**Literature update week 51 (2018)**

[1] *Roberts WC*. **From the Editor Pellagra, Osler, Roberts, Goldberger, the Atherosclerotic Diet, Niacin, the Beginning of the Atherosclerotic Epidemic, and the First Lipid-Altering Drug**. The American journal of cardiology 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30563617
***ABSTRACT***

[2] *Takata K, Nicholls SJ*. **Tackling Residual Atherosclerotic Risk in Statin-Treated Adults: Focus on Emerging Drugs**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30565156
***ABSTRACT***
Epidemiological studies and meta-analyses have consistently suggested the importance of lowering low-density lipoprotein cholesterol (LDL-C) to reduce cardiovascular (CV) events. However, these studies and mechanistic studies using intracoronary imaging modalities have reported patients who continue to experience CV events or disease progression despite optimal LDL-C levels on statins. These findings, including statin intolerance, have highlighted the importance of exploring additional potential therapeutic targets to reduce CV risk. Genomic insights have presented a number of additional novel targets in lipid metabolism. In particular, proprotein convertase subtilisin/kexin type 9 inhibitors have rapidly developed and recently demonstrated their beneficial impact on CV outcomes. Triglyceride (TG)-rich lipoproteins have been recently reported as a causal factor of atherosclerotic cardiovascular disease (ASCVD). Indeed, several promising TG-targeting therapies are being tested at various clinical stages. In this review, we present the evidence to support targeting atherogenic lipoproteins to target residual ASCVD risk in statin-treated patients.

[3] *Li D, Dai W, Cai Y et al.* **Atherosclerosis in stroke-related vascular beds and stroke risk: A 3-D MR vessel wall imaging study**. Annals of clinical and translational neurology 2018; 5:1599-1610.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30564625
***ABSTRACT***
Objectives: To investigate the characteristics of atherosclerotic plaques in stroke-related vascular beds and their relationship with stroke using three-dimensional magnetic resonance (MR) vessel wall imaging. Methods: Fifty-two symptomatic patients (mean age: 56.3 +/- 13.4 years; 38 males) were enrolled and underwent MR vessel wall imaging for stroke-related vascular beds including intracranial and extracranial carotid arteries and aortic arch and routine MR imaging for brain. The maximum wall thickness (Max WT) and luminal stenosis of each plaque were measured. The presence/absence of atherosclerotic plaque, intraplaque hemorrhage (IPH), and severe stenosis (stenosis >50%) at each vascular bed and acute ischemic lesion (AIL) were determined. The correlation between Max WT of each vascular bed and AIL was analyzed. Results: Of 52 patients, 24 (46.2%) had AILs, and 30 (57.7%), 34 (65.4%), and 11 (21.2%) had plaques in intracranial artery, extracranial carotid artery, and aortic arch, respectively. The prevalence of IPH and severe stenosis was 25% and 26.9% for intracranial arteries, 13.5% and 9.6% for extracranial carotid artery, and 3.8% and 0% for aortic arch, respectively. In discriminating AIL, Max WT of intracranial artery had the highest area-under-

the-curve (AUC = 0.84), followed by extracranial carotid artery (AUC = 0.83) and aortic arch (AUC = 0.78) after adjusted for confounding factors. The AUC of Max WT combined three stroked-related vascular beds reached 0.87. Conclusion: Extracranial carotid arteries have the highest prevalence of plaques and intraplaque hemorrhage and severe stenosis are most frequently seen in intracranial arteries in Asian symptomatic patients. The Max WT combined three stroke-related vascular beds show stronger predictive value for AIL than each vascular bed alone.

[4] *Zittermann A, Ernst JB, Prokop S et al.* **Daily Supplementation with 4000 IU Vitamin D3 for Three Years Does Not Modify Cardiovascular Risk Markers in Patients with Advanced Heart Failure: The Effect of Vitamin D on Mortality in Heart Failure Trial**. Annals of nutrition & metabolism 2018; 74:62-68.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30554193
***ABSTRACT***
BACKGROUND/AIMS: We aimed to investigate the effect of a moderately high vitamin D dose on lipid parameters and biochemical markers of vascular calcification (VC) in patients with established cardiovascular disease. METHODS: We included in this pre-specified secondary analysis of a randomized controlled trial 161 patients with advanced heart failure and 25-hydroxyvitamin D (25OHD) concentrations < 75 nmol/L (vitamin D group: n = 80; placebo group: n = 81), who received a daily vitamin D3 supplement of 4,000 IU for 3 years. We assessed between-group differences of the lipid parameters total-cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides, and the VC markers fetuin-A and non-phosphorylated undercarboxylated matrix gla protein (MGP) at study termination, with adjustment for baseline values. RESULTS: Lipid parameters, the percentage of patients with dyslipoproteinemia, and VC markers did not differ significantly between groups at study termination (p values: 0.395-0.939). Likewise, vitamin D achieved no significant treatment effect on these markers in subgroup analyses in patients with 25OHD concentrations < 30 nmol/L, nonusers of lipid-lowering drugs, or diabetic patients (p values: 0.245-0.998). CONCLUSION: Our data indicate that vitamin D does not improve the lipid profile and does not influence the calcification inhibitors fetuin-A and non-phosphorylated undercarboxylated MGP in patients with advanced heart failure.

[5] *Aw NH, Canetti E, Suzuki K, Goh J*. **Monocyte Subsets in Atherosclerosis and Modification with Exercise in Humans**. Antioxidants (Basel, Switzerland) 2018; 7.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30572572
***ABSTRACT***
Atherosclerosis is a progressive pathological remodeling of the arteries and one of its hallmarks is the presence of chronic inflammation. Notably, there is an increased proportion and activation state of specific monocyte subsets in systemic blood circulation. Monocyte subsets have distinct contributions to the formation, progression, and destabilization of the atherosclerotic plaque. Strong clinical and epidemiological studies show that regular aerobic exercise mitigates the progression of cardiovascular disease. In fact, aerobic fitness is a powerful predictor of cardiovascular mortality in adults, independent of traditional risk factors such as hypertension and hyperlipidemia. Acute bouts and chronic exercise training modulate

monocyte behavior, ranging from their recruitment from the bone marrow or marginal pool, to tissue margination and functional changes in cytokine and chemokine production. Such modulation could reflect a potential mechanism for the cardio-protective effect of exercise on atherosclerosis. This review summarizes the current knowledge of monocyte subsets and highlights what is known about their responses to exercise.

[6] *Abdeen A, Aboubakr M, Elgazzar D et al.* **Rosuvastatin attenuates piroxicam-mediated gastric ulceration and hepato-renal toxicity in rats**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 110:895-905.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30572194
***ABSTRACT***
Piroxicam (Px) is a non-steroidal anti-inflammatory drug that is widely prescribed in various inflammatory disorders. However, Px is known to induce gastric ulceration and hepato-renal toxicity. Rosuvastatin (ROSV), a member of the statin family, has anti-inflammatory and antioxidant actions independent of its anti-hyperlipidemic action. Therefore, we investigated the protective effects of ROSV against Px-induced gastric, liver, and kidney injury. Five groups of seven rats each were used; control group, ROSV group (20 mg/kg, given orally), Px group (7 mg/kg, given intraperitoneally), Px+ROSV L (7 and 10 mg/kg, respectively), and Px+ROSV H (7 and 20 mg/kg, respectively) group. The results revealed that Px induced severe gastric mucosal damage expressed by high ulcer index along with significant increases in liver and kidney function parameters including AST, ALT, creatinine, and urea. Disrupted lipid metabolism also was observed in Px-treated animals. Moreover, marked an increase in malondialdehyde (MDA) and decreases in glutathione (GSH) and catalase (CAT) levels along with enhanced activated caspase-3 expression in the gastric, hepatic, and renal tissues following Px-insult suggested a possible involvement of lipid peroxidation in Px-induced gastropathy and hepatorenal toxicity. However, in a dose-dependent manner, ROSV was able to mitigate Px-induced lipid peroxidation and apoptosis in gastric, liver, and kidney tissues.

[7] *Samarasinghe S, Avari P, Meeran K, Cegla J*. **Management of hypertriglyceridaemic pancreatitis in the acute setting and review of literature**. BMJ case reports 2018; 11.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30567142
***ABSTRACT***
Acute pancreatitis (AP) is a potentially life-threatening complication of severe hypertriglyceridaemia, which is the third most common cause of AP after gallstone disease and alcohol excess. Standard therapy involves the use of lipid-lowering agents, low-molecular-weight heparin and insulin infusion. In some cases, when standard medical therapies fail, non-pharmacological methods based on the removal of triglycerides with therapeutic plasma exchange can provide positive results in the acute phase. There are currently no guidelines covering management in the acute phase, however, these approaches should be considered in severe or very severe hypertriglyceridaemia. Here, we report the case of a 37-year-old man with recurrent AP due to hypertriglyceridaemia and review the literature.

[8] *Akintoye E, Sethi P, Harris WS et al.* **Fish Oil and Perioperative Bleeding**. Circulation. Cardiovascular quality and outcomes 2018; 11:e004584.

**Literature update week 51 (2018)**

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571332

***ABSTRACT***

Background Fish oil is among the most common natural supplements for treatment of hypertriglyceridemia or prevention of cardiovascular disease. However, concerns about theoretical bleeding risk have led to recommendations that patients should stop taking fish oil before surgery or delay in elective procedures for patients taking fish oil by some health care professionals. Methods and Results We tested the effect of fish oil supplementation on perioperative bleeding in a multinational, placebo-controlled trial involving 1516 patients who were randomized to perioperative fish oil (eicosapentaenoic acid+docosahexaenoic acid; 8-10 g for 2-5 days preoperatively, and then 2 g/d postoperatively) or placebo. Primary outcome was major perioperative bleeding as defined by the Bleeding Academic Research Consortium. Secondary outcomes include perioperative bleeding per thrombolysis in myocardial infarction and International Society on Thrombosis and Hemostasis definitions, chest tube output, and total units of blood transfused. Participants' mean (SD) age was 63 (13) years, and planned surgery included coronary artery bypass graft (52%) and valve surgery (50%). The primary outcome occurred in 92 patients (6.1%). Compared with placebo, risk of Bleeding Academic Research Consortium bleeding was not higher in the fish oil group: odds ratio, 0.81; 95% CI, 0.53-1.24; absolute risk difference, 1.1% lower (95% CI, -3.0% to 1.8%). Similar findings were seen for secondary bleeding definitions. The total units of blood transfused were significantly lower in the fish oil group compared with placebo (mean, 1.61 versus 1.92; P<0.001). Evaluating achieved plasma phospholipid omega-3 polyunsaturated fatty acids levels with supplementation (on the morning of surgery), higher levels were associated with lower risk of Bleeding Academic Research Consortium bleeding, with substantially lower risk in the third (odds ratio, 0.30 [95% CI, 0.11-0.78]) and fourth (0.36 [95% CI, 0.15-0.87]) quartiles, compared with the lowest quartile. Conclusions Fish oil supplementation did not increase perioperative bleeding and reduced the number of blood transfusions. Higher achieved n-3-PUFA levels were associated with lower risk of bleeding. These novel findings support the need for reconsideration of current recommendations to stop fish oil or delay procedures before cardiac surgery. Clinical Trial Registration URL: https://www.clinicaltrials.gov . Unique identifier: NCT00970489.

[9] *Sorokin AV, Kotani K, Elnabawi YA et al.* **Association Between Oxidation-Modified Lipoproteins and Coronary Plaque in Psoriasis**. Circulation research 2018; 123:1244-1254.

**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571459

***ABSTRACT***

RATIONALE: Psoriasis is a systemic inflammatory skin disease associated with cardiovascular disease and lipid dysfunction. However, traditional lipid parameters have limited prognostic value, whereas assessing oxidation-modified lipids in this inflammatory driven condition may capture additional risk. Recently, a study showed that psoriasis was associated with increased lipid-rich coronary plaques; therefore, investigating potential relationships with oxidation-modified lipids may speed understanding of increased cardiovascular disease in psoriasis. OBJECTIVE: To understand whether oxidation-modified lipids associate with traditional lipid phenotypes, cardiometabolic disease biomarkers, and total coronary plaque, with focus on noncalcified burden (NCB) by coronary computed tomographic angiography in psoriasis.

METHODS AND RESULTS: Psoriasis subjects and controls (n=252) had profiling for oxidation-modified LDL (low-density lipoprotein), HDL (high-density lipoprotein), Lp(a) (lipoprotein[a]), cholesterol efflux capacity, lipoprotein particle size and number by NMR spectroscopy, and PON-1 (paraoxonase-1) activity. Blinded coronary computed tomographic angiography coronary artery disease characterization included total burden, NCB, and dense-calcified burden. Compared with healthy volunteers, psoriasis subjects were older (mean age, 50.1), had increased body mass index, and homeostatic model assessment of insulin resistance. Psoriasis subjects had increase in oxidized Lp(a), Lp(a), and oxidized HDL (oxHDL; P <0.05 for all) with significant association of oxidized LDL (beta=0.10; P=0.020) and oxHDL (beta=-0.11; P=0.007) with NCB. Moreover, psoriasis subjects expressed significantly higher PON-1 (kU/microL) activity compared with healthy volunteers (8.55+/-3.21 versus 6.24+/-3.82; P=0.01). Finally, psoriasis treatment was associated with a reduction in oxHDL (U/mL; 203.79+/-88.40 versus 116.36+/-85.03; P<0.001) and with a concomitant decrease in NCB at 1 year (1.04+/-0.44 versus 0.95+/-0.32; P=0.03). CONCLUSIONS: Traditional lipids did not capture risk of lipid-rich plaque as assessed by NCB, whereas assaying oxidation-modification of lipids revealed significant association with oxidized LDL and oxHDL. The PON-1 activity was increased in psoriasis suggesting possible compensatory antioxidative effect. Psoriasis treatment was associated with a reduction in oxHDL. These findings support performance of larger studies to understand oxidation-modified lipids in inflammatory states.

[10] *Gong L, Cao Y, Yang G*. **Letter by Gong et al Regarding Article, "High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial"**. Circulation 2018; 138:2726-2727.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571268
***ABSTRACT***

[11] *Grundy SM, Stone NJ, Bailey AL et al.* **2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary**. Circulation 2018:Cir0000000000000624.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30565953
***ABSTRACT***

[12] *Kimura T, Iimuro S, Taguchi I et al.* **Response by Kimura et al to Letters Regarding Article, "High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial"**. Circulation 2018; 138:2728-2729.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571270
***ABSTRACT***

[13] *Ye Z, Su Q, Li L*. **Letter by Ye et al Regarding Article, "High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial"**. Circulation 2018; 138:2724-2725.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571271
***ABSTRACT***

[14] *Du Y, Wang S, Chen Z et al.* **Association of SLCO1B1 polymorphisms and atorvastatin safety and efficacy: A meta-analysis**. Current pharmaceutical design 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30569848
***ABSTRACT***
BACKGROUND: Atorvastatin is the best-selling statin on the market. However, some patients have to reduce the drug doses or discontinue atorvastatin therapy mainly due to adverse drug reactions (ADRs). Genetic factors play an important role in the occurrence of ADRs. AIM: This study aimed to investigate the association between SLCO1B1 polymorphisms (c.521T>C or c.388A>G) and atorvastatin safety and efficacy. METHODS: We systematically searched PubMed, Web of Science and Embase to screen relevant studies published before Sep 2018. This meta-analysis was performed to identify the relationship between SLCO1B1 c.521T>C or c.388A>G polymorphisms and atorvastatin-related ADRs by the odds ratios (ORs) and 95% confidence intervals (CIs). The relationship of SLCO1B1 polymorphisms and lipid-lowering effects [low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC)] was assessed in pooled data by calculating the mean difference (MD) with 95% CIs. All statistical tests were performed by the Review Manager 5.3 software. RESULTS: A total of 13 studies involving 1,550 atorvastatin users were included in this analysis. There was a significant association between the SLCO1B1 c.521T>C polymorphism and atorvastatin-related ADRs associated with risk allele C (dominant model: OR=1.57, P=0.01). Allele C is associated with increased lipid-lowering efficacy in people with Hyperlipidemias as compared to allele T (LDL-C/dominant model: MD=6.19, P<0.00001 and (TC)/dominant model: MD=2.07, P=0.008). No association between the SLCO1B1 c.388A>G polymorphism and ADRs or efficacy was observed (P>0.05). CONCLUSION: SLCO1B1 c.521T>C polymorphism is a valuable biomarker for the evaluation of atorvastatin safety and efficacy.

[15] *Johns DG, LeVoci L, Krsmanovic M et al.* **Characterization of anacetrapib distribution into the lipid droplet of adipose tissue in mice and human cultured adipocytes**. Drug metabolism and disposition: the biological fate of chemicals 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30567880
***ABSTRACT***
Anacetrapib is an inhibitor of cholesteryl ester transfer protein (CETP), associated with reduction in LDL-cholesterol and increase in HDL-cholesterol in hypercholesterolemic patients. Anacetrapib was not taken forward into filing/registration as a new drug for coronary artery disease, despite observation of a ~9% reduction in cardiovascular risk in a large phase III cardiovascular outcomes trial (REVEAL). Anacetrapib displayed no adverse effects throughout extensive preclinical safety evaluation, and no major safety signals were observed in clinical trials studying anacetrapib, including REVEAL. However, anacetrapib demonstrated a long terminal half-life in all species, thought to be due, in part, to distribution into adipose tissue. We sought to understand the dependence of anacetrapib's long half-life on adipose tissue, and to explore potential mechanisms which might contribute to the phenomenon. In mice, anacetrapib localized primarily to the lipid droplet of adipocytes in white adipose tissue and in vitro, anacetrapib entry into cultured human adipocytes was dependent upon the presence of a mature adipocyte and lipid droplet, but did not require active transport. In vivo, the entry of

anacetrapib into adipose tissue did not require lipase activity, as the distribution of anacetrapib into adipose was not affected by systemic lipase inhibition using oloaxamer-407, a systemic lipase inhibitor. The data from these studies support the notion that entry of anacetrapib into adipose tissue/lipid droplet does not require active transport or by mobilization and entry of fat into adipose via lipolysis.

[16] *Stiekema LCA, Stroes ESG, Verweij SL et al.* **Persistent arterial wall inflammation in patients with elevated lipoprotein(a) despite strong low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment**. European heart journal 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30561610
***ABSTRACT***
Aims: Subjects with lipoprotein(a) [Lp(a)] elevation have increased arterial wall inflammation and cardiovascular risk. In patients at increased cardiovascular risk, arterial wall inflammation is reduced following lipid-lowering therapy by statin treatment or lipoprotein apheresis. However, it is unknown whether lipid-lowering treatment in elevated Lp(a) subjects alters arterial wall inflammation. We evaluated whether evolocumab, which lowers both low-density lipoprotein cholesterol (LDL-C) and Lp(a), attenuates arterial wall inflammation in patients with elevated Lp(a). Methods and results: In this multicentre, randomized, double-blind, placebo-controlled study, 129 patients {median [interquartile range (IQR)]: age 60.0 [54.0-67.0] years, Lp(a) 200.0 [155.5-301.5] nmol/L [80.0 (62.5-121.0) mg/dL]; mean [standard deviation (SD)] LDL-C 3.7 [1.0] mmol/L [144.0 (39.7) mg/dL]; National Cholesterol Education Program high risk, 25.6%} were randomized to monthly subcutaneous evolocumab 420 mg or placebo. Compared with placebo, evolocumab reduced LDL-C by 60.7% [95% confidence interval (CI) 65.8-55.5] and Lp(a) by 13.9% (95% CI 19.3-8.5). Among evolocumab-treated patients, the Week 16 mean (SD) LDL-C level was 1.6 (0.7) mmol/L [60.1 (28.1) mg/dL], and the median (IQR) Lp(a) level was 188.0 (140.0-268.0) nmol/L [75.2 (56.0-107.2) mg/dL]. Arterial wall inflammation [most diseased segment target-to-background ratio (MDS TBR)] in the index vessel (left carotid, right carotid, or thoracic aorta) was assessed by 18F-fluoro-deoxyglucose positron-emission tomography/computed tomography. Week 16 index vessel MDS TBR was not significantly altered with evolocumab (-8.3%) vs. placebo (-5.3%) [treatment difference -3.0% (95% CI -7.4% to 1.4%); P = 0.18]. Conclusion: Evolocumab treatment in patients with median baseline Lp(a) 200.0 nmol/L led to a large reduction in LDL-C and a small reduction in Lp(a), resulting in persistent elevated Lp(a) levels. The latter may have contributed to the unaltered arterial wall inflammation.

[17] *Zhang ZL, Liu WQ, Deng XZ*. **Preclinical pharmacokinetic study of a novel lipid-lowering agent, IMM-H007**. European review for medical and pharmacological sciences 2018; 22:8939-8950.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30575938
***ABSTRACT***
OBJECTIVE: To investigate the pharmacokinetic characteristics of absorption, distribution, metabolism, and excretion in vivo after oral administration and sublingual venous injection of the small molecule IMM-H007 in hamsters. MATERIALS AND METHODS: Pharmacokinetic

characteristics, including absorption, distribution, metabolism, and excretion, were studied in vivo by LC-MS/MS after oral administration and sublingual venous injection of IMM-H007 in hamsters. Furthermore, IMM-H007 stability in artificial gastric juices, artificial intestinal juices, and Tris-HCl buffer was also analyzed. RESULTS: There was no significant matrix or impurity interference in golden hamster whole blood as shown using MS/MS analysis to detect the existence of these substances. IMM-H007, Ml, and MP exhibited good linearity in the range of 1-500 ng/mL, 2-1000 ng/mL, and 10-5000 ng/mL, respectively. The matrix effect was 71.93-105.49%, and IMM-H007, M1, and MP were stable during the process of sample disposal. These results illustrate that the HPLC MS/MS analytic method is simple, reliable, and sensitive and exhibits high specificity and which meets the clinical pharmacokinetic requirements of IMM-H007. IMM-H007 is rapidly absorbed through the oral route in hamsters. The Cmax and AUC(0-t) of the Ml and MP metabolites in male and female hamsters were increased with increasing dosage and were proportional to the dose. In addition, T1/2 and MRT(0-t) were significantly prolonged with increasing dosage, exhibiting linear dynamic characteristics and no significant gender differences. Bioavailability in male and female golden hamsters after oral administration of IMM-H007 was calculated using the sum of Ml and MP, resulting in 6.97% and 8.95%, respectively. IMM-H007 and its metabolites were stable in Tris-HCl buffer, artificial gastric juices, and artificial intestinal juices. CONCLUSIONS: We provide an experimental basis for elucidating the material pharmacodynamics actions of IMM-H007 and predicting its potential drug interactions.

[18] *Lee JH, Ahn SY, Lee HA et al.* **Dietary intake of pantothenic acid is associated with cerebral amyloid burden in patients with cognitive impairment**. Food & nutrition research 2018; 62.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30574044

***ABSTRACT***

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the deposition of amyloid-beta peptide (Abeta) in diffuse and neuritic plaques. Previous research has suggested that certain vitamins may prevent this process. In the present study, we evaluated the relationship between vitamin intake and cerebral Abeta burden in patients with cognitive impairment. This study included 19 patients with subjective cognitive impairment and 30 patients with mild cognitive impairment. All patients underwent brain MRI and (18)F-florbetaben positron emission tomography. The Food Frequency Questionnaire was used to evaluate dietary intake of the 15 vitamins. Intake of vitamin B6 ($p = 0.027$), vitamin K ($p = 0.042$), vitamin A ($p = 0.063$), riboflavin ($p = 0.063$), beta-carotene ($p = 0.081$), pantothenic acid ($p = 0.092$), and niacin ($p = 0.097$) was higher in the Abeta-positive group than in the Abeta-negative group. Multivariate linear regression analysis revealed that pantothenic acid intake was an independent determinant of cerebral Abeta burden (beta = 0.287, $p = 0.029$). No significant correlations were observed between cerebral Abeta burden and the intake of other vitamins. Our findings demonstrated that pantothenic acid intake may be associated with increased cerebral Abeta burden in patients with cognitive impairment. These results may offer insight into potential strategies for AD prevention.

[19] *Lee HN, Ryu CW, Yun SJ*. **Vessel-Wall Magnetic Resonance Imaging of Intracranial Atherosclerotic Plaque and Ischemic Stroke: A Systematic Review and Meta-Analysis**. Frontiers in neurology 2018; 9:1032.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30559708
***ABSTRACT***
Introduction: Vessel-wall magnetic resonance imaging (MRI) has been suggested as a valuable tool for assessing intracranial arterial stenosis with additional diagnostic features. However, there is limited conclusive evidence on whether vessel-wall MR imaging of intracranial atherosclerotic plaques provides valuable information for predicting vulnerable lesions. We conducted this systematic review and meta-analysis to evaluate which characteristics of intracranial-plaque on vessel-wall MRI are markers of culprit lesions. Methods: The MEDLINE, EMBASE, and Cochrane Library of Clinical Trials databases were searched for studies reporting the association between vessel-wall MRI characteristics of intracranial plaque and corresponding stroke events. Odds ratios (ORs) for the prevalence of stroke with intracranial-plaque MRI characteristics were pooled in a meta-analysis using a random-effects model. Results: Twenty studies were included in this review. We found a significant association between plaque enhancement (OR, 10.09; 95% CI, 5.38-18.93), positive remodeling (OR, 6.19; 95% CI, 3.22-11.92), and plaque surface irregularity (OR, 3.94; 95% CI, 1.90-8.16) with stroke events. However, no significant difference was found for the presence of eccentricity (OR, 1.22; 95% CI, 0.51-2.91). Conclusion: Based on current evidence, intracranial plaque contrast enhancement, positive remodeling, and plaque irregularity on MRI are associated with increased risk of stroke events. Our findings support the design of future studies on intracranial-plaque MRI and decision making for the management of intracranial atherosclerotic plaques.

[20] *Gosho M*. **Rhabdomyolysis risk from the use of two-drug combination of antidyslipidemic drugs with antihypertensive and antidiabetic medications: a signal detection analysis**. Fundamental & clinical pharmacology 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30575126
***ABSTRACT***
Rhabdomyolysis is one of the most concerning complications of antidyslipidemic drugs. Most patients with dyslipidemia take multiple medications. Our objective was to explore which two-drug combinations lead to a higher risk of rhabdomyolysis. We analyzed data from the Japanese Adverse Drug Event Report (JADER) database between April 2004 and September 2017. The primary outcome was the report of rhabdomyolysis. We assessed the risk of rhabdomyolysis for the two-drug concomitant use of antidyslipidemic drugs (statin, fibrate, and ezetimibe) with antihypertensive and antidiabetic medications. The Noren and Gosho methods were used for detecting two-drug interactions. The JADER contained 468 292 records for patient characteristics, 2 973 172 drug information records, and 741 016 adverse reactions records. Rhabdomyolysis was reported in 5 017 patients. Concomitant use of pravastatin/fenofibrate, simvastatin/mefruside, fluvastatin/temocapril, bezafibrate/temocapril, bezafibrate/spironolactone, bezafibrate/metoprolol, bezafibrate/losartan, fluvastatin/mitiglinide, or fenofibrate/glibenclamide was detected as the signal of rhabdomyolysis in this analysis. Combination therapy with the drugs listed above has the

potential of drug-drug interactions that could result in rhabdomyolysis in patients with dyslipidemia.

[21] *Bernardi S, Marcuzzi A, Piscianz E et al.* **The Complex Interplay between Lipids, Immune System and Interleukins in Cardio-Metabolic Diseases**. International journal of molecular sciences 2018; 19.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30558209
***ABSTRACT***
Lipids and inflammation regulate each other. Early studies on this topic focused on the systemic effects that the acute inflammatory response-and interleukins-had on lipid metabolism. Today, in the era of the obesity epidemic, whose primary complications are cardio-metabolic diseases, attention has moved to the effects that the nutritional environment and lipid derangements have on peripheral tissues, where lipotoxicity leads to organ damage through an imbalance of chronic inflammatory responses. After an overview of the effects that acute inflammation has on the systemic lipid metabolism, this review will describe the lipid-induced immune responses that take place in peripheral tissues and lead to chronic cardio-metabolic diseases. Moreover, the anti-inflammatory effects of lipid lowering drugs, as well as the possibility of using anti-inflammatory agents against cardio-metabolic diseases, will be discussed.

[22] *Zhu X, Yang J, Zhu W et al.* **Combination of Berberine with Resveratrol Improves the Lipid-Lowering Efficacy**. International journal of molecular sciences 2018; 19.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30563192
***ABSTRACT***
The natural compound berberine has been reported to exhibit anti-diabetic activity and to improve disordered lipid metabolism. In our previous study, we found that such compounds upregulate expression of sirtuin 1-a key molecule in caloric restriction, it is, therefore, of great interest to examine the lipid-lowering activity of berberine in combination with a sirtuin 1 activator resveratrol. Our results showed that combination of berberine with resveratrol had enhanced hypolipidemic effects in high fat diet-induced mice and was able to decrease the lipid accumulation in adipocytes to a level significantly lower than that in monotherapies. In the high fat diet-induced hyperlipidemic mice, combination of berberine (30 mg/kg/day, oral) with resveratrol (20 mg/kg/day, oral) reduced serum total cholesterol by 27.4% +/- 2.2%, and low-density lipoprotein-cholesterol by 31.6% +/- 3.2%, which was more effective than that of the resveratrol (8.4% +/- 2.3%, 6.6% +/- 2.1%) or berberine (10.5% +/- 1.95%, 9.8% +/- 2.58%) monotherapy ($p < 0.05$ for both). In 3T3-L1 adipocytes, the treatment of 12 micromol/L or 20 micromol/L berberine combined with 25 micromol/L resveratrol showed a more significant inhibition of lipid accumulation observed by Oil red O stain compared with individual compounds. Moreover, resveratrol could increase the amount of intracellular berberine in hepatic L02 cells. In addition, the combination of berberine with resveratrol significantly increases the low-density-lipoprotein receptor expression in HepG2 cells to a level about one-fold higher in comparison to individual compound. These results implied that the enhanced effect of the combination of berberine with resveratrol on lipid-lowering may be associated with upregulation of low-density-lipoprotein receptor, and could be an effective therapy for

hyperlipidemia in some obese-associated disease, such as type II diabetes and metabolic syndrome.

[23] *Shirahama R, Ono T, Nagamatsu S et al.* **Coronary Artery Plaque Regression by a PCSK9 Antibody and Rosuvastatin in Double-heterozygous Familial Hypercholesterolemia with an LDL Receptor Mutation and a PCSK9 V4I Mutation**. Intern Med 2018; 57:3551-3557.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30555118
***ABSTRACT***
The low-density lipoprotein-cholesterol (LDL-C) level of a 38-year-old man diagnosed with acute coronary syndrome was 257 mg/dL. The administration of a proprotein convertase subtilisin-kexin type 9 (PCSK9) antibody in addition to rosuvastatin plus ezetimibe was initiated, reducing his LDL-C level to 37 mg/dL. A genetic analysis revealed both an LDL receptor (LDLR) mutation and a PCSK9 V4I mutation. Nine months after revascularization, intravascular ultrasound revealed plaque regression in the coronary arteries. LDLR/PCSK9 mutation carriers are prone to coronary artery disease. Intensive LDL-C lowering by including PCSK9 antibody was associated with coronary plaque regression, suggesting the expectation of prognosis improvement.

[24] *Mansouri E, Assarehzadegan MA, Nejad-Dehbashi F, Kooti W*. **Effects of Pravastatin in Adriamycin-Induced Nephropathy in Rats**. Iranian journal of pharmaceutical research : IJPR 2018; 17:1413-1419.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30568699
***ABSTRACT***
The aim of this study is to evaluate the effects of pravastatin on Adriamycin (ADR)-induced nephropathy and the mechanisms involved. Forty rats were divided into the following 4 groups: control, ADR (15 mg.kg(-1), IP), ADR plus pravastatin (20 mg.kg(-1) which was started 5 days prior to ADR injection), and ADR plus pravastatin (20 mg.kg(-1) which was started 5 days after ADR injection). On day 20 after ADR injection, the animals were sacrificed. The results showed that administration of pravastatin decreased the levels of 24-h urinary protein (24-h UP), blood urea nitrogen (BUN), and creatinine ($p < 0.05$) which had increased after the injection of ADR; in addition, pravastatin reversed structural changes seen in ADR group. Furthermore, pravastatin elevated mRNA and protein expression of nephrin ($p < 0.05$) which had been reduced in ADR group. We conclude that pravastatin protects and treats renal injury induced by ADR.

[25] *Zingg JM*. **Vitamin E: Regulatory Role on Signal Transduction**. IUBMB life 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30556637
***ABSTRACT***
Vitamin E modulates signal transduction pathways by several molecular mechanisms. As a hydrophobic molecule located mainly in membranes it contributes together with other lipids to the physical and structural characteristics such as membrane stability, curvature, fluidity, and the organization into microdomains (lipid rafts). By acting as the main lipid-soluble antioxidant, it protects other lipids such as mono- and poly-unsaturated fatty acids (MUFA and PUFA, respectively) against chemical reactions with reactive oxygen and nitrogen species (ROS and RNS, respectively) and prevents membrane destabilization and cellular dysfunction. In cells, vitamin E affects signaling in redox-dependent and redox-independent molecular mechanisms

by influencing the activity of enzymes and receptors involved in modulating specific signal transduction and gene expression pathways. By protecting and preventing depletion of MUFA and PUFA it indirectly enables regulatory effects that are mediated by the numerous lipid mediators derived from these lipids. In recent years, some vitamin E metabolites have been observed to affect signal transduction and gene expression and their relevance for the regulatory function of vitamin E is beginning to be elucidated. In particular, the modulation of the CD36/FAT scavenger receptor/fatty acids transporter by vitamin E may influence many cellular signaling pathways relevant for lipid homeostasis, inflammation, survival/apoptosis, angiogenesis, tumorigenesis, neurodegeneration, and senescence. Thus, vitamin E has an important role in modulating signal transduction and gene expression pathways relevant for its uptake, distribution, metabolism, and molecular action that when impaired affect physiological and patho-physiological cellular functions relevant for the prevention of a number of diseases. (c) 2018 IUBMB Life, 9999(9999):1-23, 2018.

[26] *Ahmed O, Littmann K, Gustafsson U et al.* **Ezetimibe in Combination With Simvastatin Reduces Remnant Cholesterol Without Affecting Biliary Lipid Concentrations in Gallstone Patients**. Journal of the American Heart Association 2018; 7:e009876.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30561264

***ABSTRACT***

Background In randomized trials (SHARP [Study of Heart and Renal Protection], IMPROVE -IT [Improved Reduction of Outcomes: Vytorin Efficacy International Trial]), combination of statin and ezetimibe resulted in additional reduction of cardiovascular events. The reduction was greater in patients with type 2 diabetes mellitus (T2 DM ), where elevated remnant cholesterol and high cardiovascular disease risk is characteristic. To evaluate possible causes behind these results, 40 patients eligible for cholecystectomy, randomized to simvastatin, ezetimibe, combined treatment (simvastatin+ezetimibe), or placebo treatment during 4 weeks before surgery, were studied. Methods and Results Fasting blood samples were taken before treatment start and at the end (just before surgery). Bile samples and liver biopsies were collected during surgery. Hepatic gene expression levels were assessed with qPCR . Lipoprotein, apolipoprotein levels, and content of cholesterol, cholesteryl ester, and triglycerides were measured after lipoprotein fractionation. Lipoprotein subclasses were analyzed by nuclear magnetic resonance. Apolipoprotein affinity for human arterial proteoglycans ( PG ) was measured. Biomarkers of cholesterol biosynthesis and intestinal absorption and bile lipid composition were analyzed using mass spectrometry. Combined treatment caused a statistically significant decrease in plasma remnant particles and apolipoprotein B (ApoB)/lipoprotein content of cholesterol, cholesteryl esters, and triglycerides. All treatments reduced ApoB-lipoprotein PG binding. Simvastatin and combined treatment modified the composition of lipoproteins. Changes in biomarkers of cholesterol synthesis and absorption and bile acid synthesis were as expected. No adverse events were found. Conclusions Combined treatment caused atheroprotective changes on ApoB-lipoproteins, remnant particles, bile components, and in ApoB-lipoprotein affinity for arterial PG . These effects might explain the decrease of cardiovascular events seen in the SHARP and IMPROVE - IT trials. Clinical Trial Registration URL : www.clinicaltrialsregister.eu . Unique identifier: 2006-004839-30).

[27] *Kim BJ, Kwon SU, Wajsbrot D et al.* **Relationship of Inter-Individual Blood Pressure Variability and the Risk for Recurrent Stroke**. Journal of the American Heart Association 2018; 7:e009480.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30561256
***ABSTRACT***
Background Evidence suggests that patients with higher blood pressure variability ( BPV ) have a higher risk for stroke, but any link between BPV and stroke recurrence is unknown among those who had a stroke or transient ischemic attack ( TIA ). Methods and Results Data for patients with a history of stroke or TIA at enrollment were extracted from the ASCOT (Anglo Scandinavian Cardiac Outcomes Trial) and the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). BPV was defined as the within-subject standard deviation or coefficient of variation of systolic blood pressure across visits from 12 weeks poststroke or TIA onward. BPV was significantly higher in patients with a history of stroke or TIA than those without. BPV was a predictor of recurrent stroke in the pooled analysis. In the ASCOT study, 252 patients (12.3%) had a recurrent stroke among 2046 with a history of stroke. Incidence of recurrent stroke was significantly higher in the highest BPV quartile (17.8%) compared with the lowest quartile (10.5%); by treatment arm, this reached significance for the amlodipine-arm only (high- BPV : 18.7% versus low- BPV : 12.9%; P=0.029). Of the 2173 patients from the ALLHAT with a history of stroke or TIA , patients with the highest quartile of BPV had a higher incidence of recurrent stroke (9.6%) compared with the lowest quartile BPV (5.5%); by treatment arm, this reached significance for the chlorthalidone-arm only (high- BPV : 12.1% versus low- BPV : 5.4%; P=0.007). Conclusions Visit-to-visit BPV is a predictor of recurrent stroke in patients with a history of stroke or TIA on antihypertensive treatment. Considering BPV following a stroke may be important to reduce the risk for a recurrent stroke.

[28] *Ko DT, Khan AM, Kotrri G et al.* **Eligibility, Clinical Outcomes, and Budget Impact of PCSK9 Inhibitor Adoption: The CANHEART PCSK9 Study**. Journal of the American Heart Association 2018; 7:e010007.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571382
***ABSTRACT***
Background The FOURIER (Further Cardiovascular Outcomes Research With PCSK9i [Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors] in Subjects With Elevated Risk) trial found a reduction in cardiovascular events in patients with atherosclerotic cardiovascular disease ( ASCVD ). Our objective was to estimate the eligibility, clinical outcomes, and budget impact of adopting PCSK 9i in a large healthcare system. Methods and Results Ontario, Canada, residents alive in 2011, aged 40 to 85 years, were eligible for inclusion. PCSK 9i eligibility was determined on the basis of FOURIER trial definition. Hazard ratios observed in the FOURIER trial were applied to assess the number of events that could be avoided. Budget impact was calculated as the difference between projected costs of treatment adoption and events avoided if PCSK 9i were used. Of the 2.4 million included individuals, 5.3% had a history of ASCVD . We estimated that 2.7% of the general population and 51.9% of the patients with ASCVD would be eligible for PCSK 9i. Adoption of PCSK 9i in all eligible patients with ASCVD was projected to reduce primary events rates by 1.8% after 3 years. Despite cost reduction of $44 million in events, PCSK 9i adoption would have a net budget impact of $1.5 billion over 3 years. Potential benefits of PCSK

9i varied widely across subgroups, with the largest absolute risk reduction estimated to be 4.3% at 3 years in peripheral artery disease. In this subgroup of 5601 patients, the budget impact of treatment adoption was $116 million. Conclusions We estimated that approximately 1 in 2 patients with ASCVD would be eligible for PCSK 9i. The budget impact of adopting PCSK 9i for all patients with ASCVD is substantial. Selective adoption to high-risk patients will lessen the overall budgetary impact of PCSK 9i treatment.

[29] *Nasir K*. **Just Price for PCSK9 Inhibitors: No less, No More**. Journal of the American Heart Association 2018; 7:e010884.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571392
***ABSTRACT***
See Article by Ko et al .

[30] *Sato T, Arakawa M, Tashima Y et al.* **Statins Reduce Thoracic Aortic Aneurysm Growth in Marfan Syndrome Mice via Inhibition of the Ras-Induced ERK (Extracellular Signal-Regulated Kinase) Signaling Pathway**. Journal of the American Heart Association 2018; 7:e008543.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30571378
***ABSTRACT***
Background Statins reduce aneurysm growth in mouse models of Marfan syndrome, although the mechanism is unknown. In addition to reducing cholesterol, statins block farnesylation and geranylgeranylation, which participate in membrane-bound G-protein signaling, including Ras. We dissected the prenylation pathway to define the effect of statins on aneurysm reduction. Methods and Results Fbn1(C1039G/+) mice were treated with (1) pravastatin (HMG-CoA [3-hydroxy-3-methylglutaryl coenzyme A] reductase inhibitor), (2) manumycin A ( MA ; FPT inhibitor), (3) perillyl alcohol ( GGPT 1 and -2 inhibitor), or (4) vehicle control from age 4 to 8 weeks and euthanized at 12 weeks. Histological characterization was performed. Protein analysis was completed on aortic specimens to measure ERK (extracellular signal-regulated kinase) signaling. In vitro Fbn1(C1039G/+) aortic smooth muscle cells were utilized to measure Ras-dependent ERK signaling and MMP (matrix metalloproteinase) activity. Pravastatin and MA significantly reduced aneurysm growth compared with vehicle control (n=8 per group). In contrast, PA did not significantly decrease aneurysm size. Histology illustrated reduced elastin breakdown in MA -treated mice compared with vehicle control (n=5 per group). Although elevated in control Marfan mice, both phosphorylated c-Raf and phosphorylated ERK 1/2 were significantly reduced in MA -treated mice (4-5 per group). In vitro smooth muscle cell studies confirmed phosphorylated cR af and phosphorylated ERK 1/2 signaling was elevated in Fbn1(C1039G/+) smooth muscle cells (n=5 per group). Fbn1(C1039G/+) smooth muscle cell Ras-dependent ERK signaling and MMP activity were reduced following MA treatment (n=5 per group). Corroborating in vitro findings, MMP activity was also decreased in pravastatin-treated mice. Conclusions Aneurysm reduction in Fbn1(C1039G/+) mice following pravastatin and MA treatment was associated with a decrease in Ras-dependent ERK signaling. MMP activity can be reduced by diminishing Ras signaling.

[31] *Yao Y, Li B, Liu C et al.* **Reduced Plasma Kallistatin Is Associated With the Severity of Coronary Artery Disease, and Kallistatin Treatment Attenuates Atherosclerotic Plaque Formation in Mice**. Journal of the American Heart Association 2018; 7:e009562.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30554563

***ABSTRACT***

Background Kallistatin exerts beneficial effects on organ injury by inhibiting oxidative stress and inflammation. However, the role of kallistatin in atherosclerosis is largely unknown. Here, we investigated the role and mechanisms of kallistatin in patients with coronary artery disease ( CAD ), atherosclerotic plaques of apoE(-/-) mice, and endothelial activation. Methods and Results Plasma kallistatin levels were analyzed in 453 patients at different stages of CAD . Kallistatin levels were significantly lower in patients with CAD and negatively associated with CAD severity and oxidative stress. Human kallistatin cDNA in an adenoviral vector was injected intravenously into apoE(-/-) mice after partial carotid ligation, with or without nitric oxide synthase inhibitor (N(omega)-nitro-L-arginine methyl ester) or sirtuin 1 inhibitor (nicotinamide). Kallistatin gene delivery significantly reduced macrophage deposition, oxidative stress, and plaque volume in the carotid artery, compared with control adenoviral injection. Kallistatin administration increased endothelial nitrous oxide synthase, sirtuin 1, interleukin-10, superoxide dismutase 2, and catalase expression in carotid plaques. The beneficial effects of kallistatin in mice were mitigated by N(omega)-nitro-L-arginine methyl ester or nicotinamide. Furthermore, human kallistatin protein suppressed tumor necrosis factor-alpha-induced NADPH oxidase activity and increased endothelial nitrous oxide synthase and sirtuin 1 expression in cultured human endothelial cells. These effects were also abolished by N(omega)-nitro-L-arginine methyl ester or nicotinamide. Conclusions This was the first study to demonstrate that reduced plasma kallistatin levels in patients are associated with CAD severity and oxidative stress. Kallistatin treatment prevents carotid atherosclerotic plaque formation in mice by stimulating the sirtuin 1/endothelial nitrous oxide synthase pathway. These findings indicate the potential protective effects of kallistatin on atherosclerosis in human subjects and mouse models.

[32] *Sokalska A, Hawkins AB, Yamaguchi T, Duleba AJ*. **Lipophilic statins inhibit growth and reduce invasiveness of human endometrial stromal cells**. Journal of assisted reproduction and genetics 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30554393

***ABSTRACT***

PURPOSE: To compare effects of lipid-soluble statins (simvastatin, lovastatin, atorvastatin) and water-soluble statin (pravastatin) on growth and invasiveness of human endometrial stromal (HES) cells. METHODS: Endometrial biopsies were collected during the proliferative phase from five volunteers. HES cells were isolated and cultured in the absence or in the presence of simvastatin, lovastatin, atorvastatin, and pravastatin. Effects of statins on DNA synthesis, cell viability, activity of caspases 3/7 and invasiveness were evaluated. RESULTS: The proliferation of HES cells was significantly decreased by simvastatin (by 47-89%), lovastatin (by 46-78%), and atorvastatin (by 21-48%) in a concentration-dependent manner. Activity of executioner caspases 3/7 was significantly increased by simvastatin (by 10-25%), lovastatin (by 19%) and atorvastatin (by 7-10%) in a concentration-dependent manner. The greatest effects were

observed in response to simvastatin. Accounting for the effects of statins on cell number, the invasiveness of HES cells was significantly decreased in cells treated with simvastatin (by 49%), lovastatin (by 54%), and atorvastatin (by 53%). Pravastatin had little or no effects on any of the tested endpoints. CONCLUSIONS: Present findings demonstrate that only lipid-soluble among tested statins were effective in inhibition of growth and invasiveness of HES cells. These findings may have clinical relevance in treatment of endometriosis.

[33] *Ishigaki Y, Kawagishi N, Hasegawa Y et al.* **Liver Transplantation for Homozygous Familial Hypercholesterolemia**. Journal of atherosclerosis and thrombosis 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30555131
***ABSTRACT***
Pharmacological treatments to decrease low-density lipoprotein (LDL) cholesterol (LDL-C) have limited effects on patients with homozygous familial hypercholesterolemia (HoFH). Since LDL receptors are located mainly in the liver, liver transplantation is considered to be the only way to correct the hepatic cholesterol metabolism abnormalities in HoFH. Liver transplantations, including those combined with heart transplantation, for HoFH have been increasing since 1984, making this a globally established therapeutic option for HoFH. Plasma LDL-C is reported to be dramatically lowered, by 80%, after transplantation, with the rapid regression of cutaneous and tendinous xanthomas. However, long-term cardiovascular benefits remain unclear. The major concerns about liver transplantation include surgical complications, the need for lifelong immunosuppressive therapy, and rejection. In addition, organ transplantations from deceased donors are extremely rare in Japan. We experienced two pediatric siblings with HoFH who received living-donor liver transplantations from their heterozygous parents. Their plasma LDL-C levels decreased immediately and stabilized at approximately 200 mg/dL. Both developed normally with the administration of lipid-lowering medications and have been free of severe problems for more than 10 years, to date, since transplantation. In Japan, where the shortage of deceased donors is critical, the combination of living-donor liver transplant from a heterozygous donor, that is, usually a parent, and medication is regarded as a valid therapeutic option for HoFH. Further studies and clinical experience are required to establish liver transplantation as a safe and effective treatment for HoFH.

[34] *Reddy S, Kaur N, Singh J*. **A novel study to examine the association of PCSK9 rs505151 polymorphism and coronary artery disease in north Indian population**. Journal of genetics 2018; 97:1371-1378.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30555085
***ABSTRACT***
There is a drastic increase in the number of people suffering from coronary artery disease (CAD) worldwide with Indians being no exception. Being a developing country and experiencing a dramatic shift in lifestyle and eating habits, urbanization and industrialization, all these factors have collectively predisposed the Indian population towards CAD and the prevalence data arequite alarming. Genetic studies have disclosed the role of genes in CAD susceptibility and severity. One such gene is proprotein convertase subtilisin/kexin type 9 (PCSK9) which is sought to modulate the cholesterol levels and hence, has implications in CAD. We aim to explore the association of PCSK9 A/G (rs505151) polymorphism and hence, the susceptibility towards CAD

in the north Indian population. Five-hundred angiographically confirmed CAD patients and 500 healthy individuals as control were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Statistical analysis revealed a significant association with the G allele with odds ratio (OR)=1.50, 95% confidence interval (CI)=1.22-1.85 and P=0.000. Also, a strong association was observedfor CAD risk with OR=1.590, 95% CI=1.106-2.284 and P=0.012. However, the homozygous GG mutant genotype was found to be completely absent from our population. Analysis of the dominant model also revealed an association with CAD risk. Our work demonstrated for the first time the association of PCSK9 A/G (rs505151) polymorphism with CAD risk in the north Indian population.

[35] *Zhu YC, Jiang XZ, Bai QK et al.* **Evaluating the Efficacy of Atorvastatin on Patients with Carotid Plaque by an Innovative Ultrasonography**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30563776
***ABSTRACT***
BACKGROUND: The present study aimed to explore the efficacy of atorvastatin on patients with carotid plaque, applying superb microvascular imaging (SMI), and contrast-enhanced ultrasound (CEUS) for evaluating carotid intraplaque neovascularization. METHODS: A total of 82 patients (82 carotid plaques) who were randomized into treatment group and control group underwent conventional ultrasound, CEUS, and SMI examinations. Patients in treatment group received a dose of 20 mg atorvastatin per day for 6 months while those in control group received placebo instead. Lipid parameters were assessed and intraplaque neovascularization were evaluated by CEUS and SMI before and 6 months after atorvastatin treatment. RESULTS: No significant differences were found between the 2 groups at the study entry. Patients with atorvastatin treatment received marked improvement in total cholesterol, triglyceride, and LDL-cholesterol compared with those in control group ($P < .001$). In treatment group, SMI-detected intraplaque neovascularization reduced from 69.23% to 48.72% while CEUS-detected ones reduced from 76.92% to 69.23%. By contrast, the percentage of intraplaque neovascularization in control group did not change too much either by SMI (65.12%, 67.44%) or CEUS (74.41%, 74.41%). The consistency between CEUS and SMI was above .75 at all assessments ($P < .001$). CONCLUSIONS: Atorvastatin treatment works for patients with carotid plaque by reducing LDL-cholesterol and improving plaque regression. Second, the consistency between SMI and CEUS in visualizing intraplaque neovascularization is good. That indicates a high possibility to identify carotid plaque instability by a safer and cheaper ultrasonography without contrast agent.

[36] *Orsi FA, Biedermann JS, Kruip M et al.* **Rosuvastatin use reduces thrombin generation potential in patients with venous thromboembolism: a randomized controlled trial**. Journal of thrombosis and haemostasis : JTH 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30565854
***ABSTRACT***
BACKGROUND: Statin therapy could form an alternative prophylactic treatment for venous thromboembolism (VTE) if statins are proven to downregulate hemostasis and prevent recurrent VTE, without increasing bleeding risk. OBJECTIVES: The STAtins Reduce Thrombophilia

(START) trial investigated whether statin affects coagulation in patients with prior VTE. PATIENTS/METHODS: After anticoagulation withdrawal, patients were randomized to rosuvastatin 20mg/day for 4 weeks or no intervention. Plasma samples taken at baseline and at the end of the study were analyzed employing thrombin generation assay. RESULTS AND CONCLUSIONS: The study comprised 126 rosuvastatin users and 119 non-users. Mean age was 58 years, 61% were men, 49% had unprovoked VTE and 75% had cardiovascular (CV) risk factors. Endogenous thrombin potential (ETP) increased from baseline to end of study in non-statin users (mean 97.22nM*min; 95%CI 40.92 to 153.53) and decreased in rosuvastatin users (mean -24.94nM*min; 95%CI -71.81 to 21.93). The mean difference in ETP change between treatments was -120.24nM*min (95%CI -192.97 to -47.51), yielding a 10.4% ETP reduction by rosuvastatin. Thrombin peak increased in both non-statin (mean 20.69nM; 95%CI 9.80 to 31.58) and rosuvastatin users (mean 8.41nM; 95%CI -0.86 to 17.69). The mean difference in peak change between treatments was -11.88nM (95%CI -26.11 to 2.35), yielding a 5% peak reduction by rosuvastatin. Other thrombin generation parameters did not change substantially. The reduction in ETP and peak by rosuvastatin was more pronounced in the subgroups of participants with CV risk factors and with unprovoked VTE. We conclude that rosuvastatin reduces thrombin generation potential in patients who had VTE. 

[37] *Raber L, Koskinas KC, Yamaji K et al.* **Changes in Coronary Plaque Composition in Patients With Acute Myocardial Infarction Treated With High-Intensity Statin Therapy (IBIS-4): A Serial Optical Coherence Tomography Study**. JACC. Cardiovascular imaging 2018.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30553686

***ABSTRACT***

OBJECTIVES: This study assessed changes in optical coherence tomography (OCT)-defined plaque composition in patients with ST-elevation myocardial infarction (STEMI) receiving high-intensity statin treatment. BACKGROUND: OCT is a high-resolution modality capable of measuring plaque characteristics including fibrous cap thickness (FCT) and macrophage infiltration. There is limited in vivo evidence regarding the effects of statins on OCT-defined coronary atheroma composition and no evidence in the context of STEMI. METHODS: In the IBIS-4 (Integrated Biomarker Imaging Study-4), 103 patients underwent intravascular ultrasonography and OCT of 2 noninfarct-related coronary arteries in the acute phase of STEMI. Patients were treated with high-dose rosuvastatin for 13 months. Serial OCT imaging was available in 153 arteries from 83 patients. We measured FCT by using a semi-automated method. Co-primary endpoints consisted of the change in minimum FCT (measured in fibroatheromas) and change in macrophage line arc. RESULTS: At 13 months, median low-density lipoprotein cholesterol had decreased from 128 mg/dl to 73.6 mg/dl. Minimum FCT, measured in 31 lesions from 27 patients, increased from 64.9 +/- 19.9 mum to 87.9 +/- 38.1 mum ($p = 0.008$). Macrophage line arc decreased from 9.6 degrees +/- 12.8 degrees to 6.4 degrees +/- 9.6 degrees ($p < 0.0001$). The secondary endpoint, mean lipid arc, decreased from 55.9 degrees +/- 37 degrees to 43.5 degrees +/- 33.5 degrees . In lesion-level analyses (n = 191), 9 of 13 thin-cap fibroatheromata (TCFAs) at baseline (69.2%) regressed to non-TCFA morphology, whereas 2 of 178 non-TCFA lesions (1.1%) progressed to TCFAs. CONCLUSIONS: In this observational study, we found significant increase in minimum FCT, reduction in

macrophage accumulation, and frequent regression of TCFAs to other plaque phenotypes in nonculprit lesions of patients with STEMI treated with high-intensity statin therapy.

[38] *Wang X, Shi N, Shi H et al.* **Correlations of Acute Cerebral Hemorrhage Complicated with Stress Ulcer Bleeding with Acute Physiology and Chronic Health Evaluation (APACHE) II Score, Endothelin (ET), Tumor Necrosis Factor-alpha (TNF-alpha), and Blood Lipids**. Medical science monitor : international medical journal of experimental and clinical research 2018; 24:9120-9126.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30554231
***ABSTRACT***
BACKGROUND This study investigated the correlations between acute cerebral hemorrhage complicated with stress ulcer bleeding and corresponding indexes, including the Acute Physiology and Chronic Health Evaluation (APACHE) II score, vascular endothelin-1 (ET-1), tumor necrosis factor-alpha (TNF-alpha), and blood lipid factors. MATERIAL AND METHODS A total of 53 patients with acute cerebral hemorrhage complicated with stress ulcer bleeding were selected as the observation group and 50 patients with simple acute cerebral hemorrhage were selected as the control group. The APACHE II score and the levels of ET-1, TNF-alpha, and blood lipid factors, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and malondialdehyde (MDA), were detected and the correlations of were analyzed between the 2 groups of patients. RESULTS The blood lipid index TG, APACHE II score, ET-1, TNF-a, renal function indexes [blood urea nitrogen (BUN) and creatinine (Cr)], mortality rate, hemoglobin, and MDA in the observation group were significantly higher than those in the control group, while HDL-C in the observation group was obviously lower than in the control group ($p<0.05$). The APACHEII score had positive correlations with TG and TNF-alpha ($r=0.8960$, $r=0.8563$, respectively), while it was negatively correlated with TC, HDL-C, LDL-C, and ET-1 ($r=-0.909$, $r=-0.9292$, $r=-0.8543$, and $r=-0.8899$, respectively) ($p<0.001$ in all comparisons). APACHEII score, BUN, and Cr were all risk factors. CONCLUSIONS Stress ulcer in patients with acute cerebral hemorrhage is associated with blood lipid changes and inflammation, which provides clues for the diagnosis and treatment of acute cerebral hemorrhage.

[39] *Xiao Y, He S, Zhang Z et al.* **Effect of High-Dose Statin Pretreatment for Myocardial Perfusion in Patients Receiving Percutaneous Coronary Intervention (PCI): A Meta-Analysis of 15 Randomized Studies**. Medical science monitor : international medical journal of experimental and clinical research 2018; 24:9166-9176.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30557296
***ABSTRACT***
BACKGROUND For coronary artery disease, percutaneous coronary intervention (PCI) is the preferred treatment. Reperfusion injury is a common and serious complication of PCI. Studies showed that early statin therapy has a favorable prognostic impact for patients undergoing PCI. However, the effects of statins on improving post-PCI myocardial perfusion are still unclear. In this study we evaluated the potential effect of high-dose statin pretreatment on postprocedure myocardial perfusion and MACE rate in patients receiving PCI. MATERIAL AND METHODS We searched randomized controlled trials that evaluated the effect of high-dose statin

pretreatment on post-PCI TIMI flow grade and MACE in patients undergoing PCI from the databases of PubMed, Embase, and Cochrane Library. All data were pooled for analysis and were stratified by type of statin, clinical presentation, and current statin therapy status in subgroup. RESULTS Fifteen RCTs with 4240 individuals were selected. The pooled analysis showed that high-dose statin pretreatment before PCI significantly improved the final TIMI flow grade compared with the control group (OR=0.61, 95% CI: 0.46 to 0.80, p=0.0005), and showed reduced incidence of MACE (OR=0.53, 95%CI: 0.39 to 0.71, p<0.0001). In subgroup analysis, the beneficial effect of high-dose statin was significant in statin-naive treatment patients, ACS patients, and patients on atorvastatin therapy, but no difference occurred in rosuvastatin, previous statin therapy, and stable angina patients. CONCLUSIONS High-dose statin pretreatment has an important effect on postprocedure myocardial perfusion by improving the TIMI flow in patients undergoing PCI, and high-dose statin preloading also reduces the incidence of MACE.

[40] *Zhao H, Song A, Zhang Y et al.* **Effect of Resveratrol on Blood Lipid Levels in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis**. Obesity (Silver Spring, Md.) 2019; 27:94-102.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30569644
***ABSTRACT***
OBJECTIVE: Few studies have considered the effect of resveratrol on blood lipid levels, and the results of these studies are inconsistent. In this study, the first meta-analysis on the effect of resveratrol on blood lipid levels in patients with type 2 diabetes was conducted. METHODS: This study used keywords such as type 2 diabetes, total cholesterol, triglyceride (TG), high-density lipoprotein, low-density lipoprotein, and resveratrol and their abbreviations, free words, and related words to search PubMed, Cochrane Library, and Embase. The Cochrane risk of bias tool was used to evaluate the risk of bias, and Review Manager 5.3 and Stata 13.0 were used for data merging and statistical analysis. RESULTS: Ten randomized controlled trials involving a total of 363 patients with type 2 diabetes were included in the analysis. The results show that longer resveratrol intervention time (>/=6 months) can reduce TG levels. But resveratrol increased total cholesterol in patients within obesity range. In type 2 diabetes patients with obesity and in those who took lipid-lowering drugs, resveratrol increased low-density lipoprotein levels. CONCLUSIONS: Resveratrol can improve TG in patients with type 2 diabetes.

[41] *DiNicolantonio JJ, O'Keefe JH*. **Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation**. Open heart 2018; 5:e000946.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30564378
***ABSTRACT***

[42] *Carlson TL, Yildiz H, Dar Z et al.* **Lipids alter microbial transport through intestinal mucus**. PloS one 2018; 13:e0209151.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30576356
***ABSTRACT***
Mucus constitutes a protective layer which coats the gastrointestinal tract, controlling interactions of both commensal and pathogenic microbes with underlying tissues. Changes to

the mucus barrier, for example due to altered mucin expression or external stimuli, may impact interactions with microbes and thus potentially contribute to altered gut homeostasis, onset of inflammation, or pathogen invasion. Food-associated stimuli, including lipids, have been shown to change mucus barrier properties and reduce transport of model drug carriers through mucus. Here, we explore the impact of lipids, specifically triglycerides in a model intestinal medium mimicking a fed state, on Escherichia coli (E. coli) transport through mucus by directly imaging swimming patterns and analyzing associated changes in mucus structure. Lipids in model fed state intestinal contents reduced E. coli speed and track linearity within mucus. These changes may be due in part to changes in molecular interactions within the mucus network as well as crowding of the mucus network by lipid emulsion droplets, which visibly stay intact in the mucus gel. In addition, observed physical interactions between bacteria and lipid structures may impact microbial speed and trajectories. As lipids are normal food components and thus represent safe, mild stimuli, these results support exploration of lipid-based strategies to alter the mucus barrier to control interactions with microbes and potentially prevent microbial invasion of underlying epithelium.

[43] *Henriques F, Lopes MA, Franco FO et al.* **Toll-Like Receptor-4 Disruption Suppresses Adipose Tissue Remodeling and Increases Survival in Cancer Cachexia Syndrome**. Scientific reports 2018; 8:18024.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30575787
***ABSTRACT***
Cancer-induced cachexia, characterized by systemic inflammation, body weight loss, adipose tissue (AT) remodeling and muscle wasting, is a malignant metabolic syndrome with undefined etiology. Here, we show that both genetic ablation and pharmacological inhibition of TLR4 were able to attenuate the main clinical markers of cachexia in mice bearing Lewis lung carcinoma (LLC). AT remodelling was not found in LLC tumor-bearing (TB) TLR4(-/-) mice due to reduced macrophage infiltration and adipocyte atrophy. TLR4(-/-) mice were also resistant to cold-induced browning of subcutaneous AT (scAT). Importantly, pharmacological inhibition of TLR4 (Atorvastatin) reproduced the main protective effect against AT remodeling found in TLR4(-/-) TB mice. Moreover, the treatment was effective in prolonging survival and attenuating tumor mass growth when compared to non-treated-TB animals. Furthermore, tumor-induced elevation of circulating pro-inflammatory cytokines was similarly abolished in both genetic ablation and pharmacological inhibition of TLR4. These data suggest that TLR4 is a critical mediator and a promising target for novel anti-cachexia therapies.

[44] *Shyamsundar M, O'Kane C, Perkins GD et al.* **Prevention of post-operative complications by using a HMG-CoA reductase inhibitor in patients undergoing one-lung ventilation for non-cardiac surgery: study protocol for a randomised controlled trial**. Trials 2018; 19:690.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30563555
***ABSTRACT***
BACKGROUND: Postoperative pulmonary complications (PPC) and peri-operative myocardial infarction (MI) have a significant impact on the long-term mortality of surgical patients. Patients undergoing one-lung ventilation (OLV) for surgery are at a high risk of developing these complications. These complications could be associated with intensive care unit (ICU)

admissions and longer hospital stay with associated resource and economic burden. Simvastatin, a HMG-CoA reductase enzyme inhibitor has been shown to have pleiotropic anti-inflammatory effects as well as being endothelial protective. The benefits of statins have been shown in various observational studies and in small proof-of-concept studies. There is an urgent need for a well-designed, large clinical trial powered to detect clinical outcomes. The Prevention HARP 2 trial will test the hypothesis 'simvastatin 80 mg when compared to placebo will reduce cardiac and pulmonary complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy'. METHODS/DESIGN: The Prevention HARP 2 trial is a UK multi-centre, randomised, double-blind, placebo-controlled trial. Adult patients undergoing elective oesophagectomy, lobectomy or pneumonectomy will be eligible. Patients who are already on statins will be excluded from this trial. Patients will be randomised to receive simvastatin 80 mg or matched placebo for 4 days pre surgery and for up to 7 days post surgery. The primary outcome is a composite outcome of PPC and MI within 7 days post surgery. Various secondary outcome measures including clinical outcomes, safety outcomes and health economic outcomes will be collected. The study aims to recruit 452 patients in total across 12 UK sites. DISCUSSION: The results of the Prevention HARP 2 trial should add to our understanding of the benefits of peri-operative statins and influence clinical decision-making. Analysis of blood and urine samples from the patients will provide insight into the mechanism of simvastatin action. TRIAL REGISTRATION: International Standard Randomised Controlled Trials registry, ID: ISRCTN48095567 . Registered on 11 November 2016.

[45] *Hines DM, Rane P, Patel J et al.* **Treatment patterns and patient characteristics among early initiators of PCSK9 inhibitors**. Vascular health and risk management 2018; 14:409-418.
**PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=30573963

***ABSTRACT***

Purpose: To describe patient characteristics and treatment patterns among early initiators of proprotein convertase subtilisin/kexin type nine inhibitors (PCSK9is) who initiated treatment within the first 6 months of market availability. Patients and methods: This retrospective cohort study used IQVIA's longitudinal open-source point-of-sale pharmacy claims database (LRx) and PharMetrics Plus (P+) health plan claims database to identify patients initiating a PCSK9i between January 1, 2016 and June 30, 2016. The index date was defined as the date of the first PCSK9i prescription (index claim) during the enrollment window; patients were followed for >/=6 months postindex. Patient characteristics including use of baseline lipid-lowering therapy (LLT) and measures such as persistence and adherence to PCSK9i therapy were evaluated with respect to health plan type (commercial vs Medicare). Results: Overall, patients initiating PCSK9i (n=13,151) had a mean age of 66 years, and 51% were male. Approximately 67.4% of patients used some form of LLT (statin and/or ezetimibe) in the 24 months prior to initiating PCSK9i therapy. The proportion of patients covered by a commercial health plan (51.2%) was similar to that covered by Medicare (48.8%). Persistence on PCSK9i was marginally longer for patients with commercial insurance than Medicare (mean days on therapy 202.2 vs 198.5). Overall, 42.6% of patients discontinued their PCSK9i during the 180 days of follow-up. Conclusion: This study demonstrates that a large proportion of patients discontinue PCSK9i therapy at 30 and 90 days, which are the time frames for which many health plans require recertification to continue access to PCSK9i. Future studies looking at treatment patterns

among patients who initiate PCSK9i therapy after the first 180 days once health plan formularies and utilization management criteria were finalized are needed to understand more comprehensively real-world PCSK9i usage patterns.