Literature update week 18 (2018)

[1] *Danthiir V, Hosking DE, Nettelbeck T et al.* **An 18-mo randomized, double-blind, placebo-controlled trial of DHA-rich fish oil to prevent age-related cognitive decline in cognitively normal older adults**. The American journal of clinical nutrition 2018; 107:754-762.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29722833

ABSTRACT
Background: Fish oil trials in cognitively healthy older adults have yielded inconsistent results. Supplementation may differentially affect the domains that underpin cognitive performance, and effects may differ across sex or genotype. Objective: The aim of this study was to test whether docosahexaenoic acid (DHA)-rich fish oil slows 18-mo cognitive decline in cognitively healthy elders. Design: In a double-blind, randomized, placebo-controlled, parallel-group trial, cognitively healthy Australian community-dwelling adults (aged 65-90 y) consumed either 1720 mg DHA and 600 mg eicosapentaenoic acid or low-polyphenolic olive oil daily, as capsules, for 18 mo. Groups were allocated by permuted-block randomization and stratified by age. Cognitive assessment was conducted at baseline and then every 6 mo. Primary analyses tested the difference between groups in the rate of 18-mo cognitive change via latent growth curve models on any of the following: reasoning, working memory, short-term memory, retrieval fluency, and cognitive speed-related constructs. Treatment interactions with sex and APOE-epsilon4 were tested. Secondary outcomes were self-reported changes in well-being and everyday functioning, blood pressure, biomarkers of n-3 (omega-3) long-chain polyunsaturated fatty acids (LC PUFAs), lipids, glucose metabolism, inflammation, oxidative stress, DNA damage, and Mini-Mental State Examination. Results: A total of 403 people were randomly assigned. Data from those who completed baseline were analyzed (n = 390; intervention n = 194, control n = 196). Daily supplementation with 2.3 g DHA-rich fish oil for 18 mo did not maintain or improve cognitive performance. A small negative main effect was found on psychomotor speed (intervention = -0.02, 95% CI: -0.04 to 0.00; d = 0.24, P = 0.03). Treatment effects differed according to sex on retrieval fluency and some speed-based domains, including psychomotor speed, and according to APOE-epsilon4 carrier status on reaction time and reasoning. For secondary outcomes, treatment was associated with increased perceived cognitive mistakes (d = 0.24; P = 0.003), increased oxidative stress, and expected changes in fatty acid metabolism. Conclusions: Findings do not support supplementing older adults with fish oil to prevent cognitive decline. Treatment interactions with sex and APOE-epsilon4 carrier status warrant further investigation. This trial was registered at the Australia and New Zealand Clinical Trials Register (ANZCTR) as ACTRN12607000278437.

[2] *Gabriel FS, Goncalves LFG, Melo EV et al.* **Atherosclerotic Plaque in Patients with Zero Calcium Score at Coronary Computed Tomography Angiography**. Arquivos brasileiros de cardiologia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29723329

ABSTRACT
BACKGROUND: In view of the high mortality for cardiovascular diseases, it has become necessary to stratify the main risk factors and to choose the correct diagnostic modality. Studies have demonstrated that a zero calcium score (CS) is characteristic of a low risk for cardiovascular events. However, the prevalence of individuals with coronary atherosclerotic plaques and zero CS is conflicting in the specialized literature. OBJECTIVE: To evaluate the

frequency of patients with coronary atherosclerotic plaques, their degree of obstruction and associated factors in patients with zero CS and indication for coronary computed tomography angiography (CCTA). METHODS: This is a cross-sectional, prospective study with 367 volunteers with zero CS at CCTA in four diagnostic imaging centers in the period from 2011 to 2016. A significance level of 5% and 95% confidence interval were adopted. RESULTS: The frequency of atherosclerotic plaque in the coronary arteries in 367 patients with zero CS was 9.3% (34 individuals). In this subgroup, mean age was 52 +/- 10 years, 18 (52.9%) were women and 16 (47%) had significant coronary obstructions (> 50%), with involvement of two or more segments in 4 (25%) patients. The frequency of non-obese individuals (90.6% vs 73.9%, p = 0.037) and alcohol drinkers (55.9% vs 34.8%, p = 0.015) was significantly higher in patients with atherosclerotic plaques, with an odds ratio of 3.4 for each of this variable. CONCLUSIONS: The frequency of atherosclerotic plaque with zero CS was relatively high, indicating that the absence of calcification does not exclude the presence of plaques, many of which obstructive, especially in non-obese subjects and alcohol drinkers.

[3] *Raouf J, Idborg H, Englund P et al.* **Targeted lipidomics analysis identified altered serum lipid profiles in patients with polymyositis and dermatomyositis**. Arthritis research & therapy 2018; 20:83.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29720222
ABSTRACT
BACKGROUND: Polymyositis (PM) and dermatomyositis (DM) are severe chronic autoimmune diseases, characterized by muscle fatigue and low muscle endurance. Conventional treatment includes high doses of glucocorticoids and immunosuppressive drugs; however, few patients recover full muscle function. One explanation of the persistent muscle weakness could be altered lipid metabolism in PM/DM muscle tissue as we previously reported. Using a targeted lipidomic approach we aimed to characterize serum lipid profiles in patients with PM/DM compared to healthy individuals (HI) in a cross-sectional study. Also, in the longitudinal study we compared serum lipid profiles in patients newly diagnosed with PM/DM before and after immunosuppressive treatment. METHODS: Lipidomic profiles were analyzed in serum samples from 13 patients with PM/DM, 12 HI and 8 patients newly diagnosed with PM/DM before and after conventional immunosuppressive treatment using liquid chromatography tandem mass spectrometry (LC-MS/MS) and a gas-chromatography flame ionization detector (GC-FID). Functional Index (FI), as a test of muscle performance and serum levels of creatine kinase (s-CK) as a proxy for disease activity were analyzed. RESULTS: The fatty acid (FA) composition of total serum lipids was altered in patients with PM/DM compared to HI; the levels of palmitic (16:0) acid were significantly higher while the levels of arachidonic (20:4, n-6) acid were significantly lower in patients with PM/DM. The profiles of serum phosphatidylcholine and triacylglycerol species were changed in patients with PM/DM compared to HI, suggesting disproportionate levels of saturated and polyunsaturated FAs that might have negative effects on muscle performance. After immunosuppressive treatment the total serum lipid levels of eicosadienoic (20:2, n-6) and eicosapentaenoic (20:5, n-3) acids were increased and serum phospholipid profiles were altered in patients with PM/DM. The correlation between FI or s-CK and levels of several lipid species indicate the important role of lipid changes in muscle performance and inflammation. CONCLUSIONS: Serum lipids profiles are significantly altered in patients with

PM/DM compared to HI. Moreover, immunosuppressive treatment in patients newly diagnosed with PM/DM significantly affected serum lipid profiles. These findings provide new evidence of the dysregulated lipid metabolism in patients with PM/DM that could possibly contribute to low muscle performance.

[4] *Oliveira TF, Batista PR, Leal MA et al.* **Chronic Cadmium Exposure Accelerates the Development of Atherosclerosis and Induces Vascular Dysfunction in the Aorta of ApoE(-/-) Mice**. Biological trace element research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707746
ABSTRACT
Cadmium exposure is related to cardiovascular diseases, including hypertension, atherosclerosis, increased oxidative stress, endothelial dysfunction, and specific biochemical changes induced by this metal. Thus, we aimed to investigate whether cadmium exposure induces endothelial dysfunction, accelerates atherosclerotic plaque formation in the aorta, and enhances oxidative stress in apolipoprotein E knockout (ApoE(-/-)) mice. Experiments were performed in 14-week-old male wild-type and ApoE(-/-) mice. ApoE(-/-) mice received cadmium (CdCl2 100 mg/L in drinking water for 28 days) or vehicle (distilled water). After treatment, vascular reactivity to phenylephrine, acetylcholine, and sodium nitroprusside was analyzed using isolated aorta. Bone marrow cells were isolated to assess the production of nitric oxide and reactive oxygen and nitrogen species. ApoE(-/-) cadmium-treated mice had higher cholesterol levels than non-exposed mice. Cadmium exposure decreased the vasodilatation response to acetylcholine in aortic ring of ApoE(-/-) mice, though no changes in phenylephrine or sodium nitroprusside responses were observed. L-NAME reduced vasodilator responses to acetylcholine; this effect was lower in ApoE(-/-) cadmium-treated mice, suggesting reduction in nitric oxide (NO) bioavailability. Moreover, in bone marrow cells, cadmium decreased cytoplasmic levels of NO and increased superoxide anions, hydrogen peroxide, and peroxynitrite in ApoE(-/-) mice. Morphological analysis showed that cadmium exposure increased plaque deposition in the aorta by approximately 3-fold. Our results suggest that cadmium exposure induces endothelial dysfunction in ApoE(-/-) mice. Moreover, cadmium increased total cholesterol levels, which may promote the early development of atherosclerosis in the aorta of ApoE(-/-) mice. Our findings support the hypothesis that cadmium exposure might increase the risk of atherosclerosis.

[5] *Xie YD, Chen ZZ, Li N et al.* **Hydroxytyrosol nicotinate, a new multifunctional hypolipidemic and hypoglycemic agent**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 99:715-724.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29710469
ABSTRACT
Hydroxytyrosol (HT) is a natural polyphenol antioxidant that exists in olive oil. In the study of multifunctional hypolipidemic of nicotinic derivatives, we found that hydroxytyrosol nicotinate (HT-N) incorporation of niacin with HT displayed ?-glucosidase inhibitory activities in vitro, such as yeast ?-glucosidase (IC50?=?117.72??M) and rat intestinal ?-glucosidases maltase (IC50?=?31.86??M) and sucrase (IC50?=?22.99??M), and had a good control of postprandial blood glucose (PBG). HT-N shown significantly hypoglycemic action by 16.9% and protection of

pancreatic tissue in type 2 diabetic mellitus (T2DM) mouse model. HT-N also shown a potent antioxidant activity and property of anti-glycation in vitro, which were benefit for ameliorating diabetic complications. Moreover, HT-N exhibited much significant hypolipidemia, lowering plasma triglyceride (TG), total cholesterol (TC), and malonaldehyde (MDA) by 34.6%, 45.8% and 32.1% respectively, in hyperlipidemic mice induced by Triton WR 1339. The results indicated that HT-N has hypolipidemic, hypoglycemic and antioxidant actions. All these properties could be conducive to amelioration of oxidative stress, hyperlipidemia, and diabetes that HT-N may serve as a multifunctional potential therapeutic strategy in diabetic patients with hyperlipidemia.

[6] *Wu H, Zhang Y, Yang X et al.* **Whole Body Vibration Retards Progression of Atherosclerosis via Insulin-Like Growth Factor 1 in Apolipoprotein E-Deficient Mice**. BioMed research international 2018; 2018:4934861.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707570
ABSTRACT
Whole body vibration (WBV) has a marked impact on lipid metabolism and the endocrine system, which is related to the progression of atherosclerosis (AS). To investigate the effects of WBV, we measured the atherosclerotic plaque area of apolipoprotein E-knockout (ApoE(-/-)) AS mice, which were trained by WBV (15 Hz, 30 min) for 12 weeks. Simultaneously, serum levels of lipids, insulin-like growth factor 1 (IGF-1), insulin-like growth factor 1 receptor (IGF-1R), interleukin 6 (IL-6), and the mRNA and protein levels of the same in the aorta were compared between the control and WBV groups. The results indicated that WBV significantly reduced the atherosclerotic plaque area with lower very low-density lipoprotein (VLDL) and oxidized low-density lipoprotein (ox-LDL) in the blood. Moreover, the levels of IGF-1 in serum and expression of IL-6, IGF-1R, and p-IGF-1R protein in the mice aorta decreased significantly in the WBV group. In addition, we found that serum IGF-1 in mice increased to the highest concentration in 30 min after WBV for 10, 30, 60, and 120 minutes. These results suggested that appropriate WBV may delay the progression of AS, which was associated with acutely elevated serum IGF-1 and lower levels of IGF-1 and IL-6 in the aorta for long-term treatment.

[7] *Karlson BW, Nicholls SJ, Lundman P et al.* **Modeling Statin-Induced Reductions of Cardiovascular Events in Primary Prevention: A VOYAGER Meta-Analysis**. Cardiology 2018; 140:30-34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29705799
ABSTRACT
OBJECTIVE: We used individual patient data from the VOYAGER database to estimate cardiovascular (CV) risk reduction with commonly used high-intensity statins. METHODS: In patients with known atherosclerotic CV disease (ASCVD) treated with high-intensity statin therapy (n = 6,735), the predicted risk reduction was estimated using the Cholesterol Treatment Trialists' Collaboration meta-analysis, which determined risk reduction per 38.7 mg/dL statin-mediated reduction in low-density lipoprotein cholesterol. RESULTS: The greatest reductions in risk were seen in major vascular events (estimated rate ratios ranged from 0.55 with rosuvastatin [RSV] 40 mg to 0.60 with atorvastatin [ATV] 40 mg) and coronary heart disease death (estimated rate ratios ranged from 0.58 with RSV 40 mg to 0.64 with ATV 40 mg).

CONCLUSIONS: Our results show that, in individuals without clinical ASCVD, statin therapy has the potential to reduce the frequency of CV events.

[8] *Minhas JS, Wang X, Arima H et al.* **Lipid-Lowering Pretreatment and Outcome Following Intravenous Thrombolysis for Acute Ischaemic Stroke: A Post Hoc Analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study Trial**. Cerebrovasc Dis 2018; 45:213-220.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29705803
ABSTRACT
BACKGROUND: Debate exists as to whether statin pretreatment confers an increased risk of 90-day mortality and symptomatic intracranial haemorrhage (sICH) in acute ischaemic stroke (AIS) patients treated with intravenous thrombolysis. We assessed the effects of undifferentiated lipid-lowering pretreatment on outcomes and interaction with low-dose versus standard-dose alteplase in a post hoc subgroup -analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study. METHODS: In all, 3,284 thrombolysis-eligible AIS patients (mean age 66.6 years; 38% women), with information on lipid-lowering pretreatment, were randomly assigned to low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) intravenous alteplase within 4.5 h of symptom onset. Of the total number of patients, 615 (19%) received statin or other lipid-lowering pretreatment. The primary clinical outcome was combined endpoint of death or disability (modified Rankin Scale scores 2-6) at 90 days. RESULTS: Compared with patients with no lipid-lowering pretreatment, those with lipid-lowering pretreatment were significantly older, more likely to be non-Asian and more likely to have a medical history including vascular co-morbidity. After propensity analysis assessment and adjustment for important baseline variables at the time of randomisation, as well as imbalances in management during the first 7 days of hospital admission, there were no significant differences in mortality (OR 0.85; 95% CI 0.58-1.25, p = 0.42), or in overall -90-day death and disability (OR 0.85, 95% CI 0.67-1.09, p = 0.19), despite a significant decrease in sICH among those with -lipid-lowering pretreatment according to the European Co-operative Acute Stroke Study 2 definition (OR 0.49, 95% CI 0.28-0.83, p = 0.009). No differences in key efficacy or safety outcomes were seen in patients with and without lipid-lowering pretreatment between low- and standard-dose alteplase arms. CONCLUSIONS: Lipid-lowering pretreatment is not associated with adverse outcome in AIS patients treated with intravenous alteplase, whether assessed by 90-day death and disability or death alone.

[9] *Pradhan AD, Aday AW, Rose LM, Ridker PM*. **Residual Inflammatory Risk On Treatment with PCSK9 Inhibition and Statin Therapy**. Circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29716940
ABSTRACT
Background -The combination of statin therapy and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibition markedly lowers low-density lipoprotein cholesterol (LDL-C) and reduces cardiovascular event rates. Whether residual inflammatory risk as measured by on-treatment high sensitivity C-reactive protein (hsCRP) remains an important clinical issue in such patients is uncertain. Methods -We evaluated residual inflammatory risk among 9,738 patients participating in the Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE)-1

and -2 cardiovascular outcomes trials who were receiving both statin therapy and bococizumab, according to on-treatment levels of hsCRP (hsCRPOT) and LDL-COT measured 14 weeks after drug initiation. The primary endpoint was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death. Results -At 14 weeks, the mean percent change in LDL-C among statin treated patients who additionally received bococizumab was -60.5% (95% CI -61.2 to -59.8; p<0.001; median change -65.4%) as compared to 6.6% (95% CI -1.0 to 14.1; p=0.09; median change 0.0%) for hsCRP. Incidence rates for future cardiovascular events for patients treated with both statin therapy and bococizumab according to on treatment levels of hsCRP <1, 1-3, and >3 mg/L were 1.96, 2.50, and 3.59 events per 100 person-years, respectively, corresponding to multivariable adjusted hazard ratios of 1.0, 1.16 (95% CI 0.81 to 1.66), 1.62 (95% CI 1.14 to 2.30) (p-trend=0.001) after adjustment for traditional cardiovascular risk factors and LDL-COT Comparable adjusted hazard ratios for LDL-COT (<30, 30-50, >50 mg/dL) were 1.0, 0.87, and 1.21, respectively (p-trend=0.16). Relative risk reductions with bococizumab were similar across hsCRPOT groups (p-interaction=0.87). Conclusions -In this post-hoc analysis of the SPIRE trials of bococizumab in a stable outpatient population, evidence of residual inflammatory risk persisted among patients treated with both statin therapy and PCSK9 inhibition. Clinical Trial Registration -URL: https://clinicaltrials.gov Unique Identifiers: NCT01975376, NCT01975389.

[10] *Irvin MR, Aslibekyan S, Do A et al.* **Metabolic and inflammatory biomarkers are associated with epigenetic aging acceleration estimates in the GOLDN study**. Clinical epigenetics 2018; 10:56.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29713391
ABSTRACT
Background: Recently, epigenetic age acceleration-or older epigenetic age in comparison to chronological age-has been robustly associated with mortality and various morbidities. However, accelerated epigenetic aging has not been widely investigated in relation to inflammatory or metabolic markers, including postprandial lipids. Methods: We estimated measures of epigenetic age acceleration in 830 Caucasian participants from the Genetics Of Lipid Lowering Drugs and diet Network (GOLDN) considering two epigenetic age calculations based on differing sets of 5'-Cytosine-phosphate-guanine-3' genomic site, derived from the Horvath and Hannum DNA methylation age calculators, respectively. GOLDN participants underwent a standardized high-fat meal challenge after fasting for at least 8 h followed by timed blood draws, the last being 6 h postmeal. We used adjusted linear mixed models to examine the association of the epigenetic age acceleration estimate with fasting and postprandial (0- and 6-h time points) low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels as well as five fasting inflammatory markers plus adiponectin. Results: Both DNA methylation age estimates were highly correlated with chronological age (r > 0.90). We found that the Horvath and Hannum measures of epigenetic age acceleration were moderately correlated (r = 0.50). The regression models revealed that the Horvath age acceleration measure exhibited marginal associations with increased postprandial HDL (p = 0.05), increased postprandial total cholesterol (p = 0.06), and decreased soluble interleukin 2 receptor subunit alpha (IL2sRalpha, p = 0.02). The Hannum measure of epigenetic age acceleration was inversely associated with fasting HDL (p = 0.02) and positively associated with

postprandial TG (p = 0.02), interleukin-6 (IL6, p = 0.007), C-reactive protein (C-reactive protein, p = 0.0001), and tumor necrosis factor alpha (TNFalpha, p = 0.0001). Overall, the observed effect sizes were small and the association of the Hannum residual with inflammatory markers was attenuated by adjustment for estimated T cell type percentages. Conclusions: Our study demonstrates that epigenetic age acceleration in blood relates to inflammatory biomarkers and certain lipid classes in Caucasian individuals of the GOLDN study. Future studies should consider epigenetic age acceleration in other tissues and extend the analysis to other ethnic groups.

[11] *Kim MJ, Kim TH, Park Y et al.* **A study of the dietary intakes by the pre-pregnancy body mass index in pregnant women**. Clinical and experimental obstetrics & gynecology 2017; 44:27-29.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29714861
ABSTRACT
The authors analyzed the difference in weight gain and nutrition, according to the BMI before pregnancy. They divided 91 subjects into BMI group I (normal weight) and BMI group 2 (overweight) before pregnancy. In general, the BMI before pregnancy did not influence weight gain but, in the BMI group 2, the intakes of all of cholesterol, total fatty acids, vitamin B 12, iron, and copper were significantly higher. Neither group exhibited sufficient intake of vitamin B 1, vitamin B2, niacin, vitamin B6, folic acid, calcium, magnesium, iron, or zinc. Pre-pregnancy weight management and nutrition during pregnancy is very important.

[12] *Benesic A, Rotter I, Dragoi D et al.* **Development and Validation of a Test to Identify Drugs That Cause Idiosyncratic Drug-induced Liver Injury**. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29723689
ABSTRACT
BACKGROUND & AIMS: Idiosyncratic drug-induced liver injury (iDILI) is one of the most challenging diagnoses in hepatology. It is frequently impossible to identify the agent that has caused iDILI in patients who take multiple medicines. We developed an in vitro method to identify drugs that cause liver injury in patients, based on drug toxicity to monocyte-derived hepatocyte-like (MH) cells from patient blood samples. We then collected data on patients who were re-exposed to drugs found to be toxic in the MH test to validate test performance. METHODS: We performed a prospective study of patients referred to the University Hospital in Munich, Germany with acute liver injury believed to be caused by medications (300 patients are enrolled in the study and we present data from 40 patients with iDILI and re-exposure to implicated drugs). We collected data from patients on medical history, laboratory test and imaging results, findings from biopsy analyses, and medications taken. Blood samples were collected from all patients and MH cells were isolated and cultured for 10 days. MH cells were then incubated with drugs to which each patient had been exposed, and toxicity was measured based on release of lactate dehydrogenase. Agents found to be toxic to MH cells were considered as candidates for the cause of liver injury. Patients were followed for up to 6 months after liver injury and data on drug re-exposures and subsequent liver damage within the following 3-24 months were associated with findings from MH tests. RESULTS: Our test identified 10 drugs that were toxic to MH cells from 13 patients (amoxicillin/clavulanate to cells

from 2 patients; diclofenac to cells from 2 patients; methylprednisolon to cells from 2 patients; and atorvastatin, metamizole, pembrolizumab, piperacillin/tazobactam, moxifloxacin, duloxetine, or sertraline each to cells from 1 patient). Thirteen patients had a recurrence of liver injury after inadvertent re-exposure to a single drug, and the MH test correctly identified 12 of the 13 drugs that caused these liver re-injury events. All 86 drugs that were not toxic to MH cells in our assay were safely resumed by patients and not associated with liver re-injury in 27 patients. Therefore, the MH test identifies drugs that cause liver injury with 92.3% sensitivity and 100% specificity (1 false negative and 12 true positive results). CONCLUSION: We developed a test to identify drugs that cause liver injury in patients based on their toxicity to MH cells isolated from patients with DILI. We validated results from the assay and found it to identify drugs that cause DILI with 92.3% sensitivity and 100% specificity. The MH cell could be a tool to identify causes of iDILI, even in patients taking multiple medications ClinicalTrials.gov no: NCT 02353455.

[13] *Fobian AD, Elliott L, Louie T*. **A Systematic Review of Sleep, Hypertension, and Cardiovascular Risk in Children and Adolescents**. Curr Hypertens Rep 2018; 20:42.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29717377
ABSTRACT
PURPOSE OF REVIEW: Many of the risk factors for heart disease have recently been shown to develop during childhood such as left ventricular hypertrophy and fibrous plaque lesions. As risk for cardiovascular disease in children and adolescents has risen, sleep duration has decreased, and inadequate sleep in children and adolescents has been found to be associated with cardiovascular disease risk. The aims of this manuscript are to provide an updated systematic review of the literature assessing sleep, hypertension, and cardiovascular risk and evaluate the strength of the evidence based on the available research. RECENT FINDINGS: A systematic review was conducted using six databases from January 1, 2015 through March 9, 2018. We sought studies which looked at the relationship between sleep duration, sleep timing, or sleep quality and outcome variables of hypertension, inflammation, obesity, glucose or insulin, and lipids in children and adolescents. We found 24 studies which met our criteria. Nine studies included hypertension as an outcome variable; fifteen included obesity; thirteen included glucose or insulin; eight included lipids; and three included measures of inflammation. The existing literature on sleep and cardiovascular disease in children and adolescents is limited and relatively weak. Only one RCT was identified, and the overwhelming majority of studies had a high risk of bias. The strongest evidence of an association with sleep is with obesity, hypertension, and insulin sensitivity. Further research using more standardized methods and objective measures is needed to determine if a causal relationship truly exists between sleep and cardiovascular risk.

[14] *Manfrini O, Amaduzzi PL, Cenko E, Bugiardini R*. **Prognostic implications of peripheral artery disease in coronary artery disease**. Current opinion in pharmacology 2018; 39:121-128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29705248
ABSTRACT
Prevalence of peripheral arterial disease in patients with coronary artery disease is considerably higher than in the general population. A graded increase in the risk of major cardiovascular

events in a variety of clinical settings is associated with the number of arterial beds affected by peripheral arterial disease. This is not surprising, considering that both coronary artery disease and peripheral arterial disease are linked to a higher prevalence of cardiovascular risk factors and a greater incidence of atherosclerotic burden. Aggressive lipid lowering therapy is associated with less coronary and peripheral arterial disease progression and greater regression. On the contrary, blood pressure therapy should be carefully managed, considering the association of both high and low values of pressure with adverse outcomes.

[15] *Zinman B, Inzucchi SE, Wanner C et al.* **Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME(R)**. Diabetologia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29713728

ABSTRACT

AIMS/HYPOTHESIS: The global epidemic of type 2 diabetes affects women and men equally; however, the relative impact on the cardiovascular (CV) system appears greater for women than men when compared with peers without diabetes. Furthermore, women are often under-represented in CV outcome trials, resulting in less certainty about the impact of CV prevention therapies across the sexes. The EMPA-REG OUTCOME(R) trial, which included 28.5% women, found that empagliflozin, given in addition to standard of care, reduced the risk of CV death by 38%, heart failure (HF) hospitalisation by 35% and a composite endpoint for incident or worsening nephropathy by 39%. Here we report a secondary analysis of the trial to determine the relative effects of empagliflozin in women vs men. METHODS: The population studied were individuals with type 2 diabetes (HbA1c 53-86 mmol/mol [7-10%] and eGFR >30 ml min(-1) [1.73 m](-2)), with established atherosclerotic CV disease. Individuals were randomised to receive empagliflozin 10 mg or 25 mg, or placebo once daily in addition to standard of care, and followed. The trial continued until >/=691 individuals had experienced an adjudicated event included in the primary outcome. All CV outcome events, including HF hospitalisations and deaths were prospectively adjudicated by blinded clinical events committees. RESULTS: At baseline, the demographic profile of the 2004 women (age +/- standard deviation 63.6 +/- 8.8 years) compared with the 5016 men (age 63.0 +/- 8.6 years) in the trial was largely similar, with the exception that LDL-cholesterol was numerically higher in women (2.5 +/- 1.0 vs 2.1 +/- 0.9 mmol/l), consistent with lower rates of lipid-lowering therapies (75.4% vs 83.2%). Women were also less likely to have smoked (31.5% vs 69.9%). The annualised incidence rate for women in the placebo group was numerically lower than in men for CV death (1.58% vs 2.19%), numerically higher for HF hospitalisation (1.75% vs 1.33%) and similar for renal events (7.22% vs 7.75%). We did not detect any effect modification by sex within the statistical power restrictions of the analysis for CV death, HF hospitalisation and incident or worsening nephropathy (interaction p values 0.32, 0.20 and 0.85, respectively). Compared with placebo, empagliflozin increased the rates of genital infections in both women (2.5% vs 10.0%) and men (1.5% vs 2.6%). CONCLUSIONS/INTERPRETATION: CV death, HF hospitalisation and incident or worsening nephropathy rate reductions induced by empagliflozin were not different between women and men.

[16] *de Bruyn T, Ufuk A, Cantrill C et al.* **Predicting Human Clearance of OATP substrates using Cynomolgus monkey: In vitro-in vivo scaling of hepatic uptake clearance**. Drug metabolism and disposition: the biological fate of chemicals 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29720472
ABSTRACT
This work explores the utility of the cynomolgus monkey as a preclinical model to predict hepatic uptake clearance mediated by organic anion transporting polypeptide (OATP) transporters. Nine OATP substrates (rosuvastatin, pravastatin, repaglinide, fexofenadine, cerivastatin, telmisartan, pitavastatin, bosentan and valsartan) were investigated in plated cynomolgus monkey and human hepatocytes. Total uptake clearance and passive diffusion were measured in vitro from initial rates in the absence and presence of the OATP inhibitor rifamycin SV, respectively. Total uptake clearance values in plated hepatocytes ranged over three orders of magnitude in both species with a similar rank order and good agreement in the relative contribution of active transport to total uptake between cynomolgus monkey and human. In vivo hepatic clearance for these nine drugs was determined in cynomolgus monkey after intravenous dosing. Hepatic clearances showed a similar range to human parameters and good predictions from respective hepatocyte parameters (with 2.7 and 3.8-fold bias on average, respectively). The use of cross species empirical scaling factors (based on either dataset average or individual drug scaling factor from cynomolgus monkey data) improved prediction (less bias, better concordance) of human hepatic clearance from human hepatocyte data alone. In vitro intracellular binding in hepatocytes also correlated well between species. It is concluded that the minimal species differences observed for the current dataset between cynomolgus monkey and human hepatocyte uptake, both in vitro and in vivo, support future use of this preclinical model to delineate drug hepatic uptake and enable prediction of human in vivo intrinsic hepatic clearance.

[17] *Aparicio-Ugarriza R, Luzardo-Socorro R, Palacios G et al.* **What is the relationship between physical fitness level and macro- and micronutrient intake in Spanish older adults?** European journal of nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29721678
ABSTRACT
PURPOSE: The aim of this study was to assess the association between physical fitness (PF) and energy and nutrient intake in Spanish older adults. METHODS: Three hundred and twenty-four participants (59.9% females, aged over 55 years) performed a battery of four validated PF tests and participants were divided into three: low, medium, and high PF. Dietary intake was assessed by two non-consecutive 24 h dietary recalls. Energy and nutrient intake was calculated using the ALIMENTA software. Energy expenditure (EE) was calculated using a validated questionnaire. RESULTS: Median energy intake (EI) was 2135, 1999, and 2111 kcal/day in the low, medium, and high PF in males, respectively. In females, the median EI was 1576, 1564, and 1625 kcal/day in the low, medium, and high PF groups. There were significant and positive associations between participants in the high PF group and intake of phosphorous, selenium, vitamin B6, C, D, E, niacin, and folates (all $p < 0.05$). However, subjects in the high PF group presented negative associations with thiamine and riboflavin intake (all $p < 0.05$). A total of 8.3% of participants presented inadequate intake of 11 micronutrients. PF seems to affect total

nutrient intake. CONCLUSIONS: Higher protein and fat intake was observed in the high PF group compared to the other PF groups in males, although participants in the high PF group had also higher EE. However, females presented different patterns. In both sexes participants in the high PF group showed a better micronutrient intake profile than the other PF groups. There is a need to develop combined nutritional and fitness programs.

[18] *Elwan N, Salah R, Hamisa M et al.* **Evaluation of portal pressure by doppler ultrasound in patients with cirrhosis before and after simvastatin administration - a randomized controlled trial**. F1000Research 2018; 7:256.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707200
ABSTRACT
Background: Portal hypertension is one of the most frequent complications of cirrhosis. beta-adrenergic blockers, with or without organic nitrates, are currently used as hypotensive agents. Statins such as simvastatin seem to be safe for patients with chronic liver diseases and exert multiple pleiotropic actions. This study aimed to assess PTH using Doppler ultrasound in patients with cirrhosis before and after simvastatin administration. Methods: This randomized controlled clinical trial was conducted on 40 patients with cirrhosis who were randomized into 2 groups: group I included 20 patients with cirrhosis who were administered 20 mg of simvastatin daily for 2 weeks and then 40 mg daily for another 2 weeks, and group II included 20 patients with cirrhosis who did not receive simvastatin as a control group. All patients underwent full clinical examination, laboratory investigations, and abdominal Doppler ultrasound at baseline and after 30 days to evaluate portal vein diameter, blood flow volume, direction and velocity of portal vein blood flow, hepatic artery resistance and pulsatility indices, splenic artery resistance index, portal hypertension index (PHI), liver vascular index, and modified liver vascular index (MLVI). Results: There was a highly significant decrease in the hepatic artery resistance index in group I, from 0.785 +/- 0.088 to 0.717 +/- 0.086 ($P < 0.001$). There was a significant decrease in the PHI in group I , from 3.915 +/- 0.973 m/sec to 3.605 +/- 1.168 m/sec ($P = 0.024$). Additionally, there was a significant increase in the MLVI in group I from 11.540 +/- 3.266 cm/sec to 13.305 +/- 3.222 cm/sec, an increase of 15.3% from baseline ($P = 0.009$). No significant adverse effects were detected. Conclusions: Simvastatin is safe and effective in lowering portal hypertension. [ClinicalTrials.gov Identifier: NCT02994485].

[19] *Leppien E, Mulcahy K, Demler TL et al.* **Effects of Statins and Cholesterol on Patient Aggression: Is There a Connection?** Innovations in clinical neuroscience 2018; 15:24-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707423
ABSTRACT
Overview: Psychiatric adverse effects, including aggression, have been reported with the use of statin medications; however, there is little data to support or refute the theory that statins or low serum cholesterol do in fact increase a patient's risk of aggression. Objective: This study examined 1) statin use and increased aggression, measured by the requirement of either emergent psychiatric intervention referred to as "Code Green" (CG) or "Restraint and Seclusion" (RS) and 2) cholesterol level and increased aggression in psychiatric inpatients. Materials and Methods: Patient charts from January 1, 2011, to December 31, 2015 were reviewed. Statin therapy, lipid panel, and requirement of a psychiatric emergency code CG or

RS were noted. Inpatients who did not receive cholesterol-lowering therapy were used as controls. Analyses of variance (ANOVAs) were used to examine the relationship between statin use and increased aggression. Results: Eleven (9.6%) patients receiving statins required a total of 57 CGs, and five (4.4%) required 27 RSs. Conversely, 33 (28.9%) patients not receiving statins required a total of 64 CGs, and 14 (12.3%) required 27 RSs. No statistically significant relationship between statin therapy and agitation was found as evidenced by a CG (F=0.068; p=0.795) or RS (F=0.001; p=1.000). A statistically significant relationship was found between total cholesterol level and requirement of a CG (F=1.435; p=0.029) or RS (F=2.89; p=0.000). Conclusion: It is evident that psychiatric inpatients with lower total cholesterol levels are at an increased risk for loss of behavioral control.

[20] *Proto JD, Doran AC, Subramanian M et al.* **Hypercholesterolemia induces T cell expansion in humanized immune mice**. J Clin Invest 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29708512
ABSTRACT
Emerging data suggest that hypercholesterolemia has stimulatory effects on adaptive immunity and that these effects can promote atherosclerosis and perhaps other inflammatory diseases. However, research in this area has relied primarily on inbred strains of mice whose adaptive immune system can differ substantially from that of humans. Moreover, the genetically induced hypercholesterolemia in these models typically results in plasma cholesterol levels that are much higher than those in most humans. To overcome these obstacles, we studied human immune system-reconstituted mice (hu-mice) rendered hypercholesterolemic by treatment with adeno-associated virus 8-proprotein convertase subtilisin/kexin type 9 (AAV8-PCSK9) and a high-fat/high-cholesterol Western-type diet (WD). These mice had a high percentage of human T cells and moderate hypercholesterolemia. Compared with hu-mice that had lower plasma cholesterol, the PCSK9-WD mice developed a T cell-mediated inflammatory response in the lung and liver. Human CD4+ and CD8+ T cells bearing an effector memory phenotype were significantly elevated in the blood, spleen, and lungs of PCSK9-WD hu-mice, whereas splenic and circulating regulatory T cells were reduced. These data show that moderately high plasma cholesterol can disrupt human T cell homeostasis in vivo. This process may not only exacerbate atherosclerosis, but also contribute to T cell-mediated inflammatory diseases in the hypercholesterolemia setting.

[21] *Jami MM, Bhardwaj V, Merritt RJ*. **Intravenous Fish Oil Lipid Emulsion Prevents Catheter-Related Thromboses in Pediatric Patients with Intestinal Failure**. J Pediatr 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29706493
ABSTRACT
A central venous catheter is a risk factor for deep vein thrombosis. We compared the incidence of deep vein thrombosis in children with intestinal failure patients receiving soy oil lipid emulsion (n = 35) vs fish oil lipid emulsion (n = 35). Ten deep vein thrombosis occurred in the soy oil lipid emulsion group, and none in the fish oil lipid emulsion group (P < .001).

[22] *Abbasi J*. **Another Nail in the Coffin for Fish Oil Supplements**. Jama 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29710294

Literature update week 18 (2018)

ABSTRACT

[23] *Boonthos K, Puttilerpong C, Pengsuparp T, Manosuthi W*. **Short-term efficacy and safety of adding ezetimibe to currently used lipid-lowering drugs in Thai HIV-infected patients receiving protease inhibitors**. Japanese journal of infectious diseases 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29709973
ABSTRACT
Long-term complication of protease inhibitors (PIs) includes increased cardiovascular risks in HIV-infected patients due to dyslipidemia. Ezetimibe reduces LDL-C without drug interaction to PIs and statins. Furthermore, addition of ezetimibe on statins is an optional treatment in HIV-infected patients with uncontrolled dyslipidemia. The objective of this study was to determine short-term efficacy and safety of adding ezetimibe to currently used statins. Thirty-two patients received ezetimibe 10 mg daily added to their ongoing lipid-lowering therapy for 18 weeks. Serum LDL-C, total cholesterol (TC), triglycerides (TG), TC/HDL-C ratio and HDL-C were measured at baseline, week 6, 12 and 18. Safety parameters were assessed by adverse event reports and laboratory assessments throughout the study. The mean percent change from baseline to endpoint in LDL-C, TC, TG and TC/HDL-C ratio were -23.3% ($p < 0.001$), -15.0% ($p = 0.001$), -22.1% ($p = 0.004$) and -16.2% ($p = 0.018$), respectively. No adverse event or other abnormal laboratory occurred. Addition of ezetimibe to currently used lipid-lowering drugs in HIV-infected patients receiving PIs who had not achieved goal of dyslipidemia therapy had significantly improved efficacy in reducing of LDL-C, TC, TG and TC/HDL-C ratio, and the therapy was safe and well tolerated.

[24] *Bae SH, Park WS, Han S et al.* **Physiologically-based pharmacokinetic predictions of intestinal BCRP-mediated drug interactions of rosuvastatin in Koreans**. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology 2018; 22:321-329.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29719454
ABSTRACT
It was recently reported that the Cmax and AUC of rosuvastatin increases when it is coadministered with telmisartan and cyclosporine. Rosuvastatin is known to be a substrate of OATP1B1, OATP1B3, NTCP, and BCRP transporters. The aim of this study was to explore the mechanism of the interactions between rosuvastatin and two perpetrators, telmisartan and cyclosporine. Published (cyclosporine) or newly developed (telmisartan) PBPK models were used to this end. The rosuvastatin model in Simcyp (version 15)'s drug library was modified to reflect racial differences in rosuvastatin exposure. In the telmisartan-rosuvastatin case, simulated rosuvastatin CmaxI/Cmax and AUCI/AUC (with/without telmisartan) ratios were 1.92 and 1.14, respectively, and the Tmax changed from 3.35 h to 1.40 h with coadministration of telmisartan, which were consistent with the aforementioned report (CmaxI/Cmax: 2.01, AUCI/AUC:1.18, Tmax: 5 h --> 0.75 h). In the next case of cyclosporine-rosuvastatin, the simulated rosuvastatin CmaxI/Cmax and AUCI/AUC (with/without cyclosporine) ratios were 3.29 and 1.30, respectively. The decrease in the CLint,BCRP,intestine of rosuvastatin by telmisartan and cyclosporine in the PBPK model was pivotal to reproducing this finding in Simcyp. Our PBPK model demonstrated that the major causes of increase in rosuvastatin

exposure are mediated by intestinal BCRP (rosuvastatin-telmisartan interaction) or by both of BCRP and OATP1B1/3 (rosuvastatin-cyclosporine interaction).

[25] *Saini RK, Keum YS*. **Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance - A review**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29715470
ABSTRACT
Linoleic acid (LA) (n-6) and alpha-linolenic acid (ALA) (n-3) are essential fatty acids (EFAs) as they cannot be synthesized by humans or other higher animals. In the human body, these fatty acids (FAs) give rise to arachidonic acid (ARA, n-6), eicosapentaenoic acid (EPA, n-3), and docosahexaenoic acid (DHA, n-3) that play key roles in regulating body homeostasis. Locally acting bioactive signaling lipids called eicosanoids derived from these FAs also regulate diverse homeostatic processes. In general, ARA gives rise to pro-inflammatory eicosanoids whereas EPA and DHA give rise to anti-inflammatory eicosanoids. Thus, a proportionally higher consumption of n-3 PUFAs can protect us against inflammatory diseases, cancer, cardiovascular diseases, and other chronic diseases. The present review summarizes major sources, intake, and global consumption of n-3 and n-6 PUFAs. Their metabolism to biosynthesize long-chain PUFAs and eicosanoids and their roles in brain metabolism, cardiovascular disease, obesity, cancer, and bone health are also discussed.

[26] *Paththinige CS, Rajapakse J, Constantine GR et al.* **Spectrum of low-density lipoprotein receptor (LDLR) mutations in a cohort of Sri Lankan patients with familial hypercholesterolemia - a preliminary report**. Lipids in health and disease 2018; 17:100.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29720182
ABSTRACT
BACKGROUND: Hypercholesterolemia is a major determinant of cardiovascular disease-associated morbidity and mortality. Mutations in the LDL-receptor (LDLR) gene are implicated in the majority of the cases with familial hypercholesterolemia (FH). However, the spectrum of mutations in the LDLR gene in Sri Lankan patients has not been investigated. The objective of this study was to report the frequency and spectrum of variants in LDLR in a cohort of Sri Lankan patients with FH. METHODS: A series of consecutive patients with FH, diagnosed according to Modified Simon Broome criteria or Dutch Lipid Clinic Network criteria at the University Medical Unit, Colombo, were recruited. Clinical data was recorded. DNA was extracted from peripheral blood samples. The LDLR gene was screened for genetic variants by Sanger sequencing. RESULTS: A total of 27 patients [13 (48%) males, 14 (52%) females; age range 24-73 years] were tested. Clinical features found among these 27 patients were: xanthelasma in 5 (18.5%), corneal arcus in 1 (3.7%), coronary artery disease (CAD) in 10 (37%), and a family history of hypercholesterolemia and/or CAD in 24 (88.9%) patients. In the entire cohort, mean total cholesterol was 356.8 mg/dl (+/-66.4) and mean LDL-cholesterol was 250.3 mg/dl (+/-67.7). Sanger sequencing of the 27 patients resulted in the identification of known pathogenic missense mutations in 5 (18.5%) patients. Four were heterozygotes for 1 mutation each. They were c.682G > C in 2 patients, c.1720C > A in 1 patient, and c.1855 T > A in 1 patient. One patient with severe FH phenotypes was a compound heterozygote for one known mutation, c.2289G > T, and another missense variant, c.1670C > G (p.Thr557Ser), with unknown

functional impact. This latter variant has not been reported in any other population previously. CONCLUSIONS: The frequency of known mutations in the LDLR gene in this cohort of patients was markedly low compared to frequencies reported in other populations. This highlights the likelihood of a complex, polygenic inheritance of FH in Sri Lankan patients, indicating the need for a comprehensive genetic evaluation that includes the screening for mutations in other genes that cause FH, such as APOB, PCSK9, and LDLRAP1.

[27] *Chen Y, Chen X, Luo G et al.* **Discovery of Potential Inhibitors of Squalene Synthase from Traditional Chinese Medicine Based on Virtual Screening and In Vitro Evaluation of Lipid-Lowering Effect**. Molecules (Basel, Switzerland) 2018; 23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29710800
ABSTRACT
Squalene synthase (SQS), a key downstream enzyme involved in the cholesterol biosynthetic pathway, plays an important role in treating hyperlipidemia. Compared to statins, SQS inhibitors have shown a very significant lipid-lowering effect and do not cause myotoxicity. Thus, the paper aims to discover potential SQS inhibitors from Traditional Chinese Medicine (TCM) by the combination of molecular modeling methods and biological assays. In this study, cynarin was selected as a potential SQS inhibitor candidate compound based on its pharmacophoric properties, molecular docking studies and molecular dynamics (MD) simulations. Cynarin could form hydrophobic interactions with PHE54, LEU211, LEU183 and PRO292, which are regarded as important interactions for the SQS inhibitors. In addition, the lipid-lowering effect of cynarin was tested in sodium oleate-induced HepG2 cells by decreasing the lipidemic parameter triglyceride (TG) level by 22.50%. Finally. cynarin was reversely screened against other anti-hyperlipidemia targets which existed in HepG2 cells and cynarin was unable to map with the pharmacophore of these targets, which indicated that the lipid-lowering effects of cynarin might be due to the inhibition of SQS. This study discovered cynarin is a potential SQS inhibitor from TCM, which could be further clinically explored for the treatment of hyperlipidemia.

[28] *Quon J, Parkin L, Sharples K, Barson D*. **Co-prescribing of contraindicated and use-with-caution drugs in a national cohort of new users of simvastatin: how well are prescribing guidelines followed?** The New Zealand medical journal 2018; 131:35-44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29723177
ABSTRACT
AIM: To describe the use of contraindicated and use-with-caution medicines among new users of simvastatin. METHODS: We used information from Ministry of Health national datasets to establish a cohort of all patients aged >18 years who initiated simvastatin use between January 2006 and December 2013 (n=349,371). We estimated the cumulative incidences of the first dispensing of contraindicated and use-with-caution medicines during simvastatin use, and explored factors associated with co-prescription, using Kaplan-Meir and Cox regression methods, respectively. RESULTS: Eleven percent and 16% of patients were dispensed a contraindicated and use-with-caution medicine, respectively, during the first two years of simvastatin use; by seven years, the figures were 17% and 26%. Thirty-six percent of patients were co-prescribed a contraindicated medicine on >1 occasion; the corresponding proportion

for use-with-caution medicines was 84%. For a substantial proportion of those co-prescribed a use-with-caution medicine, the concomitant daily dose of simvastatin exceeded the maximum dose recommended at the time of prescribing. In the majority of cases, the prescriber of simvastatin and the contraindicated or use-with-caution medicine were the same. Co-prescribing of contraindicated medicines varied by sex, age, ethnicity and comorbidity. CONCLUSIONS: The prescription of contraindicated and use-with-caution drugs to patients taking simvastatin is not uncommon in New Zealand.

[29] *Foucault-Fruchard L, Tronel C, Bodard S et al.* **Alpha-7 nicotinic acetylcholine receptor agonist treatment in a rat model of Huntington's disease and involvement of heme oxygenase-1**. Neural regeneration research 2018; 13:737-741.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29722329
ABSTRACT
Neuroinflammation is a common element involved in the pathophysiology of neurodegenerative diseases. We recently reported that repeated alpha-7 nicotinic acetylcholine receptor (alpha7nAChR) activations by a potent agonist such as PHA 543613 in quinolinic acid-injured rats exhibited protective effects on neurons. To further investigate the underlying mechanism, we established rat models of early-stage Huntington's disease by injection of quinolinic acid into the right striatum and then intraperitoneally injected 12 mg/kg PHA 543613 or sterile water, twice a day during 4 days. Western blot assay results showed that the expression of heme oxygenase-1 (HO-1), the key component of the cholinergic anti-inflammatory pathway, in the right striatum of rat models of Huntington's disease subjected to intraperitoneal injection of PHA 543613 for 4 days was significantly increased compared to the control rats receiving intraperitoneal injection of sterile water, and that the increase in HO-1 expression was independent of change in alpha7nAChR expression. These findings suggest that HO-1 expression is unrelated to alpha7nAChR density and the increase in HO-1 expression likely contributes to alpha7nAChR activation-related neuroprotective effect in early-stage Huntington's disease.

[30] *Ochi E, Tsuchiya Y*. **Eicosahexanoic Acid (EPA) and Docosahexanoic Acid (DHA) in Muscle Damage and Function**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29710835
ABSTRACT
Nutritional supplementation not only helps in improving and maintaining performance in sports and exercise, but also contributes in reducing exercise fatigue and in recovery from exhaustion. Fish oil contains large amounts of omega-3 fatty acids, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3). It is widely known that omega-3 fatty acids are effective for improving cardiac function, depression, cognitive function, and blood as well as lowering blood pressure. In the relationship between omega-3 fatty acids and exercise performance, previous studies have been predicted improved endurance performance, antioxidant and anti-inflammatory responses, and effectivity against delayed-onset muscle soreness. However, the optimal dose, duration, and timing remain unclear. This review focuses on the effects of omega-3 fatty acid on muscle damage and function as evaluated by human

and animal studies and summarizes its effects on muscle and nerve damage, and muscle mass and strength.

[31] *Kaleem Z, Khan JA, Mushtaq Z et al.* **Assessment of potential interaction between simvastatin and clarithromycin in healthy adult male subjects**. Pak J Pharm Sci 2018; 31:801-806.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29716858
ABSTRACT
Cardiac patients with weak immune system are susceptible to bacterial infections. Their prescriptions frequently contain simvastatin and clarithromycin together. The objective of present project was to assess the potential interaction between simvastatin and clarithromycin by evaluating the clarithromycin effects on the pharmacokinetics of simvastatin in healthy adult male subjects. The study design comprised of two phases, used at interval of one week. In first phase simvastatin 20 mg alone was administered to each volunteer. In second phase, co-administration of simvastatin 20 mg with clarithromycin 250 mg was made under similar specified conditions. Blood samples were collected at specified time intervals. Simvastatin plasma concentrations were analyzed through High Performance Liquid Chromatography with UV detector at 238 nm wavelength. Using one compartment open model, MW/PHARM version 3.02 software program was used by F. Rombut for pharmacokinetic parameters calculation. Clarithromycin co-treatment resulted in 2.3 fold increase in maximum plasma concentration Cmax (from 2.47+/-0.34 ng.mL(-1) to 5.66+/-1.18 ng.mL(-1); $p<0.05$) and 3.9 fold increase in area under time versus concentration curve from 0 to 10 hours AUC0-10 (from 15.10+/-3.73 ng.hr.mL(-1) to 58.49+/-15.73 ng.hr.mL(-1); $p<0.05$) of simvastatin. These results suggest that co-prescription of simvastatin and clarithromycin should be avoided to minimize the adverse events resulting from high simvastatin concentration, without sacrificing therapeutic worth of simvastatin.

[32] *Legault MA, Tardif JC, Dube MP*. **Pharmacogenomics of blood lipid regulation**. Pharmacogenomics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29706123
ABSTRACT
Blood lipids are important modifiable risk factors for coronary heart disease and various drugs have been developed to target lipid fractions. Considerable efforts have been made to identify genetic variants that modulate responses to drugs in the hope of optimizing their use. Pharmacogenomics and new biotechnologies now allow for meaningful integration of human genetic findings and therapeutic development for increased efficiency and precision of lipid-lowering drugs. Polygenic predictors of disease risk are also changing how patient populations can be stratified, enabling targeted therapeutic interventions to patients more likely to derive the highest benefit, marking a shift from single variant to genomic approaches in pharmacogenomics.

[33] *Johnson JL, Merrilees M, Shragge J, van Wijk K*. **All-optical extravascular laser-ultrasound and photoacoustic imaging of calcified atherosclerotic plaque in excised carotid artery**. Photoacoustics 2018; 9:62-72.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707480

ABSTRACT

Photoacoustic (PA) imaging may be advantageous as a safe, non-invasive imaging modality to image the carotid artery. However, calcification that accompanies atherosclerotic plaque is difficult to detect with PA due to the non-distinct optical absorption spectrum of hydroxyapatite. We propose reflection-mode all-optical laser-ultrasound (LUS) imaging to obtain high-resolution, non-contact, non-ionizing images of the carotid artery wall and calcification. All-optical LUS allows for flexible acquisition geometry and user-dependent data acquisition for high repeatability. We apply all-optical techniques to image an excised human carotid artery. Internal layers of the artery wall, enlargement of the vessel, and calcification are observed with higher resolution and reduced artifacts with nonconfocal LUS compared to confocal LUS. Validation with histology and X-ray computed tomography (CT) demonstrates the potential for LUS as a method for non-invasive imaging in the carotid artery.

[34] *Jung Y, Cho Y, Kim N et al.* **Lipidomic profiling reveals free fatty acid alterations in plasma from patients with atrial fibrillation**. PloS one 2018; 13:e0196709.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29723222

ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its incidence is increasing worldwide. One method used to restore sinus rhythm is direct current cardioversion (DCCV). Despite the high success rate of DCCV, AF typically recurs within the first 2 weeks. However, our understanding of the pathophysiology of AF recurrence, incidence, and progression are highly limited. Lipidomic profiling was applied to identify altered lipids in plasma from patients with AF using ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry coupled with multivariate statistical analysis. Partial least-squares discriminant analysis revealed a clear separation between AF patients and healthy controls. The levels of several lipid species, including fatty acids and phospholipids, were different between AF patients and healthy controls, indicating that oxidative stress and inflammation are associated with the pathogenesis of AF. Similar patterns were also detected between recurrent and non-recurrent AF patients. These results suggest that the elevated saturated fatty acid and reduced polyunsaturated fatty acid levels in AF patients may be associated with enhanced inflammation and that free fatty acid levels may play a crucial role in the development and progression of AF.

[35] *Lin TK, Chou P, Lin CH et al.* **Long-term effect of statins on the risk of new-onset osteoporosis: A nationwide population-based cohort study**. PloS one 2018; 13:e0196713.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29723231

ABSTRACT

BACKGROUND: Several observational cohort and meta-analytical studies in humans have shown that statin users have a lower risk of fractures or greater bone mineral densities (BMD) than nonusers. However, some studies including randomized clinical trials have the opposite results, particularly in Asian populations. OBJECTIVE: This study investigates the impacts of statins on new-onset osteoporosis in Taiwan. METHODS: In a nationwide retrospective population-based cohort study, 45,342 subjects aged between 50-90 years having received statin therapy (statin-users) since January 1 2001, and observed through December 31 2013 were selected from the

National Health Insurance Research Database of Taiwan. Likewise, 115,594 patients had no statin therapy (statin-non-users) were included as controls in this study. Multivariable Cox proportional hazards analysis for drug exposures was employed to evaluate the association between statin treatment and new-onset of osteoporosis risk. We also used the long-rank test to evaluate the difference of probability of osteoporosis-free survival. RESULTS: During the 13-year follow-up period, 16,146 of all enrolled subjects (10.03%) developed osteoporosis, including 3097 statin-users (6.83%) and 13,049 statin-non-users (11.29%). Overall, statin therapy reduced the risk of new-onset osteoporosis by 48% (adjusted hazard ratio [HR] 0.52; 95% CI 0.50 to 0.54). A dose-response relationship between statin treatment and the risk of new-onset osteoporosis was observed. The adjusted hazard ratios for new-onset osteoporosis were 0.84 (95% CI, 0.78 to 0.90), 0.56 (95% CI, 0.52 to 0.60) and 0.23 (95% CI, 0.21 to 0.25) when cumulative defined daily doses (cDDDs) ranged from 28 to 90, 91 to 365, and more than 365, respectively, relative to nonusers. Otherwise, high-potency statins (rosuvastatin and atorvastatin) and moderate-potency statin (simvastatin) seemed to have a potential protective effect for osteoporosis. CONCLUSIONS: In this population-based cohort study, we found that statin use is associated with a decreased risk of osteoporosis in both genders. The osteoprotective effect of statins seemed to be more prominent with a dependency on the cumulative dosage and statin intensity.

[36] *Zhang J, Tecson KM, Rocha NA, McCullough PA*. **Usefulness of alirocumab and evolocumab for the treatment of patients with diabetic dyslipidemia**. Proceedings (Baylor University. Medical Center) 2018; 31:180-184.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29706812
ABSTRACT
In 2015, the US Food and Drug Administration (FDA) approved the anti-proprotein convertase subtilsin/kexin type 9 (PCSK9) monoclonal antibodies, alirocumab and evolocumab, to treat patients with hypercholesterolemia and mixed dyslipidemia. Since then, considerable attention has been paid to the use of these monoclonal antibodies for the treatment of diabetic dyslipidemia with a goal of reducing the risk for cardiovascular disease. Recently, consensus statements on the clinical use of PCSK9 inhibitors in patients with type 2 diabetes mellitus, who are unable to achieve the goal of low-density lipoprotein cholesterol (<70 mg/dL or <1.8 mmol/L), have been published by panels of experts in Greece, Europe (European Society of Cardiology and European Atherosclerosis Society Task Force), and the United States (American College of Cardiology Consensus Committee). On December 1, 2017, the FDA approved evolocumab to prevent heart attack, stroke, and coronary revascularization. In this article, we review recent advances concerning the pathophysiology of diabetic dyslipidemia, the physiology of PCSK9, the mechanisms of action of PCSK9 inhibitors, clinical trials examining PCSK9 inhibitors in type 2 diabetes, and perspectives of nonstatin therapy in the treatment of diabetic dyslipidemia.

[37] *Behiry S, Rabie A, Kora M et al.* **Effect of combination sildenafil and gemfibrozil on cisplatin-induced nephrotoxicity; role of heme oxygenase-1**. Renal failure 2018; 40:371-378.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707997
ABSTRACT

BACKGROUND/AIM: Cisplatin-induced nephrotoxicity in large proportion of patients. The aim of this work is to clarify the effect of combination of sildenafil and gemfibrozil on cisplatin-induced nephrotoxicity either before or after cisplatin treatment and determination of nephrotoxicity predictors among the measured tissue markers. METHODS: Thirty two adult male albino rats were divided into four equal groups (G) GI control, GII received cisplatin, GIII received sildenafil and gemfibrozil before cisplatin, GIV received sildenafil and gemfibrozil after cisplatin. Creatinine and urea were measured and animals were sacrificed and kidney was taken for histopathology. The following tissue markers were measured, heme oxygenase-1 (HO-1) activity, reduced glutathione, quantitative (real-time polymerase chain reaction) RT-PCR for gene expression of tumor necrosis factor alpha (TNF-alpha) and endothelial nitric oxide synthase (ENOS) level. RESULTS: GII developed AKI demonstrated by significantly high urea and creatinine and severe diffuse (80-90%) tubular necrosis. TNF-alpha was highly and significantly elevated while the rest of tissue markers were significantly reduced in GI1 compared to other groups. GIV showed better results compared to GIII. There was a significant positive correlation between creatinine and TNF-alpha when combining GI and GII while there were significant negative correlation between creatinine and other tissue markers in same groups. Linear regression analysis demonstrated that HO-1 was the independent predictor of AKI demonstrated by elevated creatinine among GI and GII. CONCLUSIONS: Combination of sildenafil and gemfibrozil can be used in treatment of cisplatin-induced nephrotoxicity. HO-1 is a promising target for prevention and/or treatment of cisplatin-induced nephrotoxicity.

[38] *Moradi H, Streja E, Vaziri ND*. **ESRD-induced dyslipidemia-Should management of lipid disorders differ in dialysis patients?** Semin Dial 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29707830
ABSTRACT
Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Although numerous modifiable risk factors in the pathogenesis of CVD and its associated mortality have been identified, dyslipidemia remains to be a key focus for therapy. In this regard, significant progress has been made in reducing cardiovascular mortality via the use of lipid-lowering agents such as HMG CoA reductase inhibitors (statins). Yet, despite the disproportionate risk of CVD and mortality in patients with advanced chronic and end stage renal disease (ESRD), treatment of dyslipidemia in this patient population has not been associated with a notable improvement in outcomes. Furthermore, observational studies have not consistently found an association between dyslipidemia and poor outcomes in patients with ESRD. However, it is imperative that examination of dyslipidemia and its association with outcomes take place in the context of the many factors that are unique to kidney disease and may contribute to the abnormalities in lipid metabolism in patients with ESRD. Understanding these intricacies and distinct features will be vital not only to the interpretation of the available clinical data in regards to outcomes, but also to the individualization of lipid therapy in ESRD. In this review, we will examine the nature and underlying mechanisms responsible for dyslipidemia, the association of serum lipids and lipoprotein concentrations with outcomes and the results of major trials targeting cholesterol (mainly statins) in patients with ESRD.

[39] *Zheng W, Yang W, Zhang QE et al.* **Meta-analysis of the Efficacy and Safety of Adjunctive Rosuvastatin for Dyslipidemia in Patients with Schizophrenia**. Shanghai archives of psychiatry 2018; 30:4-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29719353
ABSTRACT
Background: Metabolic syndrome in patients with schizophrenia is a major health concern. The efficacy and safety of adjunctive rosuvastatin in treating dyslipidemia were controversial. Aims: To assess the efficacy and safety of adjunctive rosuvastatin for dyslipidemia in patients with schizophrenia. Methods: We systematically searched for relevant controlled clinical trials from the following databases: PubMed, PsycINFO, Cochrane Library, China Knowledge Network, WanFang Database and Chinese Biomedical Database up to September 28, 2017. Standardized mean difference (SMD) and risk ratio (RR) along with their 95% confidence intervals (CIs) were calculated. The quality of the included studies was assessed using the Cochrane risk of bias assessment tool. The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system recommendation grading method was used as the reference standard. Results: Four studies (n=274) comparing rosuvastatin (n=138) and control (n=136) groups were identified and analyzed. Adjunctive rosuvastatin showed greater efficacy than control group in low density lipoprotein cholesterol (LDL-C) [4 trials, n=272, SMD: -1.31 (95%CI: -1.93, -0.70), I(2)=81%], total cholesterol (2 trials, n=164, SMD: -2.00 (95%CI: -2.79, -1.21); I(2)=76%) and triglycerides (2 trials, n=164, SMD: -1.05 (95%CI: -1.38, -0.72); I(2)=0%), but not in high density lipoprotein cholesterol (2 trials, n=164, SMD: 0.14 (95%CI: -0.16, 0.45); I(2)=0%). After removing one study without randomization for LDL-C, significance remained [3 trials, n=172, SMD:-1.07 (95%CI: -1.60, -0.53); I(2)=63%]. No significant group differences regarding body weight (3 trials, n=208, SMD: -0.40 (95%CI:-1.29, 0.49); I(2)=89%), body mass index (2 trials, n=164, SMD: -0.34 (95%CI: -1.23, 0.56); I(2)=87%), waist circumference (3 trials, n=208, SMD): -0.43 (95%CI: -1.31, 0.46); I(2)=89%), and fasting glucose (4 trials, n=272, SMD: -0.25 (95%CI: -0.65, 0.15); I(2)=62%) were observed. The adverse reactions and any cause discontinuation rate were similar between the groups. According to the GRADE approach, the evidence levels of main outcomes were rated as "very low" (35.3%) to "low" (64.7%). Of them, the primary outcome (LDL-C) was rated as "very low ". Conclusions: The data available on the effectiveness and safety of adjunctive rosuvastatin in treating dyslipidemia for patients with schizophrenia is insufficient to come to a definitive interpretation about its efficacy and safety. Further high quality RCTs with extended treatment duration are warranted to confirm the findings. Review registration: PROSPERO: CRD42017078230.

[40] *Lengyel E, Makowski L, DiGiovanni J, Kolonin MG*. **Cancer as a Matter of Fat: The Crosstalk between Adipose Tissue and Tumors**. Trends in cancer 2018; 4:374-384.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29709261
ABSTRACT
Obesity has been linked to the increased risk and aggressiveness of many types of carcinoma. A state of chronic inflammation in adipose tissue (AT), resulting in genotoxic stress, may contribute to carcinogenesis and cancer initiation. Evidence that AT plays a role in cancer aggressiveness is solid and mounting. During cancer progression, tumor cells engage in a metabolic symbiosis with adjacent AT. Mature adipocytes provide adipokines and lipids to

cancer cells, while stromal and immune cells from AT infiltrate carcinomas and locally secrete paracrine factors within the tumor microenvironment. This review focuses on the crosstalk between AT and tumor cells that promotes tumor growth and increases cellular lipid metabolism, metastasis, and chemoresistance.

[41] *Kaya T, Akcay EU, Erturk Z et al.* **The relationship between vitamin D deficiency and erythrocyte sedimentation rate in patients with diabetes**. Turk J Med Sci 2018; 48:424-429.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29714465
ABSTRACT
Background/aim: Vitamin D deficiency in diabetic patients has been shown to be associated with some inflammatory markers. However, its relationship with erythrocyte sedimentation rate (ESR) is still unknown. The aim of this study was to investigate the relationship between vitamin D deficiency and ESR in patients with type 2 diabetes mellitus (T2DM). Materials and methods: This cross-sectional study was conducted with 294 consecutive patients with T2DM. Serum levels of 25-hydroxyvitamin D, glycemic parameters, lipids, ESR, and C-reactive protein were measured. Patients were evaluated according to 25-hydroxyvitamin D levels as having vitamin D deficiency, vitamin D insufficiency, and vitamin D sufficiency. Results: ESR was found to be higher in patients with vitamin D deficiency than in patients who were vitamin D-sufficient ($P < 0.001$), and ESR was negatively correlated with 25-hydroxyvitamin D level ($r = -0.265$, $P < 0.001$). HbA1c and postprandial glucose levels were higher in patients with vitamin D deficiency than vitamin D-sufficient patients ($P = 0.005$ and $P = 0.019$, respectively). In receiver operating curve analysis, an ESR value of 14.5 mm/h had 70.1% sensitivity and 50.3% specificity for the prediction of vitamin D deficiency. Conclusion: The present study revealed that ESR is higher in T2DM patients with vitamin D deficiency than patients with sufficient vitamin D. There was an inverse association between ESR and vitamin D levels. Furthermore, vitamin D deficiency was related to poor glycemic control.

[42] *Hernandez-Aquino E, Muriel P*. **Beneficial effects of naringenin in liver diseases: Molecular mechanisms**. World journal of gastroenterology : WJG 2018; 24:1679-1707.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29713125
ABSTRACT
Liver diseases are caused by different etiological agents, mainly alcohol consumption, viruses, drug intoxication or malnutrition. Frequently, liver diseases are initiated by oxidative stress and inflammation that lead to the excessive production of extracellular matrix (ECM), followed by a progression to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). It has been reported that some natural products display hepatoprotective properties. Naringenin is a flavonoid with antioxidant, antifibrogenic, anti-inflammatory and anticancer properties that is capable of preventing liver damage caused by different agents. The main protective effects of naringenin in liver diseases are the inhibition of oxidative stress, transforming growth factor (TGF-beta) pathway and the prevention of the transdifferentiation of hepatic stellate cells (HSC), leading to decreased collagen synthesis. Other effects include the inhibition of the mitogen activated protein kinase (MAPK), toll-like receptor (TLR) and TGF-beta non-canonical pathways, the inhibition of which further results in a strong reduction in ECM synthesis and deposition. In addition, naringenin has shown beneficial effects on nonalcoholic fatty liver disease (NAFLD)

through the regulation of lipid metabolism, modulating the synthesis and oxidation of lipids and cholesterol. Moreover, naringenin protects from HCC, since it inhibits growth factors such as TGF-beta and vascular endothelial growth factor (VEGF), inducing apoptosis and regulating MAPK pathways. Naringenin is safe and acts by targeting multiple proteins. However, it possesses low bioavailability and high intestinal metabolism. In this regard, formulations, such as nanoparticles or liposomes, have been developed to improve naringenin bioavailability. We conclude that naringenin should be considered in the future as an important candidate in the treatment of different liver diseases.