exist in their structure design, stability, targeting efficacy, toxicity and production, which should be optimized in order to develop clinically acceptable nanoparticle based theronostics for atherosclerosis. SUMMARY: Current medications for atherosclerosis and potential theranostic nanomaterials developed for the disease are discussed in the current review. Further investigations remain to be carried out to achieve clinical translation of theranostic agents for atherosclerosis.

[35] *Shojasaadat F, Ayremlou P, Hashemi A et al.* **A randomized controlled trial comparing effects of a low-energy diet with n-3 polyunsaturated fatty acid supplementation in patients with non-alcoholic fatty liver disease**. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2019; 24:21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31007691

ABSTRACT

Background: Weight loss is the cornerstone of NAFLD management, but weight maintenance is difficult. Some studies have suggested that n-3 polyunsaturated fatty acid (n-3 PUFA) might have beneficial effects in NAFLD. We aim to compare the effects of a low-energy diet with n-3 PUFA supplementation on liver enzymes, body composition, and cardiometabolic risk factors in NAFLD. Materials and Methods: The study was a randomized controlled trial conducted in Urmia in Iran from October 2016 to May 2017. One hundred and fourteen eligible patients were randomly assigned to one of the three following groups: low-energy diet group, n-3 PUFA supplementation (fish oil) group (1500 mg/d), or control group for 12 weeks. Liver enzymes, lipid profile, insulin resistance, and body composition were assessed before and after the intervention. Results: One hundred and four patients completed the study. All groups lost weight, but the reductions were greater in the diet group (-2.97 +/- 2.79 kg, P = 0.001). The diet group had significant decreases in fat mass compared to other groups. Insulin resistance, total cholesterol, and low-density lipoprotein cholesterol significantly decreased only in the diet group, and patients who lost weight >/=4% showed significantly larger decreases in serum liver enzymes. N-3 PUFA had no beneficial effects on the study outcomes. Conclusion: We found that 1500 mg/d n-3 PUFA supplied for 12 weeks, in contrast to 3.40 +/- 2.98% weight loss, does not improve liver enzymes, body composition, and cardiometabolic risk factors in NAFLD patients.

[36] *Schlackow I, Kent S, Herrington W et al.* **Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease**. Kidney international 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31005271

ABSTRACT

Statin-based treatments reduce cardiovascular disease (CVD) risk in patients with non-dialysis chronic kidney disease (CKD), but it is unclear which regimen is the most cost-effective. We used the Study of Heart and Renal Protection (SHARP) CKD-CVD policy model to evaluate the effect of statins and ezetimibe on quality-adjusted life years (QALYs) and health care costs in the United States (US) and the United Kingdom (UK). Net costs below $100,000/QALY (US) or pound20,000/QALY (UK) were considered cost-effective. We investigated statin regimens with or without ezetimibe 10 mg. Treatment effects on cardiovascular risk were estimated per 1-mmol/L reduction in low-density lipoprotein (LDL) cholesterol as reported in the Cholesterol Treatment Trialists' Collaboration meta-analysis, and reductions in LDL cholesterol were estimated for each statin/ezetimibe regimen. In the US, atorvastatin 40 mg ($0.103/day as of January 2019) increased life expectancy by 0.23 to 0.31 QALYs in non-dialysis patients with stages 3B to 5 CKD, at a net cost of $20,300 to $78,200/QALY. Adding ezetimibe 10 mg ($0.203/day) increased life expectancy by an additional 0.05 to 0.07 QALYs, at a net cost of $43,600 to $91,500/QALY. The cost-effectiveness findings and policy implications in the UK were similar. In summary, in patients with non-dialysis-dependent CKD, the evidence suggests

that statin/ezetimibe combination therapy is a cost-effective treatment to reduce the risk of CVD.

[37] *Richter CK, Bisselou KS, Nordgren TM et al.* **n-3 Docosapentaenoic Acid Intake and Relationship with Plasma Long-Chain n-3 Fatty Acid Concentrations in the United States: NHANES 2003-2014**. Lipids 2019; 54:221-230.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31025717
ABSTRACT
The long-chain n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play a crucial role in health, but previous National Health and Nutrition Examination Survey (NHANES) analyses have shown that EPA and DHA intake in the United States is far below recommendations (~250-500 mg/day EPA + DHA). Less is known about docosapentaenoic acid (DPA), the metabolic intermediate of EPA and DHA; however, evidence suggests DPA may be an important contributor to long-chain n-3 fatty acid intake and impart unique benefits. We used NHANES 2003-2014 data (n = 45,347) to assess DPA intake and plasma concentrations, as well as the relationship between intake and plasma concentrations of EPA, DPA, and DHA. Mean DPA intake was 22.3 +/- 0.8 mg/day from 2013 to 2014, and increased significantly over time ($p < 0.001$), with the lowest values from 2003 to 2004 (16.2 +/- 1.2 mg/day). DPA intake was higher in adults (20-55 years) and seniors (55+ years) compared to younger individuals. In regression analyses, DPA intake was a significant predictor of plasma EPA (beta = 138.5; $p < 0.001$) and DHA (beta = 318.9; $p < 0.001$). Plasma DPA was predicted by EPA and DHA intake (beta = 13.15; $p = 0.001$ and beta = 7.4; $p = 0.002$), but not dietary DPA ($p = 0.3$). This indicates that DPA intake is not a good marker of plasma DPA status (or vice versa), and further research is needed to understand the factors that affect the interconversion of EPA and DPA. These findings have implications for future long-chain n-3 fatty acids dietary recommendations.

[38] *Simons LA*. **An updated review of lipid-modifying therapy**. The Medical journal of Australia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31006138
ABSTRACT
Statin drugs reduce low-density lipoprotein (LDL)-cholesterol (LDL-C) and cardiovascular risk. Ezetimibe may be used to supplement statin therapy, or used alone in cases of statin intolerance. Statin-associated side effects do occur, especially muscle symptoms and new onset diabetes, but they do not detract from the benefits of statin therapy. Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce LDL-C and cardiovascular risk. Evolocumab is subsidised in Australia for patients with familial hypercholesterolaemia when LDL-C is not adequately controlled with maximum doses of statin or ezetimibe or when statin therapy is contraindicated. Fenofibrate reduces triglycerides and cardiovascular risk in patients with type 2 diabetes when triglycerides are elevated and high-density lipoprotein (HDL) is low. A role for dietary omega-3 fatty acids and esters in reducing cardiovascular risk remains controversial. All cases of secondary cardiovascular disease prevention merit intensive lipid therapy, unless a contraindication exists. Lipid therapy is justified in cases of primary prevention when absolute risk is high, especially when lipids are highly elevated or when multiple risk factors are present. Clinical management requires a focus on the predominant lipid disorder present, namely

hypercholesterolaemia, hypertriglyceridaemia or combined hyperlipidaemia. There is an ongoing problem of poor long term persistence on lipid therapy, as well as reduced awareness by practitioners of poor risk factor control.

[39] *Liao KM, Wang SW, Lu CH et al.* **The influence of statins on aortic aneurysm after operation: A retrospective nationwide study**. Medicine (Baltimore) 2019; 98:e15368.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31027125
ABSTRACT
Aortic aneurysm (AA) is a disease with substantially higher health care costs and very high mortality upon rupture. Statins have a non-lipid-lowering pleiotropic mechanism that may be beneficial for AA in disease progression and improvement of AA patient outcomes. Previous studies have been conducted with some limitations and without considering immortal time bias, lag time, and adherence. The aim of our study was to analyze the effect of statin use on AA postoperation after controlling for these factors.All postoperative patients with a diagnosis of AA in Taiwan from 2004 to 2012 were included from the National Health Insurance Research Database. We excluded patients without computed tomography within 1 year after diagnosis and those who died within 30 days after the operation. We also analyzed the medication, medication possession ratio (MPR), immortal time bias, and lag time. Statin users were defined as those using statins for more than 30 days. Primary composite outcomes included mortality, reoperation for AA and rehospitalization for AA during the study period.Among the whole study population (n = 1633), 199/1633 (12.19%) patients were statin users, while the others (n = 1434) were not. Mortality was higher in statin nonusers than in statin users, with a mortality rate of 40% versus 22.61% (P < .0001). There was no significant difference in reoperation or rehospitalization for AA.Statin use may be beneficial for AA patients in our observational study. Prospective randomized controlled studies are needed to define the effect of statin therapy in this population.

[40] *Borghi C, Fogacci F, Cicero AFG*. **Cardiovascular Risk Reduction with Icosapent Ethyl**. The New England journal of medicine 2019; 380:1678.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31018076
ABSTRACT

[41] *Chan LN*. **Cardiovascular Risk Reduction with Icosapent Ethyl**. The New England journal of medicine 2019; 380:1677.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31018075
ABSTRACT

[42] *He W, Tian X, Yuan B et al.* **Rosuvastatin improves neurite extension in cortical neurons through the Notch 1/BDNF pathway**. Neurol Res 2019:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31023175
ABSTRACT
OBJECTIVES: Neurite outgrowth of neurons is essential for forming functional neural circuits. It is believed that neuronal neurite outgrowth is an important mechanism of brain plasticity. Rosuvastatin (RSV) is a relatively new statin and may have neuroprotective properties.

However, whether RSV exerts an effect on neurite extension and its potential mechanism in cortical neurons remains poorly documented. METHODS: Immunofluorescence method was used to examine the effect of RSV on neurite outgrowth in primary cortical neuron by measuring neurite length and confirmed the promotion effect. Then, the potential mechanisms involving the Notch1 pathway were investigated. Effects of RSV on the expression of Notch 1 and Hes1were determined using qRT-PCR. In addition, brain-derived neurotrophic factor (BDNF) expression was also assessed using qRT-PCR, and ELISA. RESULTS: RSV promoted neurite outgrowth of cortical neurons, and this effect could be partially prevented by the Notch 1 pathway inhibitor, DAPT. Subsequently, we found that Jagged 1 and Notch 1 were colocalized. In addition, we observed that the levels of both Notch 1 and Hes 1 in cortical neurons were increased after RSV, but sharply decreased after DAPT treatment. Moreover, RSV increased brain-derived neurotrophic factor (BDNF) levels in cortical neurons, but in the culture medium, and the effect could be partially suppressed by DAPT treatment. DISCUSSION: These findings indicate that RSV mediates neurite outgrowth in primary cortical neurons. The RSV-induced neuritogenic effect is mediated at least partly via the Notch1/BDNF pathway.

[43] *Chacinska M, Zabielski P, Ksiazek M et al.* **The Impact of OMEGA-3 Fatty Acids Supplementation on Insulin Resistance and Content of Adipocytokines and Biologically Active Lipids in Adipose Tissue of High-Fat Diet Fed Rats**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31013835

ABSTRACT

It has been established that OMEGA-3 polyunsaturated fatty acids (PUFAs) may improve lipid and glucose homeostasis and prevent the "low-grade" state of inflammation in animals. Little is known about the effect of PUFAs on adipocytokines expression and biologically active lipids accumulation under the influence of high-fat diet-induced obesity. The aim of the study was to examine the effect of fish oil supplementation on adipocytokines expression and ceramide (Cer) and diacylglycerols (DAG) content in visceral and subcutaneous adipose tissue of high-fat fed animals. The experiments were carried out on Wistar rats divided into three groups: standard diet-control (SD), high-fat diet (HFD), and high-fat diet + fish oil (HFD+FO). The fasting plasma glucose and insulin concentrations were examined. Expression of carnitine palmitoyltransferase 1 (CPT1) protein was determined using the Western blot method. Plasma adipocytokines concentration was measured using ELISA kits and mRNA expression was determined by qRT-PCR reaction. Cer, DAG, and acyl-carnitine (A-CAR) content was analyzed by UHPLC/MS/MS. The fish oil supplementation significantly decreased plasma insulin concentration and Homeostatic Model Assesment for Insulin Resistance (HOMA-IR) index and reduced content of adipose tissue biologically active lipids in comparison with HFD-fed subjects. The expression of CPT1 protein in HFD+FO in both adipose tissues was elevated, whereas the content of A-CAR was lower in both HFD groups. There was an increase of adiponectin concentration and expression in HFD+FO as compared to HFD group. OMEGA-3 fatty acids supplementation improved insulin sensitivity and decreased content of Cer and DAG in both fat depots. Our results also demonstrate that PUFAs may prevent the development of insulin resistance in response to high-fat feeding and may regulate the expression and secretion of adipocytokines in this animal model.

[44] *Kim TS, Chung JW*. **Associations of Dietary Riboflavin, Niacin, and Retinol with Age-related Hearing Loss: An Analysis of Korean National Health and Nutrition Examination Survey Data**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31010085
ABSTRACT
Because age-related hearing loss (ARHL) is irreversible, prevention is very important. Thus, investigating modifying factors that help prevent ARHL is critical for the elderly. Nutritional status or nutritional factors for the elderly are known to be associated with many problems related to aging. Emerging studies suggest that there was the interaction between nutrition and ARHL. We aimed to investigate the possible impact of dietary nutrients on ARHL using data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES) which included 4742 subjects aged >/= 65 years from 2010 to 2012. All participants underwent an otologic examination, audiologic evaluation, and nutritional survey. The associations between ARHL and nutrient intake were analyzed using simple and multiple regression models with complex sampling adjusted for confounding factors, such as BMI, smoking status, alcohol consumption, and history of hypertension and diabetes. Higher intake groups of riboflavin, niacin and retinol was inversely associated with ARHL prevalence (riboflavin aOR, 0.71; 95% CI, 0.54-0.94; p = 0.016, niacin aOR, 0.72; 95% CI, 0.54-0.96; p = 0.025, retinol aOR 0.66; 95% CI, 0.51-0.86; p = 0.002, respectively). Our findings suggest the recommended intake levels of riboflavin, niacin, and retinol may help reduce ARHL in the elderly.

[45] *Saad R, Hallit S, Chahine B*. **Evaluation of renal drug dosing adjustment in chronic kidney disease patients at two university hospitals in Lebanon**. Pharmacy practice 2019; 17:1304.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31015868
ABSTRACT
Background: Inappropriate medication dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. Patients are at a high risk of developing related adverse events caused by the altered effect of drugs in conjunction with the use of polypharmacy to treat comorbid conditions. This necessitates adequate renal dosing adjustments. Objective: The current study aims at assessing whether appropriate dosing adjustments were made in hospitalized patients with chronic kidney disease. Methods: A retrospective descriptive study was conducted at two university hospitals in Beirut between January and December 2016. All adult CKD patients with creatinine clearance less than 60 ml/min and receiving at least one medication that require renal dosing adjustment were included. Kidney function was estimated from serum creatinine using Cockcroft-Gault equation, and dose appropriateness was determined by comparing practice with specific guidelines. The rates of renal drug dosing adjustment were investigated, in addition to the influence of possible determinants, such as the severity of renal impairment, reason of hospital admission, and other patient characteristics. Results: 2138 patients admitted in 2016 were screened. 223 adults receiving 578 drug orders that require adjustment were included. Among the 578 orders, 215 (37%) were adjusted adequately, 284 (49%) were adjusted inadequately, and 79 (14%) were not adjusted at all. Beta-blockers were the most inadequately dosed (83.6%) class of medication, whereas lipid-lowering agents had the highest percentage of adequate dosing (65.1%). As per patient, 84.3% of patients appeared to be receiving at least one inappropriate drug dose. Conclusions: Our study

confirms that physicians are not prescribing appropriate dosing adjustments in chronic kidney disease inpatients, which may have deleterious effects. This highlights the need for more nephrology consultation and the implementation of physician education programs.

[46] *Harrison M, Spooner L, Bansback N et al.* **Preventing rheumatoid arthritis: Preferences for and predicted uptake of preventive treatments among high risk individuals**. PloS one 2019; 14:e0216075.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31022252
ABSTRACT
OBJECTIVE: To understand preferences for and estimate the likely uptake of preventive treatments currently being evaluated in randomized controlled trials with individuals at increased risk of developing rheumatoid arthritis (RA). METHODS: Focus groups were used to identify key attributes of potential preventive treatment for RA (reduction in risk of RA, how treatment is taken, chance of side effects, certainty in estimates, health care providers opinion). A web-based discrete choice experiment (DCE) was administered to people at-risk of developing RA, asking them to first choose their preferred of two hypothetical preventive RA treatments, and then between their preferred treatment and 'no treatment for now.' DCE data was analyzed using conditional logit regression to estimate the significance and relative importance of attributes in influencing preferences. RESULTS: Two-hundred and eighty-eight first-degree relatives (60% female; 66% aged 18-39 years) completed all tasks in the survey. Fourteen out of fifteen attribute levels significantly influenced preferences for treatments. How treatment is taken (oral vs. infusion beta0.983, p<0.001), increasing reduction in risk of RA (beta0.922, p<0.001), health care professional preference (beta0.900, p<0.001), and avoiding irreversible (beta0.839, p<0.001) or reversible serious side effects (beta0.799, p<0.001) were most influential. Predicted uptake was high for non-biologic drugs (e.g. 84% hydroxycholoroquine), but very low for atorvastatin (8%) and biologics (<6%). CONCLUSION: Decisions to take preventative treatments are complex, and uptake depends on how treatments can compromise on convenience, potential risks and benefits, and recommendations/preferences of health care professionals. This evidence contributes to understanding whether different preventative treatment strategies are likely to be acceptable to target populations.

[47] *Hung TH, Tsai CC, Lee HF*. **Statin use in cirrhotic patients with infectious diseases: A population-based study**. PloS one 2019; 14:e0215839.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31017946
ABSTRACT
BACKGROUND: Recent studies have shown benefits of statins in patients with liver cirrhosis. However, it is still unknown if statins have a beneficial effect on the mortality of cirrhotic patients with bacterial infections. METHODS: The Taiwan National Health Insurance Database was searched, and 816 cirrhotic patients receiving statins with bacterial infections hospitalized between January 1, 2010 and December 31, 2013 were included in the study. A one-to-four propensity score matching was performed to select a comparison group based on age, sex, and comorbid disorders. RESULTS: The overall 30-day mortalities in statin and non-statin group were 5.3% and 9.8%, respectively (P = 0.001). After Cox regression modeling adjusting for age,

sex, and comorbid disorders, the hazard ratio (HR) of statin use on 30-day mortality was 0.52 (95% confidence interval [CI]: 0.38-0.72, P<0.001). In subgroup analysis, the 30-day mortality effect of statin use was more pronounced in patients with pneumonia (HR = 0.34; 95% CI: 0.19-0.59; P<0.001) and bacteremia (HR = 0.55; 95% CI: 0.35-0.85; P = 0.008). Atovastatin (HR = 0.59; 95% CI: 0.37-0.93) and rosuvastatin (HR = 0.59; 95% CI: 0.36-0.98) were associated with a decreased 30-day mortality risk compared to patients not taking statins. CONCLUSIONS: Statin use decreases the 30-day mortality of cirrhotic patients with bacteremia and pneumonia.

[48] *Riera-Heredia N, Lutfi E, Gutierrez J et al.* **Fatty acids from fish or vegetable oils promote the adipogenic fate of mesenchymal stem cells derived from gilthead sea bream bone potentially through different pathways**. PloS one 2019; 14:e0215926.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31017945
ABSTRACT
Fish are rich in n-3 long-chain polyunsaturated fatty acids (LC-PUFA), such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, thus they have a great nutritional value for human health. In this study, the adipogenic potential of fatty acids commonly found in fish oil (EPA and DHA) and vegetable oils (linoleic (LA) and alpha-linolenic (ALA) acids), was evaluated in bone-derived mesenchymal stem cells (MSCs) from gilthead sea bream. At a morphological level, cells adopted a round shape upon all treatments, losing their fibroblastic form and increasing lipid accumulation, especially in the presence of the n-6 PUFA, LA. The mRNA levels of the key transcription factor of osteogenesis, runx2 significantly diminished and those of relevant osteogenic genes remained stable after incubation with all fatty acids, suggesting that the osteogenic process might be compromised. On the other hand, transcript levels of the main adipogenesis-inducer factor, pparg increased in response to EPA. Nevertheless, the specific PPARgamma antagonist T0070907 appeared to suppress the effects being caused by EPA over adipogenesis. Moreover, LA, ALA and their combinations, significantly up-regulated the fatty acid transporter and binding protein, fatp1 and fabp11, supporting the elevated lipid content found in the cells treated with those fatty acids. Overall, this study has demonstrated that fatty acids favor lipid storage in gilthead sea bream bone-derived MSCs inducing their fate into the adipogenic versus the osteogenic lineage. This process seems to be promoted via different pathways depending on the fatty acid source, being vegetable oils-derived fatty acids more prone to induce unhealthier metabolic phenotypes.

[49] *Freret S, Oseikria M, Le Bourhis D et al.* **Effects of a n-3 PUFA enriched diet on embryo production in dairy cows**. Reproduction (Cambridge, England) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31013477
ABSTRACT
Beneficial effects of n-3 polyunsaturated fatty acid (PUFA) supplementation on dairy cow reproduction have been previously reported. The objectives of the present study were to assess whether n-3 PUFA supplementation would affect in vitro embryo production (IVP) after ovarian stimulation. Holstein cows received a diet with 1% dry matter supplementation of either n-3 PUFA (n = 18, micro encapsulated fish oil) or a control, n-6 PUFA (n = 19, micro encapsulated soy oil). Both plasma and follicular fluid FA composition showed integration of total PUFA through the diet. All cows underwent an IVP protocol consisting of ovarian stimulation,

ultrasound-guided transvaginal oocyte retrieval (ovum pick-up, OPU, 5 per cow) followed by in vitro maturation, fertilisation and 7 days of embryo development. A tendency toward an increase in the blastocyst rate (diet effect, p = 0.0865) was observed in n-3 cows, with 49.6 +/- 5.5%, versus 42.3 +/- 5.5% in control n-6 cows. A significant increase (diet effect, p = 0.0217) in the good quality blastocyst rate (freezable blastocysts) was reported in n-3 cows (42.2 +/- 7.7%) compared to control n-6 cows (32.7 +/- 7.7%). A significant difference in lipid composition was shown in the oocytes recovered by OPU from n-3 and n-6 treated cows, by intact single-oocyte MALDI-TOF mass spectrometry. The 42 differentially abundant identified lipids were mainly involved in cell membrane structure. In conclusion, n-3 PUFA supplementation enhanced oocyte quality and modified their lipid composition. Further studies are necessary to investigate the potential link of these lipid modifications with enhanced oocyte quality.

[50] *Asgari S, Khaloo P, Khalili D et al.* **Status of Hypertension in Tehran: Potential impact of the ACC/AHA 2017 and JNC7 Guidelines, 2012-2015**. Scientific reports 2019; 9:6382.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31011156

ABSTRACT

This study aimed to determine the prevalence of hypertension, the recommended anti-hypertensive therapy and the percentage of hypertensive patients who had achieved the blood pressure (BP) target according to 2017 American College of Cardiology/American Heart Association (ACC/AHA) versus JNC7 and 8 guidelines, among Iranian population. Data of participants aged >/=20 years from the fifth phase (2012-2015) of the Tehran lipid and glucose study (N = 10,576) were analyzed, using survey analysis. The weighted prevalence of hypertension among those not on anti-hypertensive medications was 42.7 and 12.6%, applying the ACC/AHA and JNC7 guideline definitions, respectively; the corresponding values with including BP-lowering medication in definition of hypertension were 47.1% and 20.4%, respectively. However, 90% of these hypertensive people were found to have a 10-year cardiovascular disease risk of <10%. Applying the ACC/AHA guideline, anti-hypertensive medication was recommended for 21.9% of Tehranians, compared to 19.3 and 12.2% according to the JNC7 and 8 guidelines, respectively. Among Tehranians taking anti-hypertensive medication, 20% achieved the BP goal according to the ACC/AHA guideline, compared to the 42.1 and 53.6%, using JNC7 and 8 guidelines, respectively. Despite the tremendous increase in the prevalence of hypertension, most of the newly identified cases did not belong to the high-risk group.

[51] *Zhang H, Liu G, Zhou W et al.* **Neprilysin Inhibitor-Angiotensin II Receptor Blocker Combination Therapy (Sacubitril/valsartan) Suppresses Atherosclerotic Plaque Formation and Inhibits Inflammation in Apolipoprotein E- Deficient Mice**. Scientific reports 2019; 9:6509.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31019233

ABSTRACT

We assessed the effects of the sacubitril/valsartan combination drug (LCZ696), in comparison to valsartan alone, on the progression of atherosclerotic plaque formation and inflammatory gene expression in apolipoprotein E- deficient mice (apoE(-/-) mice). Seventy-two apoE(-/-) mice were fed a western diet and a constrictive silastic tube was used to elicit carotid lesion formation. The animals were separated into a control group, a valsartan group or an LCZ696

group (n = 24 in each group). Plaques in the carotid artery were harvested 12 weeks later for histological examination. The levels of pro-inflammatory genes in the plasma and lesions were detected using real-time PCR and ELISA. Valsartan or LCZ696 treatment remarkably inhibited the expression of pro-inflammatory genes, including interleukin-6, matrix metalloproteinase-8 and monocyte chemotactic protein-1, in comparison with the control group. Meanwhile, both valsartan and LCZ696 suppressed the formation of atherosclerotic plaques by decreasing plaque lipid content and cross-sectional plaque area and increasing the content of plaque collagen and fibrous cap thickness. In particular, LCZ696 performed the best in suppressing atherosclerosis and inhibiting the level of pro-inflammatory genes. LCZ696 significantly ameliorated atherosclerosis and inflammation in apoE(-/-) mice compared with valsartan.