Literature update week 32 (2018)

[1] *Xue D, Gong Z, Zhu F et al.* **Simvastatin increases cell viability and suppresses the expression of cytokines and vascular endothelial growth factor in inflamed human dental pulp stem cells in vitro**. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30088351
ABSTRACT
BACKGROUND: In recent years, simvastatin has been demonstrated to be capable of inducing odontogenic differentiation in human dental pulp stem cells (DPSCs), which makes it a promising source for endodontic treatment in pulpitis. However, a comprehensive understanding of how simvastatin affects the behavior of DPSCs and its potential in pulpitis is still lacking. OBJECTIVES: In this study, we investigated the effects of simvastatin on the viability of inflamed DPSCs. The expression of cytokines and vascular endothelial growth factor (VEGF) was also studied in response to simvastatin treatment. MATERIAL AND METHODS: We characterized the cell viability, inflammatory reactions and the production of VEGF in inflamed DPSCs, induced by lipopolysaccharides (LPS). The methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay, cell cycle, apoptosis analysis, quantitative reverse transcription polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), and western blot analyses were performed. RESULTS: We observed that a low dosage of simvastatin accelerated cell proliferation , whereas its high dosage (>15 mug/mL) suppressed propagation. A simvastatin dose of 8 mug/mL was sufficient to promote cell growth and cell cycle progression in DPSCs treated with LPS. Meanwhile, simvastatin induced apoptosis. The expression of multiple cytokines, including interleukins (IL)-1, IL-4 and IL-1beta, and especially interferon-gamma (IFN-gamma) and tumor necrosis factor-alpha (TNF-alpha), was significantly suppressed. Moreover, the protein secretion and mRNA transcription of VEGF was observed to be markedly inhibited by simvastatin by inactivating mitogen-activated protein kinase (MAPK) signaling. CONCLUSIONS: Taken together, these results suggested that simvastatin might be a potent ingredient to enhance cell proliferation, alleviate inflammation response and attune vasculogenesis in pulpitis.

[2] *Morotti K, Lopez J, Vaupel V et al.* **Adherence to and Persistence With Statin Therapy in a Veteran Population**. The Annals of pharmacotherapy 2018:1060028018792702.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30084646
ABSTRACT
BACKGROUND: A relative cardiovascular risk reduction of 25% to 35% has been reported in patients starting a statin for elevated cholesterol; yet many patients fail to consistently take these medications as directed. OBJECTIVE: To evaluate factors affecting adherence and persistence with statin therapy. METHODS: This retrospective study analyzed data from a Veterans Affairs database of facilities west of the Rocky Mountains. Patient demographics, co-morbidities, and prescription information was collected for individuals newly prescribed a statin between July 1, 2007, and December 31, 2012. Adherence was determined using the medication possession ratio (MPR). Persistence was defined as the time from initiation of therapy until a refill gap of 135 days or greater occurred. RESULTS: Of 164 687 unique patients, overall adherence to statins a mean MPR of 0.843. Approximately 63% of patients were persistent with statin therapy 675 days after statin initiation. Patients prescribed pravastatin,

atorvastatin, lovastatin, and rosuvastatin and those who took more than 1 different statin during the follow-up period had statistically significantly higher rates of adherence than those prescribed simvastatin. Older patients and those with a greater number of active prescriptions were found to be more adherent to statin medications. Patients with hypertension were more adherent to a statin, and those with diabetes mellitus and/or posttraumatic stress disorder (PTSD) were less adherent. Conclusion and Relevance: In veterans, overall statin adherence was excellent. Certain populations may benefit from interventions targeted at improving statin adherence, including younger veterans, those prescribed fewer medications, those taking simvastatin, and veterans with PTSD or diabetes mellitus.

[3] *Mayala HA, Bakari KH, Mghanga FP, ZhaoHui W*. **Clinical significance of PET-CT coronary flow reserve in diagnosis of non-obstructive coronary artery disease**. BMC research notes 2018; 11:566.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30081956
ABSTRACT
OBJECTIVE: To improve current knowledge of coronary flow reserve and non-obstructive coronary artery disease in terms of definition, features and clinical implications of measurement of coronary flow reserve (CFR), is an integrated measure of focal, diffuse, and small vessel coronary artery disease, can also be explained as a calculated ratio of hyperaemic to rest absolute myocardial blood flow. Non-obstructive coronary artery disease is defined as atherosclerotic plaque that does not obstruct blood flow or result in anginal symptoms. We also aimed at knowing the significance of PET in diagnosing coronary microvascular disease. RESULTS: In our study 92% were between 41 and 60 years. 83% were males and 17% females, more patients had hypertension about 50%, few had diabetes mellitus about 16%, while those with both hypertension and diabetes mellitus were 17%. About 83% had ST segment and T wave changes on ECG. All patients and controls had normal coronaries on coronary angiography TIMI 3 flow. On further investigation by Positron emission tomography/CT we found out 58% had abnormal CFR and 42% had normal coronary flow reserve. Our findings indicate PET/CT coronary flow reserve concept provides a platform for the diagnosis of non-obstructive coronary artery disease in patients with signs and symptoms of ischemia without angiographic obstructive CAD.

[4] *Ruel I, Brisson D, Aljenedil S et al.* **Simplified Canadian Definition for Familial Hypercholesterolemia**. The Canadian journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30093300
ABSTRACT
Familial hypercholesterolemia (FH) is an autosomal codominant lipoprotein disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) and high risk of premature atherosclerotic cardiovascular disease. Definitions for FH rely on complex algorithms that are on the basis of levels of total or LDL-C, clinical features, family history, and DNA analysis that are often difficult to obtain. We propose a novel simplified definition for FH. Definite FH includes: (1) elevated LDL-C (>/= 8.50 mmol/L); or (2) LDL-C >/= 5.0 mmol/L (for age 40 years or older; >/= 4.0 mmol/L if age younger than 18 years; and >/= 4.5 mmol/L if age is between 18 and 39 years) when associated with at least 1 of: (1) tendon xanthomas; or (2)

causal DNA mutation in the LDLR, APOB, or PCSK9 genes in the proband or first-degree relative. Probable FH is defined as subjects with an elevated LDL-C (>/= 5.0 mmol/L) and the presence of premature atherosclerotic cardiovascular disease in the patient or a first-degree relative or an elevated LDL-C in a first-degree relative. LDL-C cut points were determined from a large database comprising > 3.3 million subjects. To compare the proposed definition with currently used algorithms (ie, the Simon Broome Register and Dutch Lipid Clinic Network), we performed concordance analyses in 5987 individuals from Canada. The new FH definition showed very good agreement compared with the Simon Broome Register and Dutch Lipid Clinic Network criteria (kappa = 0.969 and 0.966, respectively). In conclusion, the proposed FH definition has diagnostic performance comparable to existing criteria, but adapted to the Canadian population, and will facilitate the diagnosis of FH patients.

[5] *Giustino G, Colantonio LD, Brown TM et al.* **Titration to High-Intensity Statin Therapy Following Acute Myocardial Infarction in Patients With and Without Diabetes Mellitus**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30078077
ABSTRACT
BACKGROUND: Patients with diabetes mellitus (DM) have a high risk for cardiovascular disease (CVD) events after an acute myocardial infarction (AMI). High-intensity statins reduce CVD risk following AMI among patients with and without DM. METHODS: We determined the proportion of Medicare beneficiaries 66 to 75 years of age taking a low/moderate-intensity statin with (n = 6718) and without (n = 6414) DM who titrated to a high-intensity statin dosage (i.e., atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) following an AMI hospitalization in 2014-2015. All patients had a pharmacy claim for a statin fill within 365 days prior to, and within 30 days after their AMI hospitalization. We excluded beneficiaries without Medicare fee-for-service coverage including pharmacy benefits during the study period and those with a pharmacy claim for a high-intensity statin prior to their AMI. RESULTS: The first statin fill following hospital discharge was for a high-intensity dosage among 37.7% and 44.4% of patients with and without DM, respectively. After multivariable adjustment, the risk ratio (RR) for titrating to a high-intensity statin comparing patients with versus without DM was 1.01 (95% CI 0.96, 1.06). Among patients whose first statin fill post-AMI was for a low/moderate-intensity dosage, 7.5% of those with DM titrated to a high-intensity statin within 182 days, compared with 9.2% of those without DM (multivariable-adjusted RR 0.90 [95% CI 0.75, 1.08]). CONCLUSIONS: Most patients taking a low/moderate-intensity statin were not titrated to a high-intensity dosage following AMI irrespective of their diabetes status, potentially leaving substantial residual risk for recurrent CVD events.

[6] *Brown M*. **Enhancing Therapy: It's about Time**. Cell 2018; 174:771-772.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30096305
ABSTRACT
How diet and obesity impact diurnal changes in physiology remains unclear. In this issue of Cell, Guan et al. report that diet-induced obesity modulates the activity of circadian gene enhancers

including those regulating lipid metabolism and show that the efficacy of lipid-lowering drugs depends on the time of administration.

[7] *Ishii H, Murohara T*. **Trade-Off Between Lipid-Lowering Therapy and Costs in Patients With Cardiovascular Disease**. Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30089745
ABSTRACT

[8] *Ajith TA*. **A recent update on the effects of omega-3 fatty acids in Alzheimer's disease**. Current clinical pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30084334
ABSTRACT
Dietary long chain polyunsaturated fatty acids belong to omega (omega)-3, -6 or -9 series. Both experimental and clinical studies demonstrated the beneficial effect of omega -3 fatty acids of fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) against human ailments including cardiovascular diseases and rheumatoid arthritis. They are metabolized in cyclooxygenase and lipooxygenase pathways and also by cytochrome P450 isozymes. Biological importance of DHA in the development of brain and retina are established as well. Recent studies highlighted the beneficial effect of omega-3 fatty acids in Alzheimer's disease (AD) which may be attributed to their antioxidant, anti-inflammatory, antiapoptotic and neurotrophic properties. The effect was obtained by the consumption of either individual or combination of omega -3 fatty acids. The anti-inflammatory effect can be ascribed to the decreased cytokines and monocytic chemotactic protein-1 level by suppressing the nuclear factor-kappa B. Further, they inhibit cyclooxygenase-2 and nitric oxide synthase-2 activities. The antiapoptotic activity is due to the lowered Bax/Bcl ratio or caspase 3 levels. They can induce the transcription factor, nuclear erythroid factor-2 mediated expression of superoxide dismutase-2 in order to facilitate the antioxidant effect. Both DHA and EPA can enhance the nerve growth factor level. Overall, they are beneficial to improve the cognitive function in very mild AD and major depressive disorder. Despite the beneficial effects, omega-3 fatty acids are easily prone to peroxidation. This review article discusses the recent update on the roles of omega -3 fatty acids in AD.

[9] *Rosenthal MD, Patel J, Staton K et al.* **Can Specialized Pro-resolving Mediators Deliver Benefit Originally Expected from Fish Oil?** Current gastroenterology reports 2018; 20:40.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30078085
ABSTRACT
PURPOSE OF THE REVIEW: Fish oil (FO) supplementation has historically been used by individuals suffering from cardiovascular disease and other inflammatory processes. However, a meta-analysis of several large randomized control trials (RCTs) suggested FO conferred no benefit in reducing cardiovascular risk. Skeptics surmised that the lack of benefit was related to FO dose or drug interactions; therefore, the widely accepted practice of FO consumption was brought into question. RECENT FINDINGS: Thereafter, Serhan et al. identified specialized pro-resolving mediators (SPMs) to be one of the bioactive components and mechanisms of action of

FO. SPMs are thought to enhance resolution of inflammation, as opposed to classic anti-inflammatory agents which inhibit inflammatory pathways. Numerous diseases, including persistent Inflammation, immunosuppression, and catabolic syndrome (PICS), are rooted in a burden of chronic inflammation. SPMs are gaining traction as potential therapeutic agents used to resolve inflammation in cardiovascular disorders, inflammatory bowel disease, sepsis, pancreatitis, and acute respiratory distress syndrome (ARDS). This narrative reviews the history of FO and the various studies that made the health benefits of FO inconclusive, as well as an overview of SPMs and their use in specific disease states.

[10] *Mantsiou C, Tziomalos K*. **Strategies to achieve low-density lipoprotein cholesterol targets in high-risk patients**. Current medical research and opinion 2018:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30086667
ABSTRACT

[11] *Bae JC, Min KW, Kim YH et al.* **Efficacy and safety of fixed-dose comBination therApy with gemigLiptin (50 mg) and rosuvAstatiN (20 mg) Compared with Each monotherapy in patients with type 2 diabetes and dyslipidaemia (BALANCE): A multicentre, randomized, double-blind, controlled, phase 3 trial**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30084112
ABSTRACT
OBJECTIVE: To evaluate the efficacy and safety of a fixed-dose combination (FDC) of gemigliptin/rosuvastatin in patients with type 2 diabetes and dyslipidaemia. RESEARCH DESIGN AND METHODS: Thirty-three hospitals in Korea participated in this randomized, double-blind trial of diabetic patients with dyslipidaemia. Two hundred ninety participants were randomly assigned at a 1:1:1 ratio to receive a FDC of gemigliptin (50 mg)/rosuvastatin (20 mg) (GEMI/ROSU FDC group), gemigliptin (50 mg) (GEMI group), or rosuvastatin (20 mg) (ROSU group). Rosuvastatin was up-titrated from 5 mg/day to 20 mg/day throughout the study period. Primary efficacy measures were changes in HbA1c and LDL-C from baseline to week 24 between the GEMI/ROSU FDC and ROSU groups and between the GEMI/ROSU FDC and GEMI groups, respectively. Secondary efficacy measures were changes in HbA1c and LDL-C between the GEMI/ROSU FDC and GEMI groups and between the GEMI/ROSU FDC and ROSU groups, respectively. RESULTS: After 24 weeks of treatment, a significant reduction in HbA1c from baseline was noted in the GEMI/ROSU FDC group (-0.81% of LS mean, $p<0.0001$ vs. ROSU group), in addition to a significant reduction in LDL-C concentration (-51.9% of LS mean percentage changes, $p<0.0001$ vs. GEMI group). HbA1c was significantly reduced from baseline in both the GEMI/ROSU FDC and GEMI groups, but the reduction in HbA1c was significantly greater in the GEMI group than in the GEMI/ROSU FDC group, despite having the same gemigliptin dose. The decrease in LDL-C over time was similar between the GEMI/ROSU FDC and ROSU groups. There were no significant differences in adverse events among the groups. CONCLUSION: The FDC of gemigliptin/rosuvastatin is effective and safe at reducing both blood glucose and LDL-C levels and could be a good therapeutic choice for type 2 diabetic patients with dyslipidaemia. This article is protected by copyright. All rights reserved.

[12] *Chen L, Liu Q, Shi Z et al.* **Interstudy reproducibility of dark blood high-resolution MRI in evaluating basilar atherosclerotic plaque at 3 Tesla**. Diagnostic and interventional radiology (Ankara, Turkey) 2018; 24:237-242.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30091714
ABSTRACT
PURPOSE: We aimed to evaluate the interscan, intraobserver, and interobserver reproducibility of basilar atherosclerotic plaque employing dark blood high-resolution magnetic resonance imaging (HR-MRI) at 3 Tesla. METHODS: Sixteen patients (14 males and 2 females) with > 30% basilar stenosis as identified by conventional magnetic resonance angiography were prospectively recruited for scan and rescan examinations on a 3 Tesla MRI system using T2-weighted turbo spin-echo protocol. Two observers independently measured the areas of vessels and lumens. Wall area was derived by subtracting the lumen area from the vessel area. Areas of vessels, lumens and walls were compared for the evaluation of interscan variability of basilar plaque. To assess the intraobserver variability, one observer reevaluated all the images of the first scan after a 4-week interval. RESULTS: Fourteen patients were included in the final analysis. No clinically significant difference was observed for interscan, intraobserver, and interobserver measurements. The intraclass correlations for vessel, lumen, and wall areas were excellent and ranged from 0.973 to 0.981 for the interscan measurements, 0.997 to 0.998 for the intraobserver measurements and 0.979 to 0.985 for the interobserver measurements. The coefficients of variation for quantitative basilar morphology measurements were 4.31%-10.35% for the interscan measurements, 1.41%-4.62% for the intraobserver measurements and 3.79%-8.46% for the interobserver measurements. Compared with the interscan and interobserver measurements, narrow intervals of the scatterplots were observed for the intraobserver measurements by Bland-Altman plots. CONCLUSION: Basilar atherosclerotic plaque imaging demonstrates excellent reproducibility at 3 Tesla. The study proves that dark blood HR-MRI may serve as a reliable tool for clinical studies focused on the progression and treatment response of basilar atherosclerosis.

[13] *Choi Y, Lee S, Jang IJ, Yu KS*. **Pharmacokinetic interaction between fimasartan and atorvastatin in healthy male volunteers**. Drug design, development and therapy 2018; 12:2301-2309.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30087555
ABSTRACT
Introduction: Major cardiovascular risk factors, including hypertension and dyslipidemia, are often comorbidities, frequently leading to concurrent prescription of angiotensin receptor blockers and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins). The study's objective was to evaluate the effect of coadministration of fimasartan and atorvastatin on their pharmacokinetics (PKs). Subjects and methods: In a randomized, open-label, three-period, six-sequence, crossover, multiple-dose study, 36 healthy subjects received 120 mg fimasartan, 40 mg atorvastatin, or both (based on their assigned sequence) once daily for 7 days in each period, with a 7-day washout between periods. Blood samples for the PK analysis of fimasartan, atorvastatin, and the 2-hydroxy atorvastatin metabolite were collected up to 48 h after the last dose. Results: The coadministration of fimasartan and atorvastatin was well tolerated and led to an increase in the peak concentration and area under the concentration-time curve at steady

state of fimasartan by 2.18-fold (95% confidence interval [CI], 1.79-2.65) and 1.35-fold (95% CI, 1.26-1.43) and those of atorvastatin increased by 1.82-fold (95% CI, 1.51-2.18) and 1.12-fold (95% CI, 1.04-1.22), respectively. Conclusion: Coadministration increased the systemic exposures of fimasartan and atorvastatin, but the clinical significance of this finding needs to be evaluated with respect to exposure responses and clinical outcomes.

[14] *Olsen SF, Halldorsson TI, Thorne-Lyman AL et al.* **Plasma Concentrations of Long Chain N-3 Fatty Acids in Early and Mid-Pregnancy and Risk of Early Preterm Birth**. EBioMedicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30082226
ABSTRACT
BACKGROUND: Fish oil supplementation has been shown to delay spontaneous delivery, but the levels and clinical significance remain uncertain. We examined the association between plasma fatty acids quantified in pregnancy and subsequent risk of early preterm birth. METHODS: In a case-control design nested in the Danish National Birth Cohort, we identified 376 early preterm cases (<34 gestational weeks, excluding preeclampsia cases) and 348 random controls. Plasma eicosapentaenoic acid plus docosahexaenoic acid (EPA+DHA% of total fatty acids), were measured twice in pregnancy, at gestation weeks 9 and 25 (medians). Odds ratios and 95% confidence intervals (CI's) for associations between EPA+DHA and early preterm risk were estimated by logistic regression, adjusted for the woman's age, height, pre-pregnancy BMI, parity, smoking, and socioeconomic factors. Hypotheses and analytical plan were defined and archived a priori. FINDINGS: Analysis using restricted cubic splines of the mean of 1st and 2nd sample measurements showed a strong and significant non-linear association (p<0.0001) in which the risk of early preterm birth steeply increased when EPA+DHA concentrations were lower than 2% and flattened out at higher levels. Women in the lowest quintile (EPA+DHA<1.6%) had 10.27 times (95% confidence interval 6.80-15.79, p<0.0001) increased risk, and women in the second lowest quintile had 2.86 (95% CI 1.79-4.59, p<0.0001) times increased risk, when compared to women in the three aggregated highest quintiles (EPA+DHA>/=1.8%). INTERPRETATION: Low plasma concentration of EPA and DHA during pregnancy is a strong risk factor for subsequent early preterm birth in Danish women.

[15] *Paneni F, Costantino S.* **PCSK9 in diabetes: sweet, bitter or sour?** European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30085009
ABSTRACT

[16] *Kong Y, Cheng L, Mao F et al.* **Inhibition of cholesterol biosynthesis overcomes enzalutamide resistance in castration-resistant prostate cancer (CRPC)**. The Journal of biological chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30089652
ABSTRACT
Enzalutamide, a nonsteroidal second-generation antiandrogen, has been recently approved for the management of castration-resistant prostate cancer (CRPC). Although patients can benefit from enzalutamide at the beginning of this therapy, acquired enzalutamide resistance usually occurs within a short period. This motivated us to investigate the mechanism involved and

possible approaches for overcoming enzalutamide resistance in CRPC. In the present study, we found that HMG-CoA reductase (HMGCR), a crucial enzyme in the mevalonate pathway for sterol biosynthesis, is elevated in enzalutamide-resistant prostate cancer cell lines. HMGCR knockdown could re-sensitize these cells to the drug, and HMGCR overexpression conferred resistance to it, suggesting that aberrant HMGCR expression is an important enzalutamide resistance mechanism in prostate cancer cells. Furthermore, enzalutamide-resistant prostate cancer cells were more sensitive to statins, which are HMGCR inhibitors. Of note, a combination of simvastatin and enzalutamide significantly inhibited the growth of enzalutamide-resistant prostate cancer cells in vitro and tumors in vivo. Mechanistically, simvastatin decreased protein levels of the androgen receptor (AR), which was further reduced in combination with enzalutamide. We observed that the decrease in AR may occur through simvastatin-mediated inhibition of the mTOR pathway, whose activation was associated with increased HMGCR and AR expression. These results indicate that simvastatin enhances the efficacy of enzalutamide-based therapy, highlighting the therapeutic potential of statins to overcome enzalutamide resistance in CRPC.

[17] *Al-Kuraishy HM, Al-Gareeb AI, Al-Buhadily AK*. **Rosuvastatin as forthcoming antibiotic or as adjuvant additive agent: In vitro novel antibacterial study**. Journal of laboratory physicians 2018; 10:271-275.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30078961

ABSTRACT

INTRODUCTION: Rosuvastatin is a lipid-lowering agent that inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase leading to a reduction of cholesterol biosynthesis. Many studies have shown an association between statins use and the reduction of sepsis. The aim of the present study was to evaluate the in vitro combined antibacterial activity of rosuvastatin and cefixime. MATERIALS AND METHODS: Five pathogenic bacteria isolates (Gram positive and Gram negative) were used for testing the antibacterial activity of rosuvastatin alone and in combination with cefixime. RESULTS: Rosuvastatin mainly inhibited Klebsiella pneumoniae and Escherichia coli where it caused zones of inhibition of (17.9 +/- 0.6 mm) and (16.9 +/- 0.3 mm), respectively; however, it moderately inhibited the growth of Staphylococcus epidermidis (12.9 +/- 0.2 mm) and Staphylococcus aureus (12.76 +/- 0.2) and produced less inhibition for Pseudomonas aeruginosa growth where it led to a zone of inhibition equal to (9.1 +/- 0.5 mm). Minimal inhibitory concentration (mug/mL) of rosuvastatin was high compared to cefixime. Fractional inhibitory concentration (FIC) of rosuvastatin was low for E. coli and K. pneumoniae compared to the other types of bacterial strains. Rosuvastatin exhibited additive effects with cefixime against E. coli and K. pneumoniae. SigmaFIC index was 0.536 and 0.734 for E. coli and K. pneumoniae, respectively. CONCLUSION: Rosuvastatin has a significant antibacterial activity against both Gram-negative and Gram-positive bacteria with a potential additive effect when used in combination with cefixime.

[18] *Carmichael OT, Pillai S, Shankapal P et al.* **A Combination of Essential Fatty Acids, Panax Ginseng Extract, and Green Tea Catechins Modifies Brain fMRI Signals in Healthy Older Adults**. The journal of nutrition, health & aging 2018; 22:837-846.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30080229

ABSTRACT
OBJECTIVES: To assess the effects of a combination of omega 3 essential fatty acids, green tea catechins, and ginsenosides on cognition and brain functioning in healthy older adults. DESIGN: Double-blind, placebo-controlled, crossover design randomized controlled trial with 26-day intervention phases and a 30-day washout period. SETTING: The Institute for Dementia Research and Prevention at the Pennington Biomedical Research Center. PARTICIPANTS: Ten independently-living, cognitively-healthy older adults (mean age: 67.3 + 2.01 years). INTERVENTION: Daily consumption of an investigational product (trade name "Cerbella TM") consisting of an emulsified liquid combination of standardized fish oil, panax ginseng extract, and green tea catechins in a flavored base of lecithin phospholipids optimized to maximize bioavailability of the active ingredients. MEASUREMENTS: Before and after supplementation with the investigational product or placebo, participants completed cognitive tests including the Mini Mental State Exam (MMSE), Stroop test, Digit Symbol Substitution Test (DSST), and Immediate and Delayed Recall tests, as well as functional magnetic resonance imaging (fMRI) during a standard cognitive task switching paradigm. RESULTS: Performance on the MMSE, Stroop test, and DSST increased significantly over one month of supplementation with the investigational product (one-sample t tests, $p<.05$) although differences between these changes and corresponding changes during supplementation with placebo were not significant (two-sample t tests, $p>.05$). During supplementation with the investigational product, brain activation during task performance increased significantly more than during supplementation with placebo in brain regions known to be activated by this task (anterior and posterior cingulate cortex). Functional connectivity during task execution between task regions (middle frontal gyrus and anterior cingulate cortex) increased significantly during supplementation with the investigational product, relative to placebo. Functional connectivity during rest between task regions (precentral gyrus and middle frontal gyrus) and default mode network regions (medial frontal gyrus and precuneus) decreased during supplementation with the investigational product relative to placebo, suggesting greater segregation of task and rest related brain activity. CONCLUSION: One-month supplementation with a combination of omega 3 essential fatty acids, green tea catechins, and ginsenosides was associated with suggestive changes in cognitive functioning as well as modification of brain activation and brain functional connectivity in cognitively healthy older adults.

[19] *Allen J, Zhang J, Quickel MD et al.* **Ron receptor signaling ameliorates hepatic fibrosis in a diet-induced non-alcoholic steatohepatitis mouse model**. J Proteome Res 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30091925

ABSTRACT
Liver fibrosis is commonly observed in the terminal stages of non-alcoholic steatohepatitis (NASH) and with no specific and effective anti-fibrotic therapies available, this disease is a major global health burden. The MSP/Ron receptor axis has been shown to have anti-inflammatory properties in a number of mouse models, due at least in part, to its ability to limit pro-inflammatory responses in tissue-resident macrophages and hepatocytes. In this study, we established the role of the Ron receptor in steatohepatitis-induced hepatic fibrosis using Ron ligand domain knockout mice on an apolipoprotein E knockout background (DKO). After 18 weeks of high-fat high-cholesterol feeding, loss of Ron activation resulted in exacerbated NASH-

associated steatosis which is precedent to hepatocellular injury, inflammation and fibrosis. 1H nuclear magnetic resonance (NMR)-based metabolomics identified significant changes in serum metabolites that can modulate the intrahepatic lipid pool in hepatic steatosis. Serum from DKO mice had higher concentrations of lipids, VLDL/LDL and pyruvate, whereas glycine levels were reduced. Parallel to the aggravated steatohepatitis, increased accumulation of collagen, inflammatory immune cells and collagen producing myofibroblasts were seen in the livers of DKO mice. Gene expression profiling revealed that DKO mice exhibited elevated expression of genes encoding Ron receptor ligand MSP, collagens, ECM remodeling proteins and pro-fibrogenic cytokines in the liver. Our results demonstrate the protective effects of Ron receptor activation on NASH-induced hepatic fibrosis.

[20] *Cheng ZJ, Dai TM, Shen YY et al.* **Atorvastatin Pretreatment Attenuates Ischemic Brain Edema by Suppressing Aquaporin 4**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30093197

ABSTRACT

BACKGROUND: Cerebral edema, a serious complication of acute cerebral infarction, has a crucial impact on morbidity and mortality in the early stage of cerebral infarction. And aquaporin 4 (AQP4), a bidirectional water transporting protein, plays a pivotal role in edema formation. At experimental model, it has proven that atorvastatin could exert pleiotropic neuroprotection on acute cerebral infarction independent of its cholesterol-lowering action. It was a common protective manifestation that atorvastatin can reduce the infarct volume and cerebral edema. However, little is known about atorvastatin improving ischemic brain edema by regulating AQP4 expression. This study intended to investigate the neuroprotection effects of atorvastatin pretreatment in rats with cerebral ischemia and further explore the potential relationship between atorvastatin and AQP4 expression. METHODS: Fifty-one adult male Sprague Dawley rats were randomly divided into 3 groups: sham, middle cerebral artery occlusion (MCAO), and atorvastatin pretreatment (Ator) group. For Ator group, 20 mg/kg of atorvastatin injectable suspension was administered once for 7 days by gavage before operation, whereas the others were administered the same volume of saline matching. Except for sham group, MCAO and Ator groups were subjected to permanent MCAO by modified intraluminal suture method. Infarct volume, neurological deficit, brain water content (BWC), immunohistochemistry, western blot, and polymerase chain reaction (PCR) were measured at 24 hours after MCAO. RESULTS: Compared with sham group, the mNSS, infarct volume, and BWC of ischemic hemisphere were significantly increased ($P < 0.001$) in MCAO group. Positive cells and protein levels of p-p38MAPK and AQP4 in peri-infarction were significantly increased ($P < 0.01$). The mRNA levels of p38MAPK and AQP4 were also prominently upregulated ($P < 0.01$). Interestingly, preadministration of atorvastatin dramatically decreased infarct volume and the BWC of ischemic hemisphere compared with MCAO group ($P < 0.05$). The overexpressions of p-p38MAPK and AQP4 in peri-infarction were significantly decreased ($P < 0.05$) and their mRNA levels were downregulated by atorvastatin pretreatment ($P < 0.05$). Neurological deficits were also dramatically improved ($P < 0.001$). CONCLUSION: To the best of our knowledge, this is the first study that demonstrates an effect of atorvastatin on expression

of AQP4, and we propose that decreased AQP4 expression through a p38MAPK-suppression pathway may be the mechanism of atorvastatin alleviating ischemic cerebral edema.

[21] *Nissen SE, Pillai SG*. **Randomized Trial Needed to Confirm Whether Dalcetrapib Improves Outcomes for Specific ADCY9 Genotype-Reply**. JAMA cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30090930
ABSTRACT

[22] *Pfeffer MA, Dube MP, Tardif JC*. **Randomized Clinical Trial Needed to Confirm Whether Dalcetrapib Improves Outcomes for Specific ADCY9 Genotype**. JAMA cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30090919
ABSTRACT

[23] *Loef M, Schoones JW, Kloppenburg M, Ioan-Facsinay A*. **Fatty acids and osteoarthritis: different types, different effects**. Joint Bone Spine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30081198
ABSTRACT
While the association between obesity and osteoarthritis used to be solely regarded as a result of increased mechanical loading, systemic factors also likely play a role in the pathophysiology of osteoarthritis. Nutrient excess leading to obesity may result in lipotoxicity, which might be involved in the development of osteoarthritis. The different fatty acid types have distinct effects on inflammation. This review focusses on the currently available studies, summarizing the effects of the different fatty acid types on osteoarthritis and involved joint tissues. In animal studies omega-3 polyunsaturated fatty acids reduced the expression of inflammatory markers, cartilage degradation and oxidative stress in chondrocytes. In contrast, these markers were increased upon omega-6 polyunsaturated fatty acid and saturated fatty acid stimulation. Additionally, a decrease in pain and dysfunction was observed upon omega-3 supplementation in cats and dogs. In line, most human in vitro studies show pro-apoptotic and pro-inflammatory actions of saturated fatty acids. While all polyunsaturated fatty acids reduced markers of oxidative stress, omega-3 polyunsaturated fatty acids additionally decreased prostaglandin production. Human intervention studies with omega-3 polyunsaturated fatty acid supplementation may indicate a beneficial effect on pain and function and might be associated with less structural damage. In contrast, an adverse effect of saturated fatty acids on osteoarthritis has been observed. Monounsaturated fatty acids have been infrequently studied and findings are inconclusive. Existing studies indicate a promising effect of especially omega-3 polyunsaturated fatty acids on osteoarthritis signs and symptoms. However, more human intervention studies are warranted to draw robust conclusions.

[24] *Calfee CS, Delucchi KL, Sinha P et al.* **Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial**. The lancet. Respiratory medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30078618
ABSTRACT

BACKGROUND: Precision medicine approaches that target patients on the basis of disease subtype have transformed treatment approaches to cancer, asthma, and other heterogeneous syndromes. Two distinct subphenotypes of acute respiratory distress syndrome (ARDS) have been identified in three US-based clinical trials, and these subphenotypes respond differently to positive end-expiratory pressure and fluid management. We aimed to investigate whether these subphenotypes exist in non-US patient populations and respond differently to pharmacotherapies. METHODS: HARP-2 was a multicentre, randomised controlled trial of simvastatin (80 mg) versus placebo done in general intensive care units (ICUs) at 40 hospitals in the UK and Ireland within 48 h of onset of ARDS. The primary outcome was ventilator-free days, and secondary outcomes included non-pulmonary organ failure-free days and mortality. In a secondary analysis of HARP-2, we applied latent class analysis to baseline data without consideration of outcomes to identify subphenotypes, and we compared clinical outcomes across subphenotypes and treatment groups. FINDINGS: 540 patients were recruited to HARP-2. One patient withdrew consent for the use of their data, so data from 539 patients were analysed. In our secondary analysis, a two-class (two subphenotype) model was an improvement over a one-class model ($p<0.0001$), with 353 (65%) patients in the hypoinflammatory subphenotype group and 186 (35%) in the hyperinflammatory subphenotype group. Additional classes did not improve model fit. Clinical and biological characteristics of the two subphenotypes were similar to previous studies. Patients with the hyperinflammatory subphenotype had fewer ventilator-free days (median 2 days [IQR 0-17] vs 18 [IQR 0-23]; $p<0.0001$), fewer non-pulmonary organ failure-free days (15 [0-25] vs 27 [21-28]; $p<0.0001$), and higher 28-day mortality (73 [39%] vs 59 [17%]; $p<0.0001$) than did those with the hypoinflammatory subphenotype. Although HARP-2 found no difference in 28-day survival between placebo and simvastatin, significantly different survival was identified across patients stratified by treatment and subphenotype ($p<0.0001$). Specifically, within the hyperinflammatory subphenotype, patients treated with simvastatin had significantly higher 28-day survival than did those given placebo ($p=0.008$). A similar pattern was observed for 90-day survival. INTERPRETATION: Two subphenotypes of ARDS were identified in the HARP-2 cohort, with distinct clinical and biological features and disparate clinical outcomes. The hyperinflammatory subphenotype had improved survival with simvastatin compared with placebo. These findings support further pursuit of predictive enrichment strategies in critical care clinical trials. FUNDING: UK Efficacy and Mechanism Evaluation Programme and National Institutes of Health.

[25] *Wang Y, Jin Y, Yun X et al.* **Co-administration with simvastatin or lovastatin alters the pharmacokinetic profile of sinomenine in rats through cytochrome P450-mediated pathways**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30096386
ABSTRACT
AIMS: Sinomenine, an anti-rheumatoid arthritis drug used in China for decades, is usually co-administered with cardiovascular (CV) drugs to reduce arthritis-related risk of cardiovascular diseases. This study was to investigate whether and how CV drugs affect the pharmacokinetic profile of sinomenine. MAIN METHODS: In rat liver microsomes (RLMs), the key metabolic enzymes of sinomenine were identified by using specific inhibitors. The influences of CV drugs,

including propranolol, verapamil, warfarin, atorvastatin, simvastatin, and lovastatin, on the metabolism of sinomenine were examined. Cocktail probe, RT-qPCR, and western blotting were performed to unveil the underlying mechanism of the drug-drug interaction. KEY FINDINGS: The key metabolic enzymes of sinomenine were identified to be CYP3A1/2 and CYP2D1 in RLMs. Among the CV drugs screened, simvastatin and lovastatin were shown to inhibit the liver metabolism of sinomenine with Ki values of 13.00 and 25.83muM, respectively. Single administration of simvastatin or lovastatin in rats increased the AUC value of sinomenine to 1.40- or 1.50-fold, and decreased the CLz/F value to 68.19% or 65.44%, respectively. In contrast, multiple administrations of simvastatin, but not lovastatin, increased the CLz/F value of sinomenine to 1.38-fold and decreased the AUC value to 71.59%. Further studies showed that the long-term administration of simvastatin could up-regulate the expression of CYP3A1/2 to account for the effect. SIGNIFICANCE: This study demonstrated the potential effect of simvastatin and lovastatin on the metabolism of sinomenine for the first time. The findings provide guidelines for the co-administration of sinomenine with simvastatin or lovastatin in clinic.

[26] *Laukkanen JA, Laukkanen T, Kunutsor SK*. **Cardiovascular and Other Health Benefits of Sauna Bathing: A Review of the Evidence**. Mayo Clinic proceedings 2018; 93:1111-1121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30077204
ABSTRACT
Sauna bathing, an activity that has been a tradition in Finland for thousands of years and mainly used for the purposes of pleasure and relaxation, is becoming increasingly popular in many other populations. Emerging evidence suggests that beyond its use for pleasure, sauna bathing may be linked to several health benefits, which include reduction in the risk of vascular diseases such as high blood pressure, cardiovascular disease, and neurocognitive diseases; nonvascular conditions such as pulmonary diseases; mortality; as well as amelioration of conditions such as arthritis, headache, and flu. The beneficial effects of sauna bathing on these outcomes have been linked to its effect on circulatory, cardiovascular, and immune functions. It has been postulated that regular sauna bathing may improve cardiovascular function via improved endothelium-dependent dilatation, reduced arterial stiffness, modulation of the autonomic nervous system, beneficial changes in circulating lipid profiles, and lowering of systemic blood pressure. This review summarizes the available epidemiological, experimental, and interventional evidence linking Finnish sauna bathing and its effects on cardiovascular outcomes and other disease conditions on the basis of a comprehensive search for observational studies, randomized controlled trials, and non-randomized controlled trials from MEDLINE and EMBASE from their inception until February 24, 2018. An overview of the postulated biological mechanisms underlying the associations between sauna bathing and its health benefits, areas of outstanding uncertainty, and implications for clinical practice is also provided.

[27] *Rakic M, Persic V, Kehler T et al.* **Possible role of circulating endothelial cells in patients after acute myocardial infarction**. Medical hypotheses 2018; 117:42-46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30077195
ABSTRACT

Acute myocardial infarction (AMI) occurs as a result of insufficient myocardial perfusion leading to cell necrosis. This is most commonly due to the obstruction of the coronary artery by ruptured atherosclerotic plaque and thrombosis. Damaged ischemic and necrotic myocardial cells release pro-inflammatory substances in tissue and plasma, leading to a systemic inflammatory response. Profound systemic inflammatory response during ischemia/reperfusion injury causes disruption of endothelial glycocalyx and detachment of endothelial cells that express von Willebrant factor (vWF). We hypothesize that circulating vWF+ endothelial cells could act as antigen presenting cells which interact with T and NK cells directly, by cell to cell contact and indirectly by cytokine and chemokine secretion, leading to the immune response towards inflammation. Analyzing the frequency, phenotype and pro-inflammatory substances produced in circulating vWF positive (+) cells in patients with AMI could be beneficial to determine the severity of the pro-inflammatory response, according to the level of endothelial dysfunction in the early period of AMI. To evaluate these hypotheses, we suggest to determine frequency, phenotype, and ability of cytokine/chemokine production in circulating vWF+ endothelial cells by simultaneous surface and intracellular cell staining, and flow cytometry analysis. Secretion of pro-inflammatory cytokines and chemokines, pro-atherogenic substances and the components of glycocalyx might be measured in supernatants of magnetically separated or sorted vWF+ endothelial cells, as well as in the serum of a patient with acute AMI by enzyme linked-immunoassay tests. The interaction of increasing concentrations of isolated circulating vWF+ endothelial cells and cognate T and NK cells might be investigated by lymphocyte proliferation rate, cytotoxic mediators' expression, and cytokine production. If our hypothesis is correct, characterization of circulating vWF+ endothelial cells could grant us greater insight into their role in pathophysiology of AMI and the degree of myocardial damage.

[28] *Ersoy N, Tasci I, Ozgurtas T et al.* **Effect of seasonal changes on nutritional status and biochemical parameters in Turkish older adults**. Nutrition research and practice 2018; 12:315-323.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30090169
ABSTRACT
BACKGROUND/OBJECTIVES: Available data suggest that seasonal changes may influence the nutritional status and overall health of elderly individuals. Therefore, this study was conducted to investigate the effects of seasonal changes and related factors on energy and nutrient intake of older adults. SUBJECTS/METHODS: Individuals aged 65 years or over were prospectively enrolled in this single-center study (male: 11, female: 20). Data were collected between May 2013 and February 2014 during winter, spring, summer and autumn. Food consumption and biochemical parameters were taken during each season to assess the seasonal nutrition status of the elderly. Upon analysis of biochemical parameters (retinol, vitamin D and vitamin C), an high-performance liquid chromatography device was utilized whereas an Immulite 2000 device was utilized during analysis of serum folic acid and parathyroid hormone. RESULTS: Fruit, fat, egg and bread consumption varied seasonally in males and females ($P < 0.05$). During winter, daily energy intake was found to be greater than in other seasons in males (557 kcal) and females (330 kcal) ($P < 0.05$). Additionally, carbohydrates, vegetable protein, n-3 fatty acid and sodium intake increased in winter, while the n-6/n-3 ratio increased in summer among males ($P < 0.05$). Dietary fiber and sodium intake in winter, vitamin C, iron and zinc intake in spring, and

cholesterol, retinol, vitamin D and niacin intake in autumn were found to be higher in females when compared to other seasons (P < 0.05). Serum parathyroid hormone level was higher in winter, and vitamin D level was higher in autumn in both genders (P < 0.05). In males, blood folic acid level was higher in winter, while vitamin C level was higher in females, and there was no seasonal variation in retinol concentration (P < 0.05). CONCLUSION: Food consumption and biochemical parameters showed significant seasonal variations in older adults. It is not clear if nutrition plans in older adults will benefit from consideration of seasonal changes in eating habits.

[29] *Bajnok L*. **[Newer evidences and recommendations in lipidology]**. Orvosi hetilap 2018; 159:1303-1309.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30078359
ABSTRACT
The correlation between cholesterol and risk reduction is unique: no J curve is seen even at extreme low levels. According to PRECISE-IVUS, the effect of intensive cholesterol lowering on plaque regression is more pronounced post-myocardial infarction syndrome than in chronic coronary disease. The importance of LDL-C lowering with ezetimibe in IMPROVE-IT (1.4 mmol/L compared to 1.8 mmol/L in the statin monotherapy arm) is expressed in several international guidelines and the indication spectrum of combination cholesterol lowering has broadened and strengthened. There is a strong evidence that myalgia during statin treatment is generally not caused by statins and it is not related to type or dose of the drug. With patience, the majority of patients can be made to become statin takers even with good quality of life; for those who cannot, ezetimibe monotherapy can be an alternative. Even though intensive cholesterol lowering is safe, avoiding statin myopathy should be emphasized. Despite the outstanding efficacy and safety of cholesterol lowering, Hungarian statin sales have decreased recently, in which driven dilettante public climate around the products may be of utmost importance. Everyone of us should counteract this according to the possibilities. Orv Hetil. 2018; 159(32): 1303-1309.

[30] *Hari P, Khandelwal P, Satpathy A et al.* **Effect of atorvastatin on dyslipidemia and carotid intima-media thickness in children with refractory nephrotic syndrome: a randomized controlled trial**. Pediatric nephrology (Berlin, Germany) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30091061
ABSTRACT
BACKGROUND: Dyslipidemia is an important cardiovascular risk factor in steroid-resistant nephrotic syndrome (SRNS). Efficacy of statins for treatment of hyperlipidemia in children with SRNS is unclear. METHODS: This prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial enrolled 30 patients with SRNS, aged 5-18 years, with serum low-density lipoprotein cholesterol (LDL-C) levels between 130 and 300 mg/dl, to receive a fixed dose of atorvastatin (n = 15, 10 mg/d) or placebo (n = 15) by block randomization in a 1:1 ratio. Primary outcome was change in serum LDL-C at 12 months. Change in levels of other lipid fractions, carotid intima-media thickness (cIMT), flow-mediated dilation (FMD) of the brachial artery, and adverse events were also evaluated. RESULTS: At the end of 12 months, atorvastatin was not superior to placebo in reducing plasma LDL-C levels, median percentage reduction

15.8% and 9.5% respectively, in atorvastatin and placebo arms (n = 14 in each; P = 0.40). Apolipoprotein B levels significantly declined with atorvastatin in modified intention-to-treat analysis (P = 0.01) but not in the per-protocol analysis. There was no significant effect on other lipid fractions, cIMT and FMD. Adverse events were similar between groups. Change in serum albumin was negatively associated with change in serum LDL-C, very low-density lipoprotein cholesterol, total cholesterol, triglyceride, and apolipoprotein B (P < 0.001), irrespective of receiving atorvastatin, age, gender, body mass index, and serum creatinine. CONCLUSIONS: Atorvastatin, administered at a fixed daily dose of 10 mg, was not beneficial in lowering lipid levels in children with SRNS; rise in serum albumin was associated with improvement in dyslipidemia.

[31] *Lapczuk-Romanska J, Wajda A, Pius-Sadowska E et al.* **Effects of simvastatin on nuclear receptors, drug metabolizing enzymes and transporters expression in Human Umbilical Vein Endothelial Cells**. Pharmacological reports : PR 2018; 70:875-880.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30092417
ABSTRACT
BACKGROUND: Vascular endothelial cells (EC) are constantly exposed to endo- and exogenous compounds, which may disturb EC function. One of the protecting mechanisms against chemicals consists of drug metabolizing enzymes and transporter proteins regulated by nuclear receptors and transcription factors. Therefore, the aim of the current study was to assess the regulation of nuclear receptors and their coordinated genes in Human Umbilical Vein Endothelial Cells (HUVEC). METHODS: HUVEC were exposed to TCDD (10nM), oltipraz (100muM) and simvastatin (1muM) for 24h. Gene expressions were evaluated using quantitative real-time PCR. The protein expression levels were determined by Western blotting. Enzymatic activity of CYP1A1/CYP1B1 was assessed by luciferin-labelled CYPs substrate. RESULTS: Our study confirmed that nuclear receptor AhR and nuclear factor Nrf2 are highly expressed in HUVECs. Treatment of HUVECs with TCDD (AhR inducer) resulted in a significant induction of AHR target genes CYP1A1, CYP1B1 and NQO1. Oltipraz (Nrf2 inducer) also markedly increased expression of NQO1 but did not affect Nrf2 mRNA nor protein levels. Under simvastatin stimulation PXR and NRF2 target transcripts were not altered, however AHR-regulated genes: CYP1A1, CYP1B1 and MDR1 were significantly induced. Western blot analysis confirmed CYP1B1 induction in TCDD-treated HUVECs, but not in the simvastatin group. Moreover, HUVEC exposure to TCDD resulted in induction of CYP1A1/CYP1B1 enzymatic activity. CONCLUSIONS: This study revealed functional expression of AhR and Nrf2 in HUVECs. Moreover, it was defined that simvastatin induced AhR and its related genes.

[32] *Lee YH, Hong N, Lee CJ et al.* **Differential association of ezetimibe-simvastatin combination with major adverse cardiovascular events in patients with or without diabetes: a retrospective propensity score-matched cohort study**. Scientific reports 2018; 8:11925.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30093717
ABSTRACT
Clinical trials suggested that the benefits of ezetimibe-statin combination therapy on major adverse cardiovascular events (MACE) might be greater in patients with diabetes. We aimed to investigate the differential association of ezetimibe-statin combination with incident MACE by

presence of diabetes. In this retrospective cohort study, subjects treated with simvastatin 20 mg plus ezetimibe 10 mg (S + E) or simvastatin 20 mg alone (S) between 2005 and 2015 were 1:1 matched using propensity score as stratified by diabetes. Primary outcome was newly-developed MACE composed of cardiovascular death, ACS, coronary revascularization, or non-hemorrhagic stroke. During 5,077 and 12,439 person-years, the incidence rates of MACE were 24.9, 20.1, 35.3, and 22.8/1000 person-years among no diabetes S, no diabetes S + E, diabetes S, and diabetes S + E, respectively. Relative to no diabetes S, adjusted HR (aHR) for MACE in diabetes S was 1.23 (p = 0.086), whereas S + E was associated with a lower risk of MACE in both non-diabetic patients (aHR 0.76, p = 0.047) and diabetic patients (aHR 0.60, p = 0.007) with significant difference (relative excess risk due to interaction = -0.39, p = 0.044). In conclusion, reduction of MACE risk associated with ezetimibe plus simvastatin therapy relative to simvastatin alone was greater in patients with diabetes than in patients without diabetes.

[33] Kemnic TR, Coleman M. Vitamin E, Deficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing
StatPearls Publishing LLC.; 2018.

[34] *Li XJ, Mu YM, Qin QF et al.* **Chronic high-dosage fish oil exacerbates gut-liver axis injury in alcoholic steatohepatitis in mice: the roles of endotoxin and IL-4 in Kupffer cell polarization imbalance**. Toxicology research 2017; 6:611-620.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30090529

ABSTRACT

In the present study, intestinal tight junctions (TJs) and Kupffer cell polarization were investigated in an alcoholic steatohepatitis (ASH) mouse model to uncover the potential side effects of overexposure to fish oil or omega-3 fatty acids. The mice were fed ad libitum with a liquid diet containing ethanol and fish oil. In the meantime, ethanol was given every 5-7 days by gavage to simulate binge drinking. After the 7(th) binge, steatosis, necrosis, inflammatory infiltration, and bridging fibrosis were observed in the liver by histological staining. After the 13(th) binge, the inducers, markers and other downstream genes/proteins of the Kupffer cell M1/M2 phenotype in the liver, serum, and small intestine were analysed. The results suggested that a chronic high dosage of fish oil alone reduced the mRNA levels of most genes tested and showed a tendency to damage the intestinal zonula occludens-1 localization and reduce the number of M2 Kupffer cells. Meanwhile, the combination of fish oil and ethanol damaged the intestinal TJs, resulting in an increased endotoxin level in the liver. Gut-derived endotoxin polarized Kupffer cells to the M1 phenotype, whereas the number of cells with the M2 phenotype (markers: CD163 and CD206) was decreased. Interleukin-4 (IL-4), an M2 Kupffer cell inducer, was also decreased. Moreover, in vitro experiments showed that IL-4 reversed eicosapentaenoic acid-induced CD163 and CD206 mRNA suppression in RAW 264.7 cells. Overall, our results showed that a chronic high dosage of fish oil exacerbated gut-liver axis injury in alcoholic liver disease in mice, and endotoxin/IL-4-induced Kupffer cell polarization imbalance might play an important role in that process.

[35] *Li Y, Mao H, Xu Y et al.* **Application research on PPARalpha-transgenic mice in preclinical safety evaluation of gemfibrozil**. Toxicology research 2017; 6:98-104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30090481

ABSTRACT
To explore the feasibility of peroxisome proliferator-activated receptor (PPAR)alpha transgenic mice applying in preclinical safety evaluation for peroxisome proliferators (PPs). Both PPARalpha transgenic mice and C57BL/6J mice were assigned as treated groups (PT and CT groups) and control groups (PC and CC groups). Gemfibrozil was administered into treated groups for 4 weeks. Body weight, blood biochemistry, enzyme activity and histological examinations were performed at scheduled time. The results showed that significant hypolipidaemic effects were induced in the treated groups after gemfibrozil treatment whereas the changes of non-esterified fatty acid and high density lipoproteincholesterol were different between the two treated groups. All the enzyme activities examined increased significantly in PT and CT groups except catalase which displayed no obvious change in the PT group. Pathology results showed a significant increase of the liver weight and the liver weight ratio in the CT group while no obvious changes were observed in the PT group. Hypertrophy of hepatocytes was discovered in CT and PT groups in histological examination, while the extent and incidence of hepatocyte hypertrophy in the CT group were higher than those in the PT group. The data suggest that PPARalpha transgenic mice could serve as a useful tool for preclinical safety assessment of PP drugs.

[36] *Bigazzi F, Sbrana F, Berretti D et al.* **Reduced incidence of cardiovascular events in hyper-Lp(a) patients on lipoprotein apheresis. The G.I.L.A. (Gruppo Interdisciplinare Aferesi Lipoproteica) pilot study**. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30087087

ABSTRACT
BACKGROUND: Lipoprotein apheresis (LA) is the elective therapy for homozygous and other forms of Familial Hypercholesterolemia, Familial Combined Hypercholesterolemia, resistant/intolerant to lipid lowering drugs, and hyper-lipoproteinemia(a). Lipoprotein(a) [Lp(a)] has been classified as the most prevalent genetic risk factor for coronary artery disease and aortic valve stenosis. AIM: Our multicenter retrospective study has the aim to analyze the incidence of adverse cardiovascular events (ACVE) before and during the LA treatment, in subjects with elevated level of Lp(a) (>60 mg/dL) [hyper-Lp(a)] and chronic ischemic heart disease. METHODS: We collected data of 23 patients (mean age 63 +/- 9 years, male 77%; from hospital of Pisa 11/23, Pistoia 7/23, Verona 2/23, Padova 2/23 and Ferrara 1/23), with hyper-Lp(a), pre-apheresis LDL-cholesterol <100 mg/dL, cardiovascular disease, on maximally tolerated lipid lowering therapy and LA treatment (median 7 years, interquartile range 3-9 years). The LA treatment was performed by heparin-induced LDL precipitation apheresis (16/23), dextran-sulphate (4/23), cascade filtration (2/23) and immunoadsorption (1/23). The time lapse between first cardiovascular event and beginning of apheresis was 6 years (interquartile range 1-12 years). RESULTS: The recorded ACVE, before and after the LA treatment inception, were 40 and 10 respectively ($p < 0.05$), notably, the AVCE rates/year were 0.43 and 0.11 respectively ($p < 0.05$) with a 74% reduction of event occurrence. CONCLUSIONS: Our data confirm long-term efficacy and positive impact of LA on morbidity in patients with hyper-Lp(a) and chronic ischemic heart disease on maximally tolerated lipid lowering therapy.

Literature update week 32 (2018)