Literature update week 06 (2018)

[1] *Halade GV, Dorbane A, Ingle KA et al.* **Comprehensive targeted and non-targeted lipidomics analyses in failing and non-failing heart**. Analytical and bioanalytical chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29411084
ABSTRACT
Myocardial infarction (MI) and subsequent progressive heart failure pathology is the major cause of death worldwide; however, the mechanism of this pathology remains unclear. The present work aimed at testing the hypothesis whether the inflammatory response is superimposed with the formation of bioactive lipid resolving molecules at the site of the injured myocardium in acute heart failure pathology post-MI. In this view, we used a robust permanent coronary ligation model to induce MI, leading to decreased contractility index with marked wall thinning and necrosis of the infarcted left ventricle. Then, we applied mass spectrometry imaging (MSI) in positive and negative ionization modes to characterize the spatial distribution of left ventricle lipids in the infarcted myocardium post-MI. After micro-extraction, liquid chromatography coupled to tandem mass spectrometry was used to confirm the structures of the imaged lipids. Statistical tools such as principal component analysis were used to establish a comprehensive visualization of lipid profile changes in MI and no-MI hearts. Resolving bioactive molecules such as resolvin (Rv) D1, RvD5, RvE3, 17-HDHA, LXA4, and 18-HEPE were detected in negative ion mode MSI, whereas phosphatidyl cholines (PC) and oxidized derivatives thereof were detected in positive ion mode. MSI-based analysis demonstrated a significant increase in resolvin bioactive lipids with comprehensive lipid remodeling at the site of infarction. These results clearly indicate that infarcted myocardium is the primary location of inflammation-resolution pathomechanics which is critical for resolution of inflammation and heart failure pathophysiology. Graphical abstract Applied scheme to determine comprehensive lipidomics in failing and non-failing heart.

[2] *Chen Z, Li C, Lin K et al.* **MicroRNAs in acute myocardial infarction: Evident value as novel biomarkers?** Anatol J Cardiol 2018; 19:140-147.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29424735
ABSTRACT
Traditional circulating biomarkers play a fundamental role in the diagnosis and prognosis of acute myocardial infarction (AMI). However, they have several limitations. microRNAs (miRs), a class of RNA molecules that do not encode proteins, function directly at the RNA level by inhibiting the translation of messenger RNAs. Due to their significant roles in disease development, they can be used as biomarkers. Accumulating evidence has revealed an attractive role of miRs as biomarkers of AMI and its associated symptoms, including vulnerable atherosclerotic plaques, and their role in disease diagnosis, platelet activation monitoring, and prognostic outcome prediction. This manuscript will highlight the recent updates regarding the involvement of miRs as biomarkers in AMI and emphasize their value in vulnerable atherosclerotic plaque prediction and monitoring of platelet activation.

[3] *Wang KY, Hsu KC, Liu WC et al.* **Relationship Between Xanthelasma Palpebrarum and Hyperlipidemia**. Annals of plastic surgery 2018; 80:S84-s86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29424765
ABSTRACT

BACKGROUND: Xanthelasma palpebrarum is a common periorbital lesion that occurs in middle-aged woman. Dyslipidemia was strongly associated with the occurrence of xanthelasma. Different treatment methods for xanthelasma were applied with comparable results. MATERIALS AND METHODS: This was a retrospective chart review series performed at a single institute. The surgical pathology of 69 patients who received surgical excision from 1994 to 2012 was obtained. In addition, International Classification of Diseases, Ninth Revision, Clinical Modification code of xanthelasma (374.51) of 44 patients who underwent nonsurgical treatment at an outpatient department was acquired from 2006 to 2012. The serum lipid levels, comorbidities, recurrence, and treatment methods were obtained and analyzed with Statistical Analysis System (SAS) 9.4. RESULTS: Of a total of 113 identified patients, 50 had lipid profile data. Of these 50 patients, 25 (50%) had dyslipidemia, which is higher than general population in Taiwan. The recurrence rate was 17.5%, and there was no statistical difference in the recurrence rate between the different treatment methods. CONCLUSIONS: Xanthelasma was found to be associated with dyslipidemia. Thus, we recommend patients with xanthelasma to check their lipid profile and receive diet control and lipid-lowering medications for lipid abnormalities.

[4] *Ajufo E, Rader DJ*. **New Therapeutic Approaches for Familial Hypercholesterolemia**. Annual review of medicine 2018; 69:113-131.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29414257
ABSTRACT
Familial hypercholesterolemia (FH) is a common genetic condition characterized by elevated plasma levels of low-density lipoprotein cholesterol (LDL-C), premature atherosclerotic cardiovascular disease, and considerable unmet medical need with conventional LDL-C-lowering therapies. Between 2012 and 2015, the US Food and Drug Administration approved four novel LDL-C-lowering agents for use in patients with FH based on the pronounced LDL-C-lowering efficacy of these medicines. We review the four novel approved agents, as well as promising LDL-C-lowering agents in clinical development, with a focus on their mechanism of action, efficacy in FH cohorts, and safety.

[5] *Gragnano F, Calabro P*. **Role of dual lipid-lowering therapy in coronary atherosclerosis regression: Evidence from recent studies**. Atherosclerosis 2018; 269:219-228.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29407597
ABSTRACT
Despite recent therapeutic advances, there is an unmet need in cardiovascular disease prevention. Clinical trials and meta-analyses have established that LDL-C lowering, particularly by statin therapy, reduces the progression of coronary atherosclerosis and the risk of coronary events. Insufficient LDL-C reduction and high residual risk in a significant proportion of statin-treated patients signify that additional therapies are required to deliver more effective coronary care. Pharmacological inhibition of cholesterol absorption (with ezetimibe) and PCSK9 activity (with evolocumab or alirocumab) provides potentially useful approaches for the therapeutic modulation of LDL-C metabolism in statin-treated patients. In recent trials, combination strategies involving a statin and non-statin agent (ezetimibe or evolocumab) have been shown to promote coronary atherosclerosis regression and improve cardiovascular

outcomes in patients with moderate-to-high cardiovascular risk. This review summarizes recent evidence on the effects of dual lipid-lowering therapy on coronary atherosclerosis.

[6] *Yamamoto H, Yoshida N, Shinke T et al.* **Impact of CD14(++)CD16(+) monocytes on coronary plaque vulnerability assessed by optical coherence tomography in coronary artery disease patients**. Atherosclerosis 2018; 269:245-251.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29407600
ABSTRACT
BACKGROUND AND AIMS: This study examined the impact of CD14(++)CD16(+) monocytes on coronary plaque vulnerability, as assessed by optical coherence tomography (OCT), and investigated their association with daily glucose fluctuation. Although increased CD14(++)CD16(+) monocyte levels have been reported to increase cardiovascular events, their impact on coronary plaque vulnerability in coronary artery disease (CAD) patients with or without diabetes mellitus (DM) remains unclear. METHODS: This prospective observational study included 50 consecutive patients with CAD, receiving lipid-lowering therapy and undergoing coronary angiography and OCT. Patients were divided into 3 tertiles according to the CD14(++)CD16(+) monocyte percentages assessed by flow cytometry. Standard OCT parameters were assessed for 97 angiographically intermediate lesions (diameter stenosis: 30-70%). Daily glucose fluctuation was analyzed by measuring the mean amplitude of glycemic excursion (MAGE). RESULTS: CD14(++)CD16(+) monocytes negatively correlated with fibrous cap thickness (r=-0.508, p<0.01). The presence of thin-cap fibroatheroma (TCFA) was increased stepwise according to the tertile of CD14(++)CD16(+) monocytes (0 [tertile 1] vs. 5 [tertile 2] vs. 10 [tertile 3], p<0.01). CD14(++)CD16(+) monocytes were a significant determinant of TCFA (OR 1.279, p=0.001). In non-DM patients, a significant relationship was found between CD14(++)CD16(+) monocytes and MAGE (r=0.477, p=0.018). CONCLUSIONS: CD14(++)CD16(+) monocytes were associated with coronary plaque vulnerability in CAD patients with well-regulated lipid levels both in DM and non-DM patients. Cross-talk between glucose fluctuation and CD14(++)CD16(+) monocytes may enhance plaque vulnerability, particularly in non-DM patients. CD14(++)CD16(+) monocytes could be a possible therapeutic target for coronary plaque stabilization.

[7] *Yao L, Folsom AR, Alonso A et al.* **Association of carotid atherosclerosis and stiffness with abdominal aortic aneurysm: The atherosclerosis risk in communities (ARIC) study**. Atherosclerosis 2018; 270:110-116.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29407878
ABSTRACT
BACKGROUND AND AIMS: Individuals with atherosclerosis and stiffness often have increased abdominal aortic diameters, but prospective evidence linking them to the risk of abdominal aortic aneurysm (AAA) is limited. METHODS: We prospectively examined the relationship of carotid atherosclerosis and stiffness with future risk of AAA in ARIC. At Visits 1 (1987-89) or 2 (1990-1992), we assessed carotid atherosclerosis (represented by greater carotid intima-media thickness [cIMT] or presence of atherosclerotic plaque) and lower carotid distensibility (reflected by a higher carotid Beta Index). We identified incident, clinical AAAs during follow-up through 2011 using hospital discharge codes, Medicare outpatient diagnoses, or death

certificates. RESULTS: Participants' mean age at baseline was 54.2 years (SD 5.8), 45% were male and 73% white. During a median of 22.5 years of follow-up, 542 clinical AAAs were ascertained. After multivariable adjustment, the presence of carotid atherosclerotic plaque at baseline was associated with 1.31 (95% CI: 1.10-1.57; p=0.003) times higher risk of clinical AAA. Greater cIMT and Beta Index were also associated with clinical AAA with a dose-response across quartiles (p trend for both: 0.006; hazard ratios [95% CI] for the highest vs. lowest quartiles: 1.55 [1.13-2.11] and 1.68 [1.16-2.43], respectively). The associations of cIMT and Beta Index with AAA were independent of each other. CONCLUSIONS: This prospective population-based study found that indices of greater carotid atherosclerosis and lower carotid distensibility are markers of increased AAA risk.

[8] *Suciu CF, Prete M, Ruscitti P et al.* **Oxidized low density lipoproteins: The bridge between atherosclerosis and autoimmunity. Possible implications in accelerated atherosclerosis and for immune intervention in autoimmune rheumatic disorders**. Autoimmunity reviews 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29425936
ABSTRACT
Atherosclerotic vasculopathy is a multifactorial process causing vessels damage and cardiovascular diseases, the leading causes of death worldwide. Atherosclerotic plaque is the asymptomatic primary, elementary, lesion of atherosclerotic vasculopathy. Accumulation of the oxidized low-density lipoprotein (oxLDL) at sub endothelial sites is now recognized as one of the major trigger events in plaque formation. The concomitant presence at the plaque site of cells belonging to either natural or adaptive immunity, the detection of autoantibodies to oxLDL, the cross-reactivity of oxLDL with anti-phospholipid antibodies, in addition to the clinical evidence of increased rates of cardiovascular events in several rheumatic diseases, has stimulated intensive research to define interconnections between the immune system and traditional risk factors at the molecular levels in order to explain accelerated atherosclerosis. Here, we critically review the results of previous and recent studies, which have disclosed molecules of both innate or adaptive immunity involved in atherosclerosis, focusing primarily on B cells and autoantibodies, where data are more consolidated. Particular attention has also been paid to molecules that may be predictive markers of atherosclerosis progression and can be potential targets for immune intervention to delay the atherosclerotic process. The latter include CD20 antigen, molecules involved in the BAFF-BAFF receptor axis, inflammatory molecules and modified LDL. The successful results of a recent randomized controlled clinical trial targeting inflammasome with anti-IL1beta monoclonal antibody in non-autoimmune conditions, prove that specific immunotherapy can be a promising and effective strategy to control atherosclerosis in rheumatic diseases as well.

[9] *Li Z, Liu Q*. **Hepatitis C virus regulates proprotein convertase subtilisin/kexin type 9 promoter activity**. Biochem Biophys Res Commun 2018; 496:1229-1235.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29397939
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory serine protease mainly expressed in liver. Although PCSK9 has been shown to inhibit hepatitis C virus (HCV) entry and replication, whether HCV regulates PCSK9 transcription has not been well studied. PCSK9

promoter activity is modulated by numerous transcription factors including sterol-regulatory element binding protein (SREBP)-1a, -1c, -2, hepatocyte nuclear factor-1 (HNF-1), and forkhead box O3 (FoxO3). Since they are differently regulated by HCV, we studied the effects of these transcription factors on PCSK9 promoter activity in the context of HCV infection and replication. We demonstrated that PCSK9 promoter activity was up-regulated after HCV infection and in HCV genomic replicon cells. We also studied the effects of HCV proteins on the PCSK9 promoter activity. While HCV structural proteins core, E1, and E2 had no effect, NS2, NS3, NS3-4A, NS5A and NS5B enhanced, and p7 and NS4B decreased PCSK9 promoter activity. Furthermore, we showed that transcription factors SREBP-1c, HNF-1alpha and specificity protein 1 increased PCSK9 promoter activity in HCV replicon cells, whereas SREBP-1a, HNF-1beta and FoxO3 had an inhibitory effect. These results demonstrated the molecular mechanisms of how HCV modulates PCSK9 promoter activity and advanced our understanding on the mutual interactions between HCV and PCSK9.

[10] *Al-Saiedy M, Pratt R, Lai P et al.* **Dysfunction of pulmonary surfactant mediated by phospholipid oxidation is cholesterol-dependent**. Biochimica et biophysica acta 2018; 1862:1040-1049.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29413906
ABSTRACT
Pulmonary surfactant forms a cohesive film at the alveolar air-lung interface, lowering surface tension, and thus reducing the work of breathing and preventing atelectasis. Surfactant function becomes impaired during inflammation due to degradation of the surfactant lipids and proteins by free radicals. In this study, we examine the role of reactive nitrogen (RNS) and oxygen (ROS) species on surfactant function with and without physiological cholesterol levels (5-10%). Surface activity was assessed in vitro in a captive bubble surfactometer (CBS). Surfactant chemistry, monolayer fluidity and thermodynamic behavior were also recorded before and after oxidation. We report that physiologic amounts of cholesterol combined with oxidation results in severe impairment of surfactant function. We also show that surfactant polyunsaturated phospholipids are the most susceptible to oxidative alteration. Membrane thermodynamic experiments showed significant surfactant film stiffening after free radical exposure in the presence of cholesterol. These results point to a previously unappreciated role for cholesterol in amplifying defects in surface activity caused by oxidation of pulmonary surfactant, a finding that may have implications for treating several lung diseases.

[11] *Liang H, Feng Y, Cui R et al.* **Simvastatin protects against acetaminophen-induced liver injury in mice**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 98:916-924.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29421861
ABSTRACT
The present study aimed to investigate the effect of simvastatin on acetaminophen (APAP) hepatotoxicity in a mouse model. Male C57BL/6 mice were allocated into the following groups: control, APAP, APAP+SIM10, APAP+SIM20, APAP+SIM100 and APAP+SIM200 groups. The mice in the APAP group were treated with saline intraperitoneally (i.p.) 72h before and 24h or 72h after APAP challenge (i.p., 400mg/kg of APAP). The simvastatin-treated groups were treated

with different doses of simvastatin i.p. (10, 20, 100 and 200mg/kg/day) as in the APAP group. After 24h or 72h of APAP challenge, blood and liver samples were collected to detect hepatic injury and liver regeneration. The results showed that low doses of simvastatin (10 and 20mg/kg) could significantly reverse the histological change and decrease hepatic injury. Simvastatin also reduced the serum cytokine levels and transcriptional levels of tumor necrosis factor-alpha and interleukin-6 in the liver. The malonyldialdehyde and myeloperoxidase levels significantly decreased in the simvastatin treatment groups compared with the APAP group. Simvastatin restored the decrease in superoxide dismutase, catalase, glutathione and glutathione peroxidase activities induced by APAP hepatotoxicity. In addition, simvastatin inhibited hepatic C/EBP-homologous protein expression and hepatocyte apoptosis. However, simvastatin had no effect on liver regeneration after APAP hepatotoxicity. Moreover, high doses could aggravate APAP-induced liver injury. In conclusion, low doses of simvastatin had a significant therapeutic effect in APAP-induced liver injury by inhibiting oxidative stress, inflammation and apoptosis. However, high doses of simvastatin had adverse hepatotoxicity.

[12] *Dahl M, Frost L, Sogaard R et al.* **A population-based screening study for cardiovascular diseases and diabetes in Danish postmenopausal women: acceptability and prevalence**. BMC cardiovascular disorders 2018; 18:20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29402233
ABSTRACT
BACKGROUND: Reducing women's cardiovascular risk and the economic costs associated with cardiovascular diseases (CVD) and diabetes (DM) continues to be a challenge. Whether a multifaceted CVD screening programme is beneficial as a preventive strategy in women remains uncertain. The aim of this study was to investigate the prevalence of CVD and DM as well as the acceptability toward screening and preventive actions. METHODS: An observational study was performed among all women born in 1936, 1941, 1946 and 1951 living in Viborg Municipality, Denmark, from October 2011. In total, 1984 were invited to screening for abdominal aortic aneurysm (AAA), peripheral arterial disease (PAD), carotid plaque (CP), hypertension (HT), atrial fibrillation (AF), DM and dyslipidaemia. Participants with positive tests were offered prophylactic intervention including follow-up consultations in case of AAA, PAD and/or CP. Participants with AAA >/= 50 mm were referred to specialists in vascular surgery. Women with AF or potential familial hypercholesterolaemia (FH) were referred to cardiology work-up. RESULTS: Among those invited, 1474 (74.3%) attended screening, but the attendees' share decreased with increasing age groups ($p < 0.001$). AAA was diagnosed in 10 (0.7%) women, PAD in 101 (6.9%) and CP in 602 (40.8%). The percentage of women with these conditions rose with increasing age group ($p < 0.05$). Unconfirmed potential HT was observed in 94 (6.4%), unknown AF in 6 (0.4%), DM in 14 (1%) and potential FH in 35 (2.4%). None of these findings differed across age groups. Among the 631 women diagnosed with AAA, PAD and/or CP, 182 (28.8%) were already in antiplatelet and 223 (35.3%) in lipid-lowering therapy prior to screening. Antiplatelet therapy was initiated in 215 (34.1%) and lipid-lowering therapy in 191 (30.3%) women. Initiation of antiplatelet and lipid-lowering therapy was further recommended to 134 (21.2%) and 141 (22.4%) women, respectively, who hesitated to follow the recommendation. CONCLUSIONS: The study recorded an acceptable total attendance rate, even though a significantly lower attendance rate was observed in the eldest women. The identified hesitation

towards prophylactic therapy may affect the rationale and effectiveness of CVD screening, and hesitation seems a critical issue that should be addressed in the design of future screening programmes.

[13] *Wallace A, Albadawi H, Hoang P et al.* **Statins as a preventative therapy for venous thromboembolism**. Cardiovascular diagnosis and therapy 2017; 7:S207-s218.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29399524
ABSTRACT
The anti-inflammatory effects of statins have likely not been used to their fullest extent, particularly in reducing venous thromboembolic events. Current therapy for thrombotic events hinges on anticoagulation via heparin, warfarin or new oral anticoagulants. Interventional procedures with thrombectomy may also play a critical role. Unfortunately, thrombotic events can occur and recur despite meticulous anticoagulation therapy. Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), two complicated and prevalent diseases that can cause chronic disease states such as post-thrombotic syndrome (PTS). In 2009 the JUPITER trial demonstrated that rosuvastatin may be effective when dealing with vascular inflammation by providing an anti-inflammatory effect. Multiple subsequent studies have looked at this association with some promising findings. The mechanism of action for statins is not entirely understood but there has been a variety of proposals and subsequent testing of inflammatory biomarkers. Additional prospective trials are needed to confirm the possible benefit of VTE reduction through an anti-inflammatory effect, but if this can be shown then statins may become a safe adjunctive therapy for VTE prevention.

[14] *Ochin C, Garelnabi M*. **Berberine encapsulated PLGA-PEG nanoparticles modulates PCSK-9 in HepG2 cells**. Cardiovascular & hematological disorders drug targets 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29422010
ABSTRACT
BACKGROUND: The developments of new parenteral approaches to target PCSK-9 for the treatment LDL-Cholesterol has yielded impressive results; and have shown significant decreases in the risk of mortality associated with hypercholesterolemia. However improved and convenient alternate approaches that exploit the beneficial drug target properties of PCSK-9 also need to be explored and developed. One such approach is the oral administration of Berberine using nanotechnology. METHODS: Nanoprecipitation encapsulation and physiochemical characterization of Berberine Chloride in PLGA-PEG-PLGA block copolymer has been developed and characterized in Hep-G2 cells using Berberine Chloride encapsulated nanoparticle (BC-NP). Evaluation of PCSK-9, SREBP-1, LDL-r, HNF-1alpha mRNAs and PCSK-9 protein expression was performed using quantitative real-time PCR (qPCR) and median fluorescence intensity (MFI) of flow cytometric studies respectively. Pearson's correlation analysis of PCSK-9 mRNA and protein levels in Berberine chloride delivery was performed. RESULTS: The PCSK-9 mRNA gene expression shows a relationship to the release of Berberine from the encapsulating PLGA-PEG-PLGA polymer in a time dependent manner. SREBP-1a mRNA expression was significantly down regulated upon 48-hour treatment with BC-NP (150microM) and High FD (150microM) concentrations. LDL-receptor and HNF1alpha mRNA mRNA expression was significantly up regulated upon 48-hour treatment with BC-NP (150microM),

Low-FD (10microM) and High FD (150microM) concentrations. CONCLUSION: Nanotechnology drug delivery approach of Berberine modulates PCSK-9 in HepG2 cells, this approach may result in improving the drug pharmacokinetic performance and the intended target outcome. Further studies in animal models are needed to validate this result and explore the potential mechanistic components and function.

[15] *Pala R, Genc E, Tuzcu M et al.* **L-Carnitine supplementation increases expression of PPAR-gamma and glucose transporters in skeletal muscle of chronically and acutely exercised rats**. Cell Mol Biol (Noisy-le-grand) 2018; 64:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29412788
ABSTRACT
In this study, the effects of L-Carnitine supplementation on the lipid peroxidation and expression of PPAR-gamma and glucose transporters in the liver and muscles of chronically and acutely exercised rats were investigated. A total of 42 male Wistar Albino rats (8-week-old) were divided into six groups as follows: Control, L-Carnitine, Chronic Exercise (CE), Chronic Exercise + L-Carnitine, Acute Exercise (AE) and L-Carnitine + Acute Exercise. Chronic exercise consists of 30 m/min, 30 min/day, and 5 days/week for 6 weeks. Rats in the acute exercise groups were run on the treadmill at 30 m/min until exhaustion. L-Carnitine was given at the level of 300 mg per kilogram of diet for 6 weeks. There was no significant difference in the levels of serum ALT, AST, urea, creatinine and glucose levels between the exercise and L-Carnitine groups (P > 0.05). Cholesterol and triglyceride levels decreased by L- carnitine supplementation and chronic exercise in control groups but increased in the AE groups compared to the control group without reinforcement (P < 0.05). Serum, muscle, heart, and liver malondialdehyde (MDA) concentrations were lower in CE and higher in the AE groups (P < 0.001). However, L-Carnitine supplementation reduced MDA levels (P < 0.05). Liver and muscle PPAR-gamma, liver GLUT-2 and muscle GLUT-4 mRNA expressions were lower in AE group than in all other groups (P < 0.001). Both chronic exercise and supplemental L-Carnitine increased liver and muscle PPAR-gamma, GLUT-2 and GLUT-4 mRNA expression (P <0.05). As a result, although acute exercise increased oxidative stress, chronic exercise reduced oxidative stress by lowering lipid peroxidation level. L-Carnitine supplementation decreased oxidative stress and improved glucose and lipid metabolism by regulation of PPAR-gamma, GLUT-2 and GLUT-4 mRNA expression in rats.

[16] *Santos AL, Preta G*. **Lipids in the cell: organisation regulates function**. Cell Mol Life Sci 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29427074
ABSTRACT
Lipids are fundamental building blocks of all cells and play important roles in the pathogenesis of different diseases, including inflammation, autoimmune disease, cancer, and neurodegeneration. The lipid composition of different organelles can vary substantially from cell to cell, but increasing evidence demonstrates that lipids become organised specifically in each compartment, and this organisation is essential for regulating cell function. For example, lipid microdomains in the plasma membrane, known as lipid rafts, are platforms for concentrating protein receptors and can influence intra-cellular signalling. Lipid organisation is

tightly regulated and can be observed across different model organisms, including bacteria, yeast, Drosophila, and Caenorhabditis elegans, suggesting that lipid organisation is evolutionarily conserved. In this review, we summarise the importance and function of specific lipid domains in main cellular organelles and discuss recent advances that investigate how these specific and highly regulated structures contribute to diverse biological processes.

[17] *Halak S, Ostling G, Edsfeldt A et al.* **Spotty Carotid Plaques Are Associated with Inflammation and the Occurrence of Cerebrovascular Symptoms**. Cerebrovascular diseases extra 2018; 8:16-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29402768
ABSTRACT
BACKGROUND: Echolucent carotid plaques have been related to an increased risk of ischemic cerebrovascular events. The aim of the present study was to evaluate whether a new objective ultrasonographic parameter, the statistical geometric feature (SGF), reflecting spottiness of carotid plaques, can be associated with cerebrovascular symptoms and with a rupture-prone plaque phenotype. METHODS: The plaques of 144 patients who underwent carotid endarterectomy were included in this study. SGF and plaque area were estimated by outlining the plaque on ultrasound (US) images. The correlation coefficient for inter- and intraobserver variability was 0.69 and 0.93, respectively. The SGF values were normalized to the degree of stenosis (SGF/DS). The plaques collected at surgery 1 day after the US were analyzed histologically, and inflammatory markers and matrix metalloproteinases (MMPs) were measured. RESULTS: Patients with ipsilateral hemispheric symptoms had higher SGF/DS compared to patients without symptoms (0.82 [0.59-1.16] vs. 0.70 [0.56-0.89], p = 0.01). Analysis of plaque components revealed a positive correlation between SGF/DS and the percentage of the plaque area stained for lipids, macrophages, and hemorrhage. A correlation was also found between SGF/DS and plaque expression of interleukin-6, monocyte chemoattractant protein-1, macrophage inflammatory protein-1beta, vascular endothelial growth factor A, C-C motif chemokine 3 and 20, and MMP-9. An inverse correlation was found with plaque levels of osteoprotegerin. CONCLUSIONS: The present study supports the concept that spottiness is a feature of the carotid plaques rich in inflammation and can be associated with the typical phenotype of high-risk plaques.

[18] *Kim HN, Kweon SS, Shin MH*. **Detection of Familial Hypercholesterolemia Using Next Generation Sequencing in Two Population-Based Cohorts**. Chonnam medical journal 2018; 54:31-35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29399563
ABSTRACT
We aimed to evaluate the prevalence of familial hypercholesterolaemia (FH) in a subject with hypercholesterolaemia from two population-based cohorts in South Korea. A total of 283 subjects with total cholesterol levels of 290 mg/dL (7.5 mmol/L) or higher were selected from the Namwon and Dong-gu Studies. We used next generation sequencing (NGS) to detect mutations in low-density lipoprotein receptors (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes. We have confirmed 17 different mutations of the LDLR, APOB and PCSK9 in 23 subjects (8.1%). Eleven LDLR variants and one APOB variant

have been previously reported. One LDLR and two PCSK9 rare variants were identified in the variants database, but not in the FH mutation database. Two novel LDLR variants were found, p.Leu680Val, and p.Thr734Phe. No LDLR, APOB or PCSK9 deletions nor insertions were found. When the subjects were restricted to 110 subjects with a total cholesterol >/=310 mg/dL, only 10 variants were found in the 10 subjects (9.1%). These results suggest that given the low prevalence of FH mutations in subjects with high total cholesterol levels, NGS-based testing for a population-based approach to FH detection may not be cost-effective.

[19] *Anzai T*. **Inflammatory Mechanisms of Cardiovascular Remodeling**. Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29415911
ABSTRACT
Inflammation and fibrosis play an important role in the development and progression of cardiovascular diseases. Acute coronary syndrome (ACS) is caused by rupture of inflamed atherosclerotic plaque and subsequent atherothrombosis. Recent studies have shown that inflammatory markers such as C-reactive protein (CRP) can predict ACS development and have demonstrated the effectiveness of new therapeutic approaches targeting inflammation. Studies have also shown that an enhanced inflammatory response after myocardial infarction (MI) is associated with cardiac rupture, ventricular aneurysm formation, and exacerbation of left ventricular (LV) remodeling. Inflammation is a physiological reaction in which fibrosis is induced to facilitate the healing of tissue damage. However, when an excessive inflammatory response consisting mainly of monocytes/macrophages is induced by various factors, impaired reparative fibrosis and resulting pathological remodeling processes may occur. A similar phenomenon is observed in abdominal aortic aneurysm (AAA) expansion. In contrast, myocardial diseases such as inflammatory dilated cardiomyopathy (DCMI) and valvular diseases such as aortic valve stenosis (AS) are characterized by chronic inflammation mediated mainly by T lymphocytes and the associated enhancement of reactive fibrosis. Thus, inflammation can take 2 paths (the inhibition or promotion of fibrosis), depending on the phase of inflammation, inducing pathological cardiovascular remodeling. Elucidation of the regulatory mechanisms of inflammation and fibrosis will contribute to the development of new therapeutic approaches for cardiovascular diseases.

[20] *Lin TK, Liou YS, Lin CH et al.* **High-potency statins but not all statins decrease the risk of new-onset osteoporotic fractures: a nationwide population-based longitudinal cohort study**. Clinical epidemiology 2018; 10:159-165.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29403315
ABSTRACT
Background: Statins have been linked to new-onset osteoporotic fractures (NOFs), and different statins may alter the risk for the development of NOFs. Aim: In this study, we investigated the association between different statins and the development of NOFs. Patients and methods: This was a longitudinal cohort study performed using data from claim forms submitted to the Taiwan Bureau of National Health Insurance, including case patients with NOFs from January 2004 to December 2013 and non-NOF subjects. We estimated the hazard ratios (HRs) of NOFs associated with statin use. Nonuser subjects served as the reference group. Results: A total of

44,405 patients with NOFs were identified from among 170,533 patients with hyperlipidemia during the study period. The risk of developing NOFs after adjusting for age, sex, comorbidities, and concurrent medication use was lower among users of atorvastatin (HR, 0.77; 95% CI, 0.71-0.84) and rosuvastatin (HR, 0.72; 95% CI, 0.64-0.81) than among simvastatin users. Lovastatin, pravastatin, fluvastatin, and pitavastatin were not associated with the risk of developing NOFs compared with simvastatin users. Conclusion: This study supports previous reports regarding a beneficial effect of statin use and NOF risk, but not all statins. Patients taking atorvastatin or rosuvastatin were at lower risk of developing NOFs compared with simvastatin users during the 10-year follow-up. Other statins such as pravastatin, fluvastatin, lovastatin, and pitavastatin were not associated with NOFs. This study also highlighted that high-potency statin has a dose-response effect on lower NOF risk.

[21] *Alves Ferreira M, Oliveira Gomes AP, Guimaraes de Moraes AP et al.* **Green tea extract outperforms metformin in lipid profile and glycaemic control in overweight women: A double-blind, placebo-controlled, randomized trial**. Clinical nutrition ESPEN 2017; 22:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29415825
ABSTRACT
BACKGROUND & AIMS: Both green tea and metformin are used as adjuvants to treat and prevent complications associated with obesity; however, studies comparing their action and interaction in non-diabetic overweight women have not been reported. Thus, the current study evaluated the effects of green tea extract and metformin, both individually and in combination, on type 2 diabetes risk factors in non-diabetic overweight women. METHODS: A total of 120 overweight women were randomly assigned in a double-blind manner to 1 of 4 groups, as follows: control (n = 29; 1 g of cellulose), green tea (n = 32; 1 g of dry green tea extract), metformin (n = 28; 1 g of metformin), and green tea + metformin (n = 31; 1 g of dry green tea extract + 1 g of metformin). Each group took the indicated capsules daily for 12 weeks. Anthropometric measurements, body composition, and fasting blood samples were evaluated. RESULTS: Although no significant interactions were observed in glycaemic control (p = 0.07), green tea in the absence of metformin reduced fasting glucose (-4.428 +/- 2.00; p = 0.031), but when combined the lowering effect was nullified. In contrast, metformin increased HbA1c concentration (0.048 +/- 0.189%; p = 0.017) and also reduced body weight (-1.318 +/- 0.366 kg; p = 0.034) and LM (lean mass) (-1.249 +/- 0.310; p = 0.009). Regarding lipid parameters, green tea significantly reduced total cholesterol and LDL-c. CONCLUSIONS: Green tea was superior to metformin in improving glycaemic control and lipid profile in non-diabetic overweight women and, therefore, green tea extract is a promising alternative for reducing type 2 diabetes risk in overweight women.

[22] *Hong SJ, Jeong HS, Ahn JC et al.* **A Phase III, Multicenter, Randomized, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial**. Clinical therapeutics 2018; 40:226-241.e224.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29402522

ABSTRACT
PURPOSE: Combination therapy with ezetimibe and statins is recommended in cases of statin intolerance or insufficiency. The objective of this study was to compare the efficacy and safety of combination therapy with ezetimibe and rosuvastatin versus those of rosuvastatin monotherapy in patients with hypercholesterolemia. METHODS: I-ROSETTE (Ildong ROSuvastatin & ezETimibe for hypercholesTElolemia) was an 8-week, double-blind, multicenter, Phase III randomized controlled trial conducted at 20 hospitals in the Republic of Korea. Patients with hypercholesterolemia who required medical treatment according to National Cholesterol Education Program Adult Treatment Panel III guidelines were eligible for participation in the study. Patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio. The primary end point was the difference in the mean percent change from baseline in LDL-C level after 8 weeks of treatment between the ezetimibe/rosuvastatin and rosuvastatin treatment groups. All patients were assessed for adverse events (AEs), clinical laboratory data, and vital signs. FINDINGS: Of 396 patients, 389 with efficacy data were analyzed. Baseline characteristics among 6 groups were similar. After 8 weeks of double-blind treatment, the percent changes in adjusted mean LDL-C levels at week 8 compared with baseline values were -57.0% (2.1%) and -44.4% (2.1%) in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively ($P < 0.001$). The LDL-C-lowering efficacy of each of the ezetimibe/rosuvastatin combinations was superior to that of each of the respective doses of rosuvastatin. The mean percent change in LDL-C level in all ezetimibe/rosuvastatin combination groups was >50%. The number of patients who achieved target LDL-C levels at week 8 was significantly greater in the ezetimibe/rosuvastatin group (180 [92.3%] of 195 patients) than in the rosuvastatin monotherapy group (155 [79.9%] of 194 patients) ($P < 0.001$). There were no significant differences in the incidence of overall AEs, adverse drug reactions, and serious AEs; laboratory findings, including liver function test results and creatinine kinase levels, were comparable between groups. IMPLICATIONS: Fixed-dose combinations of ezetimibe/rosuvastatin significantly improved lipid profiles in patients with hypercholesterolemia compared with rosuvastatin monotherapy. All groups treated with rosuvastatin and ezetimibe reported a decrease in mean LDL-C level >50%. The safety and tolerability of ezetimibe/rosuvastatin therapy were comparable with those of rosuvastatin monotherapy. ClinicalTrials.gov identifier: NCT02749994.

[23] *Ghobadi S, Hassanzadeh-Rostami Z, Mohammadian F et al.* **Comparison of blood lipid-lowering effects of olive oil and other plant oils: a systematic review and meta-analysis of 27 randomized placebo-controlled clinical trials**. Critical reviews in food science and nutrition 2018:0.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29420053

ABSTRACT
OBJECTIVE: We aim to report a systematic review and meta-analysis of randomized controlled trials (RCTs) on effects of olive oil consumption compared with other plant oils on blood lipids. METHODS: PubMed, web of science, Scopus, ProQuest, and Embase were systematically searched until September 2017, with no age, language and design restrictions. Weighed mean

difference (WMD) and 95% confidence interval (CI) were expressed as effect size. Sensitivity analyses and pre specified subgroup was conducted to evaluate potential heterogeneity. Meta-regression analyses were performed to investigate association between blood lipid-lowering effects of olive oil and duration of treatment. RESULTS: Twenty-seven trials, comprising 1089 participants met the eligibility criteria. Results of this study showed that compared to other plant oils, high-density lipoprotein level increased significantly more for OO (1.37 mg/dl: 95% CI: 0.4, 2.36). Also OO consumption reduced total cholesterol (TC) (6.27 mg/dl, 95% CI: 2.8, 10.6), Low-density lipoprotein (LDL-c) (4.2 mg/dl, 95% CI: 1.4, 7.01), and triglyceride (TG) (4.31 mg/dl, 95% CI: 0.5, 8.12) significantly less than other plant oils. There were no significant effects on Apo lipoprotein A1 and Apo lipoprotein B. CONCLUSION: This meta-analysis suggested that OO consumption decreased serum TC, LDL-c, and TG less but increased HDL-c more than other plant oils.

[24] *Zanetti HR, Roever L, Goncalves A, Resende ES*. **Human Immunodeficiency Virus Infection, Antiretroviral Therapy, and Statin: a Clinical Update**. Current atherosclerosis reports 2018; 20:9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29423787
ABSTRACT
PURPOSE OF REVIEW: This clinical update is intended to focus in relationship between HIV infection and use of antiretroviral therapy (ART) and statin. RECENT FINDINGS: Though ART significantly changed the course of HIV infection, it is related to numerous side effects principally to the lipid profile. In this way, statins became one of the most used lipid-lowering therapies in this population. In our clinical update, we evaluated studies that demonstrate the relationship and molecular mechanisms that HIV infection and ART use trigger dyslipidemia and also the use of statin to reduce this condition. We have demonstrated that use of statin can be used in dyslipidemic HIV-infected people as long as there is no drug interaction with ART. Recently, studies using rosuvastatin have shown greater effects when compared to the other statins.

[25] *Katsiki N, Giannoukas AD, Athyros VG, Mikhailidis DP*. **Lipid-lowering treatment in peripheral artery disease**. Current opinion in pharmacology 2018; 39:19-26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29413998
ABSTRACT
Peripheral artery disease (PAD) is characterized by increased cardiovascular (CV) risk, limb morbidity and all-cause mortality. According to the current guidelines (2016) of the American Heart Association/American College of Cardiology on the management of PAD patients, statin therapy is recommended for PAD patients in order to treat dyslipidemia and reduce CV risk. The present narrative review discusses the use of statins and other lipid-lowering drugs such as ezetimibe, fibrates, niacin, anacetrapib and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in PAD patients in terms of both CV and limb outcomes. The clinical implications of hypolipidemic drug therapy in special patient populations including those with metabolic syndrome, non-alcoholic fatty liver disease, chronic kidney disease and type 2 diabetes mellitus, which may frequently co-exist with PAD, are also considered.

[26] *Filippatos TD, Liontos A, Christopoulou EC, Elisaf MS*. **Novel Hypolipidaemic Drugs: Mechanisms Of Action And Main Metabolic Effects**. Current vascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29424317

ABSTRACT
Over the last 3 decades, hypolipidaemic treatment has significantly reduced both cardiovascular (CV) risk and events, with statins being the cornerstone of this achievement. Nevertheless, residual CV risk and unmet goals in hypolipidaemic treatment make novel options necessary. Recently marketed monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) have shown the way towards innovation, while other ways of PCSK9 inhibition like small interfering RNA (Inclisiran) are already being tested. Other effective and well tolerated drugs affect known paths of lipid synthesis and metabolism, such as bempedoic acid blocking acetyl-coenzyme A synthesis at a different level than statins, pemafibrate selectively acting on peroxisome proliferator-activated receptor (PPAR)-alpha receptors and oligonucleotides against apolipoprotein (a). Additionally, other novel hypolipidaemic drugs are in early phase clinical trials, such as the inhibitors of apolipoprotein C-III, which is located on triglyceride (TG)-rich lipoproteins, or the inhibitors of angiopoietin-like 3 (ANGPTL3), that play a key role in lipid metabolism, aiming to beneficial effects on TG levels and glucose metabolism. Among others, gene therapy substituting the loss of essential enzymes is already used for lipoprotein lipase (LPL) deficiency in autosomal chylomicronaemia and is expected to eliminate the lack of low-density lipoprotein (LDL) receptors in patients with homozygous familial hypercholesterolaemia. Experimental data of high-density lipoprotein (HDL) mimetics infusion therapy have shown a beneficial effect on atherosclerotic plaques. Thus, many novel hypolipidaemic drugs targeting different aspects of lipid metabolism are being investigated, although they need to be assessed in large trials to prove their CV benefit and safety.

[27] *Gormsen LC, Sondergaard E, Christensen NL et al.* **Metformin does not Affect Postabsorptive Hepatic Free Fatty Acid Uptake, Oxidation or Resecretion in Humans: A 3-months Placebo Controlled Clinical Trial in Patients with Type 2 Diabetes and Healthy Controls**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29405635

ABSTRACT
AIMS: Metformin is due to its well-documented glucose lowering effect the most commonly used drug in patients with T2D. However, metformin have also in pre-clinical studies been shown to improve lipid metabolism, possibly through modulation of intrahepatic partitioning of fatty acids towards oxidation and away from reesterification and resecretion as triglycerides. MATERIALS AND METHODS: To explore whether these pre-clinical findings can be translated to a human setting, we performed a 3-month randomized, placebo controlled, parallel-group clinical trial in patients with T2D (24 patients) and healthy controls (12 subjects). T2D subjects received either placebo (PLA) or 1000 mg metformin bid. (MET) whereas healthy subjects were all treated with metformin (CONT). Hepatic fatty acid metabolism was measured by [(11) C]palmitate PET, hepatic triglyceride secretion and peripheral oxidation by ex-vivo labelled [1-(14) C]VLDL-TG and VLDL-particle size by TG/ApoB ratio. Body composition was assessed by DXA and whole body lipid oxidation by indirect calorimetry. RESULTS: Metformin treatment for

three months produced the anticipated decrease in FPG in the MET group [FPG (mM): 7.9+/-1.8 (study day 1) vs. 6.4+/-1.1 (study day 2)] whereas patients in the PLA group and healthy controls had similar FPG levels before and after the trial (mixed model group vs. time interaction, p=0.003). However, contrary to our hypothesis, metformin treatment did not affect hepatic lipid metabolism or peripheral oxidation. CONCLUSION: The observed beneficial effects on lipid metabolism during metformin treatment in humans appear to be secondary to long-term alterations in body composition or glucose homeostasis.

[28] *Jackisch L, Kumsaiyai W, Moore JD et al.* **Differential expression of Lp-PLA2 in obesity and type 2 diabetes and the influence of lipids**. Diabetologia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29427237
ABSTRACT
AIMS/HYPOTHESIS: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a circulatory macrophage-derived factor that increases with obesity and leads to a higher risk of cardiovascular disease (CVD). Despite this, its role in adipose tissue and the adipocyte is unknown. Therefore, the aims of this study were to clarify the expression of Lp-PLA2 in relation to different adipose tissue depots and type 2 diabetes, and ascertain whether markers of obesity and type 2 diabetes correlate with circulating Lp-PLA2. A final aim was to evaluate the effect of cholesterol on cellular Lp-PLA2 in an in vitro adipocyte model. METHODS: Analysis of anthropometric and biochemical variables from a cohort of lean (age 44.4 +/- 6.2 years; BMI 22.15 +/- 1.8 kg/m(2), n = 23), overweight (age 45.4 +/- 12.3 years; BMI 26.99 +/- 1.5 kg/m(2), n = 24), obese (age 49.0 +/- 9.1 years; BMI 33.74 +/- 3.3 kg/m(2), n = 32) and type 2 diabetic women (age 53.0 +/- 6.13 years; BMI 35.08 +/- 8.6 kg/m(2), n = 35), as part of an ethically approved study. Gene and protein expression of PLA2 and its isoforms were assessed in adipose tissue samples, with serum analysis undertaken to assess circulating Lp-PLA2 and its association with cardiometabolic risk markers. A human adipocyte cell model, Chub-S7, was used to address the intracellular change in Lp-PLA2 in adipocytes. RESULTS: Lp-PLA2 and calcium-independent PLA2 (iPLA2) isoforms were altered by adiposity, as shown by microarray analysis ($p < 0.05$). Type 2 diabetes status was also observed to significantly alter gene and protein levels of Lp-PLA2 in abdominal subcutaneous (AbdSc) ($p < 0.01$), but not omental, adipose tissue. Furthermore, multivariate stepwise regression analysis of circulating Lp-PLA2 and metabolic markers revealed that the greatest predictor of Lp-PLA2 in non-diabetic individuals was LDL-cholesterol ($p = 0.004$). Additionally, in people with type 2 diabetes, oxidised LDL (oxLDL), triacylglycerols and HDL-cholesterol appeared important predictors, accounting for 59.7% of the variance ($p < 0.001$). Subsequent in vitro studies determined human adipocytes to be a source of Lp-PLA2, as confirmed by mRNA expression, protein levels and immunochemistry. Further in vitro experiments revealed that treatment with LDL-cholesterol or oxLDL resulted in significant upregulation of Lp-PLA2, while inhibition of Lp-PLA2 reduced oxLDL production by 19.8% ($p < 0.05$). CONCLUSIONS/INTERPRETATION: Our study suggests adipose tissue and adipocytes are active sources of Lp-PLA2, with differential regulation by fat depot and metabolic state. Moreover, levels of circulating Lp-PLA2 appear to be influenced by unfavourable lipid profiles in type 2 diabetes, which may occur in part through regulation of LDL-cholesterol and oxLDL metabolism in adipocytes.

[29] *Golomb BA, Verden A, Messner AK et al.* **Amyotrophic Lateral Sclerosis Associated with Statin Use: A Disproportionality Analysis of the FDA's Adverse Event Reporting System**. Drug Saf 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29427042
ABSTRACT
INTRODUCTION: Apparent elevations in reporting of amyotrophic lateral sclerosis (ALS)-like conditions associated with statin use have been previously described from data obtained via US and European databases. OBJECTIVE: The aim of this study was to examine US FDA Adverse Event Reporting System (FAERS) data to compare reporting odds ratios (RORs) of ALS and ALS-like conditions between statins and other drugs, for each statin agent. METHODS: We assessed for disproportional rates of reported ALS and ALS-related conditions for each statin agent separately by using the ROR formula. FAERS data were analyzed through September 2015. RESULTS: RORs for ALS were elevated for all statins, with elevations possibly stronger for lipophilic statins. RORs ranged from 9.09 (6.57-12.6) and 16.2 (9.56-27.5) for rosuvastatin and pravastatin (hydrophilic) to 17.0 (14.1-20.4), 23.0 (18.3-29.1), and 107 (68.5-167) for atorvastatin, simvastatin, and lovastatin (lipophilic), respectively. For simvastatin, an ROR of 57.1 (39.5-82.7) was separately present for motor neuron disease. CONCLUSION: These findings extend previous evidence showing that significantly elevated ALS reporting extends to individual statin agents, and add to concerns about potential elevated occurrence of ALS-like conditions in association with statin usage.

[30] *Wu H, Shang H, Wu J*. **Effect of ezetimibe on glycemic control: a systematic review and meta-analysis of randomized controlled trials**. Endocrine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29397561
ABSTRACT
PURPOSE: Given the increased risk of incident diabetes and the side effects on glycemic control with statin treatment, statin and ezetimibe combination therapy has been widely used. However, whether the same concern exists in ezetimibe remains uncertain. This meta-analysis aimed to investigate the influence of ezetimibe treatment on glycemic control. METHODS: Articles were searched from PubMed, EMBASE, and Cochrane Library. Randomized controlled trials (RCTs) were included if they compared the effects of ezetimibe with placebo, ezetimibe plus statin with the same statin, or low-dose stain plus ezetimibe with high-dose statin on FBG and glycosylated hemoglobin A1c (HbA1c). RESULTS: Of the 2440 articles retrieved, 16 RCTs were included. Ezetimibe did not cause side effects on FBG (WMD -0.62, 95% CI: -3.13 to 1.90) and HbA1c (WMD 0.07, 95% CI: -0.07 to 0.20%). No significant changes in FBG (WMD -1.78, 95% CI: -6.33 to 2.77%) and HbA1c (WMD -0.05, 95% CI: -0.14 to 0.05%) were observed in ezetimibe plus low-dose statin treatment compared with high-dose statin. According to subgroup analysis, in comparison with high-dose statin, ezetimibe plus low-dose statin taken for more than 3 months showed a significant decrease in FBG (WMD -7.12, 95% CI: -13.86 to -0.38%) compared with that taken for less than 3 months (WMD 0.90, 95% CI: -2.91 to 4.71%). Nevertheless, this difference was invalid when the study conducted by Dagli et al. was removed. CONCLUSIONS: Compared with high-dose statin therapy, ezetimibe with low-dose statin for more than 3 months may have a beneficial tendency of effects on glycemic control.

[31] *Kirkman MS, Mahmud H, Korytkowski MT*. **Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes Mellitus**. Endocrinology and metabolism clinics of North America 2018; 47:81-96.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29407058
ABSTRACT
People with type 2 diabetes mellitus are at high risk of morbidity and mortality from cardiovascular disease (CVD). Based on observed relationships between hyperglycemia and CVD, several large clinical trials have investigated the ability of treatment strategies to achieve hemoglobin A1c less than 7% (53 mmol/mol) as a way of reducing this risk. These studies demonstrate that intensified glycemic therapy may reduce CVD risk in younger patients with recent-onset type 2 diabetes mellitus but not in high-risk older individuals with established disease. Attention to blood pressure and lipid-lowering therapies with modified glycemic goals for older high-risk individuals is recommended.

[32] *Ong TTX, Blanch EW, Jones OAH*. **Predicted environmental concentration and fate of the top 10 most dispensed Australian prescription pharmaceuticals**. Environmental science and pollution research international 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29399743
ABSTRACT
A basic environmental risk assessment was carried out for the top 10 dispensed pharmaceuticals in Melbourne, Australia, in contrast to the more commonly assessed measure of the most used drugs by physical mass. This allowed for the evaluation of compounds that had not previously been the subject of risk assessment. Estimations of the possible fate and behaviour of the target pharmaceuticals in sewage treatment plants were also made. The predicted removal rates of most drugs within standard sewage treatment were expected to be low, with the exception of the statins, which had high removal rates. Each pharmaceutical was predicted to be present in Melbourne wastewater at the nanogram per litre range or lower. All compounds were predicted to be of low toxicity risk, although it was not possible to model mixture effects. Atorvastatin and Irbesartan were also found to possess the potential to possibly bioaccumulate in the aquatic food chain but not to the extent that would require regulation or labelling.

[33] *Alhayali A, Selo MA, Ehrhardt C, Velaga S*. **Investigation of supersaturation and in vitro permeation of the poorly water soluble drug ezetimibe**. Eur J Pharm Sci 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29408604
ABSTRACT
The interplay between supersaturation, precipitation and permeation characteristics of the poorly water-soluble drug ezetimibe (EZ) was investigated. Supersaturation and precipitation characteristics of EZ in the presence of Caco-2 cells were compared to those in a cell-free environment. The effect of the water-soluble polymer polyvinyl pyrrolidone (PVP-K30) on the supersaturation, precipitation and transport of EZ was also investigated and the amount of drug taken up by Caco-2 cells was quantified. A one-compartment setup without Caco-2 cells (i.e. in the wells of cell-culture plates) was used to mimic a non-sink in vitro dissolution chamber. The two-compartment Caco-2 cell monolayer setup (with apical and basolateral compartments) was

used to investigate how the absorption of EZ affects supersaturation. EZ in varying degrees of supersaturation (DS; 10, 20, 30 and 40) was introduced into the one-compartment setup or the apical chamber of the two-compartment setup. Samples were collected at specific times to determine supersaturation, precipitation and permeation. At the end of the study, Caco-2 cells were lysed and the intracellular amount of EZ was quantified. In the one-compartment setup, a high DS was associated with rapid precipitation. Supersaturation was maintained for longer time periods and precipitation was lower in the presence of Caco-2 cells. There were no significant differences in the absorption rate of the drug, even at high concentrations on the apical side. Permeability coefficients for all supersaturated solutions (i.e. DS 10-40) were significantly ($p<0.05$) different from those when EZ was present in crystalline form. Both concentrations of PVP-K30 (i.e. 0.05% and 0.1% w/v) improved solubility and supersaturation of EZ when added to the apical side, however, the increase in absorption at the higher concentration was not proportional. The amount of intracellular EZ increased with increasing DS in the apical side, until the saturation limit was reached in the cells (i.e. at DS 30 and higher). This study demonstrated that precipitation of EZ could be overestimated when supersaturation was investigated without the implementation of an absorption compartment in vitro, both in the absence and in the presence of polymer.

[34] *Zambrano T, Hirata RDC, Hirata MH et al.* **Statins differentially modulate microRNAs expression in peripheral cells of hyperlipidemic subjects: A pilot study**. Eur J Pharm Sci 2018; 117:55-61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29427701
ABSTRACT
AIM: Although statins are considered a cornerstone for the treatment of high cholesterol levels due to their powerful cholesterol-lowering effects, response to drug administration is still one of the main pitfalls of statin treatment. So far, the reasons underlying this undesired outcome are still poorly understood, but recently, various studies have suggested that miRNAs may be involved. Therefore, we aimed at evaluating the effect of short-term low-dose treatment with 2 statins on miRNAs expression in patients with hypercholesterolemia. METHODS: A total of 40 hypercholesterolemic (HC) subjects following 1month of atorvastatin (10mg/day; n=20) or simvastatin (10mg/day; n=20) were included. Multiple available boinformatic algorithms (TargetScan, miRanda, DianaLab, MicroCosm and PicTar) were employed to select miRNAs regulating genes involved in cholesterol metabolism and statin response. Differential miRNAs expression was determined in peripheral cells using the miScript(R) miRNA PCR Array platform. Pathways involving differentially expressed miRNAs were explored using the Ingenuity Pathway Analysis software. RESULTS: Atorvastatin repressed miR-29a-3p, miR-29b-3p, miR-300, miR-33a-5p, miR-33b-5p and miR-454-3p in HC subjects. On the contrary, simvastatin did not show any effect on miRNAs expression. Network analysis indicated that atorvastatin-modulated miRNAs regulate key cholesterol genes (ABCA1, HMGCR, INSIG1, LDLR, LPL, SCAP and SREBF1). Further subgroups analyses showed that miR-106b-5p, miR-17-3p and miR-590-5p were repressed in HC subjects within the lower quartile of atorvastatin response (lower LDL-C reduction), while the expression of miR-106b-5p, miR-17-3p and miR-183-5p was higher in the upper quartile of simvastatin response (higher LDL-C reduction) ($p<0.05$). CONCLUSION: We show that a miRNAs-mediated epigenetic mechanism is differentially affected by statins

therapy in vivo, which could be implicated in the variable response to these drugs. Further studies are necessary to disclose their particular role in the cholesterol-reduction response to statins.

[35] *Niu H, Wei Z, Zhang Y et al.* **Atorvastatin improves coronary flow and endothelial function in patients with coronary slow flow**. Experimental and therapeutic medicine 2018; 15:904-908.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29399097
ABSTRACT
The underlying mechanisms behind the effect of atorvastatin on patients with coronary slow flow (CSF) remain largely unknown. To investigate the possible underlying molecular mechanisms 108 patients were divided into atorvastatin group and control group. Coronary flow was quantified according to corrected TIMI frame count (CTFC). Serum high sensitivity C-reactive protein (hs-CRP), lipids, ET-1, interleukin (IL)-6, NO, circulating endothelial progenitor cell (cEPC) count, adhesion, migration and proliferation were measured in pretreatment and post-treatment. After respective treatment, the atorvastatin group had significantly decreased levels of TC, TG, LDL-C, hs-CRP, ET-1 and IL-6 and increased NO compared to the control group. The atorvastatin group had a more significant improvement of CTFC, effective rate, cEPC number, EPC adhesion, migration and proliferation compared to the control group. In conclusion, atorvastatin can be used in treatment of CSF by suppressing inflammation and improving endothelial function.

[36] *Wang X, Li W, Hao L et al.* **The therapeutic potential of CETP inhibitors: a patent review**. Expert Opin Ther Pat 2018:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29424255
ABSTRACT
INTRODUCTION: Epidemiological studies have identified that high levels of low-density lipoprotein-cholesterol (LDL-C) and low levels of high-density lipoprotein-cholesterol (HDL-C) are two independent causes of cardiovascular disease (CVD). Statins, niacin and fibrate are used for the treatment of CVD. However, some defects are shown in the treatment process. Thus, there is a demand for better treatment strategies that confer preferable efficacy with fewer side effects. Cholesteryl ester transfer protein (CETP) promotes the movement of CEs from HDL to LDL and VLDL in exchange for triglycerides (TGs). Areas covered: In this review, we reviewed the development and therapeutic applications of CETP inhibitors. A comprehensive review of the patents and pharmaceutical applications between 2009 and 2017 has been highlighted. Expert opinion: Recently, CETP inhibitors have attracted considerable interest in atherosclerosis-related disease. There are four drugs (torcetrapib, anacetrapib, evacetrapib and dalcetrapib) that have been clinically evaluated in phase III clinical trials and showed promising results in raising HDL-C levels, but there were suboptimal performances in reducing the risk of cardiovascular events with all the compounds. The correlation between plasma HDL-C levels and CVD incidence needs further verification. The timeline is still long for CETP inhibitors to emerge from the treatment of CVD.

[37] *Tracey TJ, Steyn FJ, Wolvetang EJ, Ngo ST*. **Neuronal Lipid Metabolism: Multiple Pathways Driving Functional Outcomes in Health and Disease**. Frontiers in molecular neuroscience 2018; 11:10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29410613
ABSTRACT
Lipids are a fundamental class of organic molecules implicated in a wide range of biological processes related to their structural diversity, and based on this can be broadly classified into five categories; fatty acids, triacylglycerols (TAGs), phospholipids, sterol lipids and sphingolipids. Different lipid classes play major roles in neuronal cell populations; they can be used as energy substrates, act as building blocks for cellular structural machinery, serve as bioactive molecules, or a combination of each. In amyotrophic lateral sclerosis (ALS), dysfunctions in lipid metabolism and function have been identified as potential drivers of pathogenesis. In particular, aberrant lipid metabolism is proposed to underlie denervation of neuromuscular junctions, mitochondrial dysfunction, excitotoxicity, impaired neuronal transport, cytoskeletal defects, inflammation and reduced neurotransmitter release. Here we review current knowledge of the roles of lipid metabolism and function in the CNS and discuss how modulating these pathways may offer novel therapeutic options for treating ALS.

[38] *Woudberg NJ, Pedretti S, Lecour S et al.* **Pharmacological Intervention to Modulate HDL: What Do We Target?** Frontiers in pharmacology 2017; 8:989.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29403378
ABSTRACT
The cholesterol concentrations of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) have traditionally served as risk factors for cardiovascular disease. As such, novel therapeutic interventions aiming to raise HDL cholesterol have been tested in the clinical setting. However, most trials led to a significant increase in HDL cholesterol with no improvement in cardiovascular events. The complexity of the HDL particle, which exerts multiple physiological functions and is comprised of a number of subclasses, has raised the question as to whether there should be more focus on HDL subclass and function rather than cholesterol quantity. We review current data regarding HDL subclasses and subclass-specific functionality and highlight how current lipid modifying drugs such as statins, cholesteryl ester transfer protein inhibitors, fibrates and niacin often increase cholesterol concentrations of specific HDL subclasses. In addition this review sets out arguments suggesting that the HDL3 subclass may provide better protective effects than HDL2.

[39] *Desai P, Wallace R, Anderson ML et al.* **An analysis of the association between statin use and risk of endometrial and ovarian cancers in the Women's Health Initiative**. Gynecologic oncology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29422345
ABSTRACT
BACKGROUND: Statins have anti proliferative activity in vitro against endometrial and ovarian cancer and can affect levels of reproductive hormones. We analyzed data from the Women's Health Initiative (WHI) to assess whether statins are associated with risk of endometrial and ovarian cancer. METHODS: The WHI study included 161,808 postmenopausal women in which

incident cases of endometrial (n=1377) and ovarian cancer (n=763) were identified over an average of 10.8 (SD+3.3) years. Information on statin use and risk factors was collected at baseline and follow-up. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association of statin use and risk of endometrial and ovarian cancer. All statistical tests were two-sided. RESULTS: Statins were used at baseline by 7.5% women and by up to 25% at year nine. The multivariable adjusted HR for risk of endometrial cancer for baseline statin use was 0.74, 95% C.I. 0.59-0.94 and for ovarian cancer was 1.15, 95% C.I. 0.89-1.50. In time-dependent models, statins were not associated with endometrial cancer (HR 0.91, 95% C.I. 0.76-1.08) however there was an increased risk of ovarian cancer (HR 1.30, 95% CI 1.04-1.62), largely attributed to the effect of the hydrophilic statin, pravastatin (1.89, 95% CI 1.24-2.88). CONCLUSIONS: There was a reduction in risk of endometrial cancer among statin users at baseline but not in time-dependent models. Pravastatin use was associated with an increased risk of ovarian cancer. Analyses of larger numbers of cases are needed to evaluate these findings.

[40] *Zimmer M, Bista P, Benson EL et al.* **CAT-2003: A novel sterol regulatory element-binding protein inhibitor that reduces steatohepatitis, plasma lipids, and atherosclerosis in apolipoprotein E*3-Leiden mice**. Hepatology communications 2017; 1:311-325.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29404461
ABSTRACT
CAT-2003 is a novel conjugate of eicosapentaenoic acid (EPA) and niacin designed to be hydrolyzed by fatty acid amide hydrolase to release EPA inside cells at the endoplasmic reticulum. In cultured liver cells, CAT-2003 blocked the maturation of sterol regulatory element-binding protein (SREBP)-1 and SREBP-2 proteins and decreased the expression of multiple SREBP target genes, including HMGCR and PCSK9. Consistent with proprotein convertase subtilisin/kexin type 9 (PCSK9) reduction, both low-density lipoprotein receptor protein at the cell surface and low-density lipoprotein particle uptake were increased. In apolipoprotein E*3-Leiden mice fed a cholesterol-containing western diet, CAT-2003 decreased hepatic inflammation and steatosis as evidenced by fewer inflammatory cell aggregates in histopathologic sections, decreased nuclear factor kappa B activity in liver lysates, reduced inflammatory gene expression, reduced intrahepatic cholesteryl ester and triglyceride levels, and decreased liver mass. Plasma PCSK9 was reduced and hepatic low-density lipoprotein receptor protein expression was increased; plasma cholesterol and triglyceride levels were lowered. Aortic root segments showed reduction of several atherosclerotic markers, including lesion size, number, and severity. CAT-2003, when dosed in combination with atorvastatin, further lowered plasma cholesterol levels and decreased hepatic expression of SREBP target genes. Conclusion: SREBP inhibition is a promising new strategy for the prevention and treatment of diseases associated with abnormal lipid metabolism, such as atherosclerosis and nonalcoholic steatohepatitis. (Hepatology Communications 2017;1:311-325).

[41] *Bass AR, Szymonifka JD, Rondina MT et al.* **Postoperative Myocardial Injury and Inflammation Is Not Blunted by a Trial of Atorvastatin in Orthopedic Surgery Patients**. HSS journal : the musculoskeletal journal of Hospital for Special Surgery 2018; 14:67-76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29398998

ABSTRACT
Background: Orthopedic patients are at risk for adverse postoperative cardiovascular outcomes. Questions/Purposes: This pilot randomized controlled trial (RCT) of atorvastatin vs. placebo in orthopedic surgery patients was performed in order to assess: (1) the prevalence of perioperative myocardial injury; (2) the effect of atorvastatin on perioperative inflammation; and (3) the feasibility of performing a large RCT of statin therapy in orthopedic patients. Methods: Hip fracture (hip Fx) and total hip and knee replacement (THR and TKR) patients were randomized 1:1 to atorvastatin 40 mg daily vs. placebo, starting preoperatively and continuing until postoperative day (POD) 45. High-sensitivity cardiac troponin I (hs-cTnI), high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) were measured preoperatively and on POD 2. Patients were monitored for adverse events until POD 90. Results: Five hundred fifty-six patients were screened, 22 were recruited (4 hip Fx, 11 THR, 7 TKR), and 2 withdrew. Most (80%) had detectable hs-cTnI (> 1.1 pg/mL) preoperatively. Twenty percent had a perioperative rise in hs-cTnI (>/= 10 pg/mL), which was not blunted by atorvastatin. Hs-CRP rose in 19/20 patients, and IL-6 rose in all patients. However, atorvastatin did not blunt the rise in these inflammatory biomarkers. On POD 2, IL-6 and hs-cTnI levels correlated (rho = 0.59, p = 0.02). Recruitment was limited by the high prevalence of statin use in the screened population and a high prevalence of exclusions among hip fracture patients. Conclusion: Perioperative myocardial injury and inflammation are common in orthopedic patients and do not appear to be reduced in those randomized to atorvastatin. Trial Registration: NCT02197065.

[42] *Poppe KK, Doughty RN, Harwood M et al.* **Identification, risk assessment, and management of patients with atrial fibrillation in a large primary care cohort**. International journal of cardiology 2018; 254:119-124.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29407079

ABSTRACT
BACKGROUND: Atrial fibrillation (AF) is associated with increased risk of cardiovascular disease (CVD) complications including stroke. We investigated the assessment and management of cardiovascular risk among patients with AF aged 35-74years, by ethnic group, in a large cohort of people receiving a CVD risk assessment in primary care (PREDICT). METHODS: PREDICT was linked to national dispensing, hospitalisation and mortality records. AF was present if recorded in PREDICT or during a prior hospitalisation; medications were those dispensed </=6months before or after a PREDICT assessment; the CHA2DS2-VASc score and a New Zealand (NZ) adjusted Framingham CVD risk were calculated. Data were linked to outcomes of stroke or major adverse cardiovascular event (MACE). RESULTS: 12,739 (2.8%) of 447,020 people aged 35-74years had AF. Maori, the indigenous population of NZ, had the highest proportion of AF, which by age group, was similar to that among Europeans 10years older. 77% were at high stroke risk, of whom 42% received anticoagulation; 54% were at high CVD risk, of whom 67% received both lipid- and blood pressure-lowering medication. Per category of predicted risk, stroke risk was overestimated and risk of MACE was underestimated. CONCLUSIONS: The burden of AF and risk factors differed by ethnic group thus recommendations to screen for AF above a universal age threshold may introduce inequity in the detection and management of associated risk. The high burden of comorbidities at younger ages among many ethnic groups

contributes to the poor performance of available risk assessment tools, further compounding potential inequity.

[43] *Saren G, Yi X, Gong Y*. **Pleiotropic effects and biological activities of atorvastatin: The sun never set**. International journal of cardiology 2018; 254:261.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29407106
ABSTRACT

[44] *Kiburg KV, Ward GM, O'Neal DN, MacIsaac RJ*. **Lipid-lowering therapy use and achievement of cholesterol targets in an Australian diabetes clinic**. Internal medicine journal 2018; 48:201-204.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29415350
ABSTRACT
We documented temporal changes in the use of lipid-lowering medications and achievement of cholesterol targets in an Australian diabetes clinic. The number of patients using lipid-lowering therapy for primary or secondary cardiovascular prevention increased from 6 to 69% between 1993-1995 and 2014-2016, which corresponded to a decrease in low-density lipoprotein cholesterol levels from 3.7 to 2.4 mmol/L ($P < 0.01$).

[45] *deFilippi C, Christenson R, Joyce J et al.* **Statin Effects on Myocardial Fibrosis Markers in People Living with HIV**. Journal of acquired immune deficiency syndromes (1999) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29419569
ABSTRACT
BACKGROUND: In observational studies, HIV patients have higher levels of soluble ST2 (sST2), galectin-3, growth differentiation factor-15 (GDF-15) than non-HIV controls. As statins exert pleiotropic immunomodulatory effects that may affect markers of myocardial fibrosis, the objective of the current study is to determine if biomarkers of myocardial fibrosis reflecting subclinical pathology may be modified by statin therapy in patients with HIV. SETTING: and Methods: 40 HIV+ men and women participated in a single center 12-month randomized, double-blind placebo controlled trial of atorvastatin 40mg qd vs. placebo. At baseline and 12-months sST2, GDF-15, galectin-3, were measured. RESULTS: The changes in sST2 were -0.310 [-4.195,2.075] vs. 1.163 [0.624, 4.715]ng/mL, median[IQR] atorvastatin vs. placebo (p=0.04). The change in sST2 was significantly related to changes in monocyte activation markers sCD14 (r=0.63, p<0.0001) and MCP (r=0.52, p=0.0009), markers of generalized inflammation hs-IL-6 (r=0.58, p=0.0002), oxLDL (r=0.49, p=0.002), and GDF-15 (r=0.54, p=0.0008). CONCLUSION: sST2, a member of the IL-1 receptor family and a marker of fibrosis and inflammation increases over time among HIV patients and this increase is attenuated by statin therapy in HIV. This effect may relate to immunomodulatory mechanisms of statins.

[46] *Filippatos TD, Panagiotopoulou T, Tzavella E, Elisaf MS*. **Hypolipidemic Drugs and Diabetes Mellitus-Mechanisms and Data From Genetic Trials**. Journal of cardiovascular pharmacology and therapeutics 2018:1074248418757011.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29409336
ABSTRACT

Clinical trials and meta-analyses have shown that statins can dose dependently increase the incidence of new-onset diabetes mellitus (DM) especially in patients with underlying abnormalities of carbohydrate homeostasis. Mendelian randomization studies support these findings since genetic variants in the gene encoding the target of statins, the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, are associated with increased incidence of new-onset DM, suggesting that the so-called diabetogenic effect of statins is an "on-target effect" possibly related to their main mechanism of action, that is the increased low-density lipoprotein (LDL) receptor expression. Additionally, Mendelian randomization studies have shown that genetic variants as proxies of other drugs that increase LDL receptor expression (ezetimibe and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) also increase the risk of new-onset DM. This concept is supported by the fact of decreased DM prevalence in patients with familial hypercholesterolemia who have decreased LDL receptor expression. In contrast, hypolipidemic drugs, such as the cholesteryl ester transfer protein inhibitors, that decrease LDL cholesterol without directly interfering with the LDL receptor expression do not seem to detrimentally affect carbohydrate homeostasis. However, the clinical trials of ezetimibe and PCSK9 inhibitors have not shown an increased DM risk, possibly suggesting that other potential non-well-defined "off-target effects" of hypolipidemic drugs may affect carbohydrate homeostasis. Thus, the long-term effect of hypolipidemic drugs on DM risk depends not only on their final mechanism of hypolipidemic action but also on other "on-target" and "off-target" effects of these drugs.

[47] *Zhong Z, Wu H, Li B et al.* **Analysis of SLCO1B1 and APOE genetic polymorphisms in a large ethnic Hakka population in southern China**. Journal of clinical laboratory analysis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29424099

ABSTRACT

OBJECTIVE: Statins are the most widely used lipid-lowering drugs, which have a significant effect on the inhibition of cardiovascular disease. The efficacy and side effects of statins are associated with the polymorphisms of SLCO1B1 and APOE genes. The purpose of this study was to analyze the SLCO1B1 and APOE gene polymorphisms in the Hakka population of southern China. METHODS: A total of 3249 subjects including 2019 males and 1230 females participated in this study. Polymerase chain reaction (PCR)-fluorescence probe technique for polymorphisms analysis and analyzed the genotypes frequencies of SLCO1B1 and APOE genes. RESULTS: The frequencies of SLCO1B1 521T>C between men and women were statistically significant (SLCO1B1 521TT, chi(2) = 8.431, P = .004; SLCO1B1 521TC, chi(2) = 7.436, P = .007). The frequencies of haplotypes *1b/*1b (40.07%) and *1a/*1b (32.56%) of SLCO1B1 gene accounted for 72.63%, followed by *1b/*15(14.40%), *1a/*1a (5.82%), *1a/*15 (5.57%), *15/*15 (1.45%), and *1a/*5 (0.12%). The frequencies of haplotypes *1a/*15 and *1b/*1b of SLCO1B1 gene between men and women were statistically significant (*1a/*15, chi(2) = 6.789, P = .009; *1b/*1b, chi(2) = 3.998, P = .004). In this study, genotype varepsilon3/varepsilon3 accounted for 69.04%, followed by varepsilon3/varepsilon4 (16.19%), varepsilon2/varepsilon3 (11.60%), varepsilon2/varepsilon4 (1.35%), varepsilon4/varepsilon4 (1.08%), and varepsilon2/varepsilon2 (0.74%) in all subjects, in which varepsilon3 had the greatest allele frequency (82.93%), followed by varepsilon4 (9.85%) and varepsilon2 (7.22%). We found that 47 subjects carrying the SLCO1B1 521 (CC) polymorphism who had not any myopathy caused by statins.

CONCLUSIONS: We analyzed the SLCO1B1 and APOE gene polymorphisms in the Hakka population of southern China. This study provides a reference for the individualized meditation for Hakka population in this area.

[48] *Galema-Boers AM, Lenzen MJ, Engelkes SR et al.* **Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid-lowering therapy**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29398430
ABSTRACT
BACKGROUND: Despite lipid-lowering therapy (LLT), some patients with familial hypercholesterolemia (FH) still develop cardiovascular events. Data about the quantification and factors contributing to this residual risk are lacking. OBJECTIVE: This study assessed how many patients with FH developed a cardiovascular event despite LLT and which factors contribute to this risk. METHODS: We performed a time-dependent analysis in a cohort of consecutive heterozygous FH patients using stable LLT to evaluate first and subsequent cardiovascular events. Univariate and multivariate regression analyses were conducted to study the association between clinical characteristics and cardiovascular events. RESULTS: Of 821 FH patients (median age 47.4 [interquartile range (IQR) 35.3-58.3] years) treated with LLT for a median period of 9.5 (IQR 5.1-14.2) years, 102 patients (12%) developed cardiovascular disease (CVD) in 8538 statin-treated person-years. Patients who developed a cardiovascular event had a median age of 52.0 (IQR 43.8-59.3) years. These patients more often had previous cardiovascular events (32% vs 9%, P < .001), a family history of premature CVD (58% vs 40%, P = .001), hypertension (70% vs 22%, P < .001), higher on-treatment low-density lipoprotein cholesterol (162 +/- 54 vs 135 +/- 58 mg/dL, P < .001), lower on-treatment high-density lipoprotein cholesterol (50 +/- 15 vs 54 +/- 15 mg/dL, P < .001), and were smokers (32% vs 14%, P < .001), compared to patients without cardiovascular events. In 31 patients (30%), a subsequent cardiovascular event occurred with a median interval of 5.7 (IQR 2.4-9.3) years between events. They were more often smokers (32% vs 10%, P = .01) compared to patients with a single cardiovascular event. CONCLUSIONS: Despite LLT, FH patients still develop cardiovascular events and especially subsequent events. Classical risk factors such as smoking and hypertension are driving factors for this risk, indicating the high priority of optimizing risk factor reduction in addition to maximum LLT.

[49] *Masana L, Girona J, Ibarretxe D et al.* **Clinical and pathophysiological evidence supporting the safety of extremely low LDL levels-The zero-LDL hypothesis**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29398429
ABSTRACT
While the impact of very low concentrations of low-density lipoprotein cholesterol (LDL-C) on cardiovascular prevention is very reassuring, it is intriguing to know what effect these extremely low LDL-C concentrations have on lipid homoeostasis. The evidence supporting the safety of extremely low LDL levels comes from genetic studies and clinical drug trials. Individuals with lifelong low LDL levels due to mutations in genes associated with increased LDL-LDL receptor (LDLR) activity reveal no safety issues. Patients achieving extremely low LDL

levels in the IMPROVE-IT and FOURIER, and the PROFICIO and ODYSSEY programs seem not to have an increased prevalence of adverse effects. The main concern regarding extremely low LDL-C plasma concentrations is the adequacy of the supply of cholesterol, and other molecules, to peripheral tissues. However, LDL proteomic and kinetic studies reaffirm that LDL is the final product of endogenous lipoprotein metabolism. Four of 5 LDL particles are cleared through the LDL-LDLR pathway in the liver. Given that mammalian cells have no enzymatic systems to degrade cholesterol, the LDL-LDLR pathway is the main mechanism for removal of cholesterol from the body. Our focus, therefore, is to review, from a physiological perspective, why such extremely low LDL-C concentrations do not appear to be detrimental. We suggest that extremely low LDL-C levels due to increased LDLR activity may be a surrogate of adequate LDL-LDLR pathway function.

[50] *Otvos JD, Guyton JR, Connelly MA et al.* **Relations of GlycA and lipoprotein particle subspecies with cardiovascular events and mortality: A post hoc analysis of the AIM-HIGH trial**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29409728
ABSTRACT
BACKGROUND: The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes trial showed no incremental benefit of extended-release niacin (ERN) therapy added to simvastatin in subjects with cardiovascular disease (CVD). OBJECTIVES: To examine the effects of ERN treatment on lipoprotein particles and GlycA, a new marker of systemic inflammation, and their relations with incident CVD events including mortality. METHODS: GlycA and very low-density lipoprotein, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) particle subclasses were quantified by nuclear magnetic resonance spectroscopy using available stored baseline (n = 2754) and 1-year in-trial (n = 2581) samples. Associations with CVD events and all-cause mortality were assessed using multivariable Cox proportional hazards regression adjusted for age, sex, diabetes, treatment assignment, and lipoproteins. RESULTS: Compared to placebo, ERN treatment lowered very low-density lipoprotein and LDL and increased HDL particle concentrations, increased LDL and HDL particle sizes (all P < .0001), but did not affect GlycA. Baseline and in-trial GlycA levels were associated with increased risk of CVD events: hazard ratio (HR) per SD increment, 1.17 (95% confidence interval [CI], 1.06-1.28) and 1.13 (1.02-1.26), respectively. However, none of the lipoprotein particle classes or subclasses was associated with incident CVD. By contrast, all-cause mortality was significantly associated with both GlycA (baseline HR: 1.46 [1.22-1.75]; in-trial HR: 1.41 [1.24-1.60]) and low levels of small HDL particles (baseline HR: 0.69 [0.56-0.86]; in-trial HR: 0.69 [0.56-0.86]). CONCLUSIONS: This Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes trial post hoc substudy indicates that inflammation, as indexed by GlycA, is unaffected by ERN treatment but is significantly associated with the residual risk of CVD and death in patients treated to low levels of LDL cholesterol.

[51] *Spiro J, Butts M*. **Atorvastatin-Induced Dermatomyositis: Resolution With Change in Statin?** Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29424763
ABSTRACT

[52] *Wong ITY, Huang Y, Zhou Y*. **Drug Eruption to Rosuvastatin With Recurrence on Simvastatin: A Case Report**. Journal of cutaneous medicine and surgery 2018:1203475418756376.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29400079
ABSTRACT

[53] *Mennitti LV, Oyama LM, Santamarina AB et al.* **Early exposure to distinct sources of lipids affects differently the development and hepatic inflammatory profiles of 21-day-old rat offspring**. Journal of inflammation research 2018; 11:11-24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29403301
ABSTRACT
Introduction: Maternal diet composition of fatty acids during pregnancy and lactation seems to modify the fetal programming, epigenetic pattern and offspring phenotype. Aim: Herein, we investigated the effects of maternal consumption of normal-fat diets with distinct lipid sources during pregnancy and lactation on the somatic development and proinflammatory status of 21-day-old rat offspring. Materials and Methods: On the first day of pregnancy, female Wistar rats were divided into four groups as follows: soybean oil (M-SO), lard (M-L), hydrogenated vegetable fat (M-HVF) and fish oil (M-FO). Diets were maintained during pregnancy and lactation. Male offspring constituted the SO, L, HVF and FO groups. Pups were weighed and measured weekly. Lipopolysaccharide serum concentration was determined. Tumor necrosis factor alpha, interleukin (IL)-6 and IL-10 in the liver were evaluated by enzyme-linked immunosorbent assay. Liver gene expressions were determined by real-time polymerase chain reaction. Protein expressions in the liver were analyzed by Western blotting. Results: We observed an increase in body weight and adiposity in L and HVF groups. Moreover, HVF group showed an increase in the toll-like receptor 4 mRNA levels, IL10Ralpha and phosphorylated form of IkappaB kinase (IKK; p-IKKalpha+beta) protein expression. The FO group presented a decrease in body weight, relative weight of retroperitoneal adipose tissue, ADIPOR2 gene expression, lipopolysaccharide and p-IKKalpha+beta and phosphorylated form of nuclear transcription factor kappa B (NFkappaB) p50 (p-NFkappaB p50) protein expression. Conclusion: Summarily, whereas maternal intake of normal-fat diets based on L and HVF appear to affect the somatic development negatively, only early exposure to HVF impairs the pups' proinflammatory status. In contrast, maternal diets based on FO during pregnancy and lactation have been more beneficial to the adiposity and toll-like receptor 4 signaling pathway of the 21-day-old rat offspring, particularly when compared to L or HVF diets.

[54] *Wang S, Zhang X, Zhai L et al.* **Atorvastatin Attenuates Cognitive Deficits and Neuroinflammation Induced by Abeta1-42 Involving Modulation of TLR4/TRAF6/NF-kappaB Pathway**. Journal of molecular neuroscience : MN 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29417448
ABSTRACT

Inflammatory damage aggravates the progression of Alzheimer's disease (AD) and the mechanism of inflammatory damage may provide a new therapeutic window for the treatment of AD. Toll-like receptor 4 (TLR4)-mediated signaling can regulate the inflammatory process. However, changes in TLR4 signaling pathway induced by beta-amyloid (Abeta) have not been well characterized in brain, especially in the hippocampus. In the present study, we explored the changes of TLR4 signaling pathway induced by Abeta in the hippocampus and the role of atorvastatin in modulating this signal pathway and neurotoxicity induced by Abeta. Experimental AD rats were induced by intrahippocampal injection of Abeta1-42, and the rats were treated with atorvastatin by oral gavage from 3 weeks before to 6 days after injections of Abeta1-42. To determine the spatial learning and memory ability of rats in the AD models, Morris water maze (MWM) was performed. The expression of the glial fibrillary acidic protein (GFAP), ionized calcium binding adapter molecule-1 (Iba-1), TLR4, tumor necrosis factor receptor-associated factor 6 (TRAF6), and nuclear transcription factor (NF)-kappaB (NF-kappaB) protein in the hippocampus was detected by immunohistochemistry and Western blot. Compared to the control group, increased expression of TLR4, TRAF6, and NF-kappaB was observed in the hippocampus at 7 days post-injection of Abeta ($P < 0.01$). Furthermore, atorvastatin treatment significantly ameliorated cognitive deficits of rats, attenuated microglia and astrocyte activation, inhibited apoptosis, and down-regulated the expression of TLR4, TRAF6, and NF-kappaB, both at the mRNA and protein levels ($P < 0.01$). TLR4 signaling pathway is thus actively involved in Abeta-induced neuroinflammation and atorvastatin treatment can exert the therapeutic benefits for AD via the TLR4 signaling pathway.

[55] *Levitt Katz LE, Bacha F, Gidding SS et al.* **Lipid Profiles, Inflammatory Markers, and Insulin Therapy in Youth with Type 2 Diabetes**. J Pediatr 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29398050

ABSTRACT

OBJECTIVES: Data regarding atherogenic dyslipidemia and the inflammation profile in youth with type 2 diabetes is limited and the effect of insulin therapy on these variables has not previously been studied in youth. We determined the impact of insulin therapy on lipid and inflammatory markers in youth with poorly controlled type 2 diabetes. STUDY DESIGN: In the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) multicenter trial, 285 participants failed to sustain glycemic control on randomized treatment (primary outcome, glycated hemoglobin A1c [HbA1c] at >/=8% for 6 months); 363 maintained glycemic control (never reached primary outcome). Statins were used for a low-density lipoprotein cholesterol of >/=130 mg/dL. Upon reaching the primary outcome, insulin was started. Changes in lipids and inflammatory markers (slopes over time) were examined. RESULTS: Progression of dyslipidemia was related to glycemic control. In those with the primary outcome, insulin therapy impacted HbA1c modestly, and dampened the increase in total cholesterol, low-density lipoprotein cholesterol, and total apolipoprotein B, although statin use increased from 8.6% to 22% year after the primary outcome. The increase in triglycerides and plasma nonesterified fatty acids stabilized after insulin was started, independent of HbA1c. There was an increase in high-sensitivity C-reactive protein that continued after insulin initiation, related to HbA1c and percent overweight. CONCLUSIONS: Worsening dyslipidemia and inflammation over time raise concern regarding premature development of atherosclerosis in youth with type 2 diabetes.

Insulin therapy has a limited benefit in the absence of glycemic control. Strategies to achieve better glycemic control are needed. TRIAL REGISTRATION: ClinicalTrials.gov: NCT00081328.

[56] *Delgado-Leon TG, Salas-Pacheco JM, Vazquez-Alaniz F et al.* **Apoptosis in pancreatic beta-cells is induced by arsenic and atorvastatin in Wistar rats with diabetes mellitus type 2**. Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS) 2018; 46:144-149.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29413104
ABSTRACT
INTRODUCTION: Diabetes Mellitus type 2 (T2D) is a multifactorial disease. However, it is known that there is an important effect in pancreatic beta-cells caused by apoptosis of pro-apoptotic proteins, possibly related to arsenic exposure and atorvastatin treatment. OBJECTIVE: The goal of this study was to evaluate the effects of atorvastatin treatment on apoptosis of pancreatic beta-cells in Wistar rats with induced diabetes type 2 exposed to arsenic. MATERIAL & METHODS: T2D in Wistar rats was induced by administration of Streptozotocin. The plasmatic glucose concentrations were measured using the glucose oxidase method, and the concentration of glycated hemoglobin (HbA1c) in whole blood was determined. Exposure to arsenic was measured from urine using atomic absorption with hydride generation, and pro-apoptotic proteins in pancreatic beta-cells were observed using the Western blotting technique. RESULTS: Caspase-3 was present in rats that were treated with 10mg/kg of oral atorvastatin and exposed to 0.01 and 0.025mg/L of arsenic, but no others proteins were present, such as pro Caspase-8, bcl-2, and Fas. The glycemic levels were 129.2+/-7.0mg/dL in the control group and 161.8+/-14.6mg/dL and 198.3+/-18.2mg/dL ($p<.05$) in the study groups. HbA1c increased from 2.53% to 3.64% ($p<.05$) in the control and study groups. CONCLUSIONS: Atorvastatin treatment and arsenic exposure alone are capable of generating apoptosis in pancreatic beta-cells of Wistar rats with T2D. Together, all of these factors induce apoptosis in pancreatic cells.

[57] *Polak M, Dorynska A, Szafraniec K, Pajak A*. **Cardiovascular risk assessment, cardiovascular disease risk factors, and lung function parameters**. Kardiol Pol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29399756
ABSTRACT
BACKGROUND: Decreased lung function is related to higher cardiovascular disease (CVD) incidence and mortality. However, little is known about the relationship between the risk factors of CVD and pulmonary function. AIM: To assess the relationship between the prevalence of cardiovascular risk factors, the total CVD risk and pulmonary function. METHODS: The analysis included 4,104 men and women in the age range of 45-69 years, participants of the Polish part of the HAPIEE Project (Health,Alcohol andPsychosocial factorsInEasternEurope), who provided valid measurements of 1s forced expiratory volume (FEV(1)) and forced vital capacity (FVC) using Micro-Medical Microplus spirometer. The prevalence of CVD risk factors was defined as follows: hypertension (SBP >/= 140 mmHg or DBP >/= 90 mmHg or taking hypertension medication), diabetes (glucose >/= 7.1mmol/l or self-reported diabetes), hypercholesterolemia (total cholesterol >/= 5 mmol/l or LDL-cholesterol >/= 3 mmol/l or taking lipid lowering medication). Categories of total CVD risk were defined according to 2016

European Guidelines on cardiovascular disease prevention in clinical practice. The analysis of covariance was used to compare the lung function in the CVD risk factors and the total CVD risk categories. R: ESULTS: : Mean values of FEV(1) and FVC, adjusted for age and height were significantly higher in men than in women (3.02 L; 95% CI = 2.96-3.08 L vs. 2.52 L; 95% CI = 2.45-2.63 L for FEV(1) and 3.62 L; 95% CI = 3.56-3.69 L vs 3.05 L; 95% CI = 2.98-3.12 L for FVC). Obesity was significantly associated with FVC in men and women; it was associated with FEV(1) only in men. Compared with participants with normal BMI, obese men and women had 280 ml and 112 ml lower mean FVC, respectively. Men without hypertension had almost 100 ml higher mean FVC than those with hypertension. The difference in FVC in women was approximately 80 ml. Diabetes was associated with lower value of FVC in both genders and with FEV(1) in women. A significant negative trend was observed in the mean FVC and FEV(1) by the considered CVD risk categories. CONCLUSIONS: Impaired lung function was associated with higher CVD risk what could be explained partly by adverse association between lung function and prevalence of obesity, hypertension, diabetes.

[58] *Al-Zakwani I, Al-Mahruqi F, Al-Rasadi K et al.* **Sex disparity in the management and outcomes of dyslipidemia of diabetic patients in the Arabian Gulf: findings from the CEPHEUS study**. Lipids in health and disease 2018; 17:25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29402296
ABSTRACT
BACKGROUND: Little is known about sex gap in the management and outcomes of dyslipidemia among diabetics in the Arabian Gulf. The aim if this study was to determine sex differences in the management and outcomes of dyslipidemia in diabetic patients in the Arabian Gulf. METHODS: This study was derived from the Centralized Pan-Middle-East Survey on the management of hypercholesterolemia. Patients recruited were aged >/=18 years on lipid lowering drugs for >/=3 months (stable medication for >/=6 weeks). Outcomes were based on the joint Consensus Statement of the American Diabetes Association and American College of Cardiology Foundation. Analyses were performed using univariate and multivariate logistic regression techniques. RESULTS: The mean age of the cohort (n = 3336) was 57 +/- 11 years and 45% (n = 1486) were females. Females were less likely to be on rosuvastatin (7.6% vs 12%; P < 0.001), atorvastatin (41% vs 46%; P = 0.005) and combination hypolipidemic therapy (5.6% vs 2.8%; P < 0.001) but more likely to be on simvastatin (51% vs 39%; P < 0.001) than males. Females, especially those with very high atherosclerotic cardiovascular disease (ASCVD) risk status, were also less likely to achieve LDL-cholesterol [adjusted odds ratio (aOR), 0.58; 95% confidence interval (CI): 0.40-0.86; P = 0.006], non-HDL-cholesterol [aOR, 0.68; 95% CI: 0.46-0.99; P = 0.048] and apolipoprotein B [aOR, 0.64; 95% CI: 0.44-0.92; P = 0.016] lipid targets. CONCLUSIONS: Diabetic women were less likely to be on optimal hypolipemic therapy and consequently less likely to attain lipid goals compared to men. This shows a sex gap on dyslipidemia treatment in the region. Diabetic women with very high ASCVD risk status need to be aggressively treated to lower their risk of cardiovascular events.

[59] *Demir C, Anil C, Bozkus Y et al.* **Do Statins Affect Thyroid Volume and Nodule Size in Patients with Hyperlipidemia in a Mildly to Moderately Iodine-Deficient Region? A**

Literature update week 06 (2018)

Prospective Study. Medical principles and practice : international journal of the Kuwait University, Health Science Centre 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29402848
ABSTRACT
OBJECTIVE: The objective of this study was to assess the anti-proliferative pleiotropic effects of statins on thyroid function, volume and nodularity. SUBJECTS AND METHODS: One hundred and six hyperlipidemic patients were included in this prospective study. Sixty nine patients in the statin groups received atorvastatin (16 patients received 10 mg, 18 received 20 mg) or rosuvastatin (20 patients received 10 mg, 15 received 20 mg); 37 patients in the control group assessed as not requiring drugs only made lifestyle changes. All patients were evaluated for lipid variables [total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C)], and thyroid function and structure using ultrasonography on admission and 6 months later. RESULTS: After 6 months, no differences in thyroid function, thyroid volume, number of thyroid nodules or nodule size were observed in statin and control groups. In subgroup analysis, total thyroid volume decreased more in patients receiving 20 mg of rosuvastatin than that in the control group ($P<0.05$). Maximum nodule size decreased more in those receiving 10 mg of rosuvastatin ($P<0.05$). CONCLUSIONS: Our results suggest an association between rosuvastatin treatment and smaller thyroid volume and maximum nodule diameter; this could be attributable to the anti-proliferative effects of statin therapy on the thyroid.

[60] *Lutjohann D, Meyer S, von Bergmann K, Stellaard F*. **Cholesterol Absorption and Synthesis in Vegetarians and Omnivores**. Molecular nutrition & food research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29427539
ABSTRACT
SCOPE: Vegetarian diets are considered health promoting, however, a plasma cholesterol lowering effect is not always observed. We investigated the link between vegetarian diet-induced alterations in cholesterol metabolism. METHODS AND RESULTS: We studied male and female omnivores, lacto-ovo vegetarians, lacto vegetarians and vegans. Cholesterol intake, absorption and fecal sterol excretion were measured as well as plasma concentrations of cholesterol and non-cholesterol sterols. These served as markers for cholesterol absorption, synthesis and catabolism. The biliary cholesterol secretion rate was estimated. Flux data were related to bodyweight. Individual vegetarian diet groups were statistically compared to the omnivore group. Lacto vegetarians absorbed 44% less dietary cholesterol, synthesized 22% more cholesterol and showed no differences in plasma total and LDL cholesterol. Vegan subjects absorbed 90% less dietary cholesterol, synthesized 35% more cholesterol and had a similar plasma total cholesterol, but a 13% lower plasma LDL cholesterol. No diet-related differences in biliary cholesterol secretion and absorption were observed. Total cholesterol absorption was lower only in vegans. Total cholesterol input was similar under all vegetarian diets. CONCLUSIONS: Unaltered biliary cholesterol secretion and higher cholesterol synthesis blunt the lowered dietary cholesterol intake in vegetarians. LDL cholesterol was significantly lower only in vegans.

Literature update week 06 (2018)

[61] *Nordestgaard BG, Nicholls SJ, Langsted A et al.* **Advances in lipid-lowering therapy through gene-silencing technologies**. Nature reviews. Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29417937
ABSTRACT
New treatment opportunities are emerging in the field of lipid-lowering therapy through gene-silencing approaches. Both antisense oligonucleotide inhibition and small interfering RNA technology aim to degrade gene mRNA transcripts to reduce protein production and plasma lipoprotein levels. Elevated levels of LDL, remnant lipoproteins, and lipoprotein(a) all cause cardiovascular disease, whereas elevated levels of triglyceride-rich lipoproteins in some patients can cause acute pancreatitis. The levels of each of these lipoproteins can be reduced using gene-silencing therapies by targeting proteins that have an important role in lipoprotein production or removal (for example, the protein products of ANGPTL3, APOB, APOC3, LPA, and PCSK9). Using this technology, plasma levels of these lipoproteins can be reduced by 50-90% with 2-12 injections per year; such dramatic reductions are likely to reduce the incidence of cardiovascular disease or acute pancreatitis in at-risk patients. The reported adverse effects of these new therapies include injection-site reactions, flu-like symptoms, and low blood platelet counts. However, newer-generation drugs are more efficiently delivered to liver cells, requiring lower drug doses, which leads to fewer adverse effects. Although these findings are promising, robust evidence of cardiovascular disease reduction and long-term safety is needed before these gene-silencing technologies can have widespread implementation. Before the availability of such evidence, these drugs might have roles in patients with unmet medical needs through orphan indications.

[62] *Moya C, Manez S.* **Paraoxonases: metabolic role and pharmacological projection**. Naunyn-Schmiedeberg's archives of pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29404699
ABSTRACT
Atherosclerosis is one of the leading causes of death in Western countries, with high-density lipoproteins (HDL) playing an important protective role due to their ability to inhibit oxidation of low-density lipoproteins (LDL), thus relieving vascular subendothelial damage. One of the proteins constituting HDL particles is paraoxonase-1 (PON1), an enzyme able to hydrolyze aryl esters, lactones, and organophosphates. Other closely related paraoxonases are designated as PON2, which is a protein localized inside many different kinds of cells, and PON3, not only present in HDL but also in mitochondria and endoplasmic reticulum, as well. Given that the amount and the activity of PON1 in human serum are significantly lower in people suffering from cardiovascular diseases, enhancing both parameters might contribute to their treatment and prevention. One of the physiologically interesting substrates for the abovementioned hydrolytic cleavage is homocysteine thiolactone (HTL), an atherothrombotic active form of homocysteine. Although it was therefore postulated that PON1 would participate in preventing the HTL-mediated lipid peroxidation, some attention is recently paid to other enzymes, like biphenyl hydrolase-like protein, that seem to more selectively involved in lowering this risk factor. The aim of this paper is to elucidate the role of paraoxonases, especially PON1, by reviewing the latest studies in order to understand both its physiological role and modulation by drugs, nutrients, and plant extracts.

[63] *Caro-Maldonado A, Camacho L, Zabala-Letona A et al.* **Low-dose statin treatment increases prostate cancer aggressiveness**. Oncotarget 2018; 9:1494-1504.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29416709
ABSTRACT
Prostate cancer is diagnosed late in life, when co-morbidities are frequent. Among them, hypertension, hypercholesterolemia, diabetes or metabolic syndrome exhibit an elevated incidence. In turn, prostate cancer patients frequently undergo chronic pharmacological treatments that could alter disease initiation, progression and therapy response. Here we show that treatment with anti-cholesterolemic drugs, statins, at doses achieved in patients, enhance the pro-tumorigenic activity of obesogenic diets. In addition, the use of a mouse model of prostate cancer and human prostate cancer xenografts revealed that in vivo simvastatin administration alone increases prostate cancer aggressiveness. In vitro cell line systems supported the notion that this phenomenon occurs, at least in part, through the direct action on cancer cells of low doses of statins, in range of what is observed in human plasma. In sum, our results reveal a prostate cancer experimental system where statins exhibit an undesirable effect, and warrant further research to address the relevance and implications of this observation in human prostate cancer.

[64] *Solanki A, Bhatt LK, Johnston TP*. **Evolving targets for the treatment of atherosclerosis**. Pharmacology & therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29414673
ABSTRACT
Atherosclerosis is a progressive disease of large arteries and a leading cause of cardiovascular diseases and stroke. Chronic inflammation, aberrant immune response, and disturbances to key enzymes involved with lipid metabolism are characteristic features of atherosclerosis. Apart from targeting the derangements in lipid metabolism, therapeutic modulation to regulate chronic inflammation and the immune system response may prove to be very promising strategies in the management of atherosclerosis. In recent years, various targets have been studied for the treatment of atherosclerosis. PCSK9, a serine protease, actively targets the LDL-R and causes lysosomal degradation, which leads to excessive accumulation of LDL-C. Regulatory T cells (Tregs) and Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) affects the adaptive and innate immune response, respectively, and thus, therapeutic intervention of either of these targets would directly modulate disease progression. Advanced atherosclerotic lesions are characterized by an accumulation of apoptotic cells. Cluster of differentiation-47 (CD47), an anti-phagocytic known as the "don't eat me" signaling molecule, inhibits efferocytosis, which causes accumulation of cell debris in plaque. ADAMTS and Notch signaling potentially affect the formation of neointima by modulation of extracellular matrix components such as macrophages and vascular smooth muscle cells. This review provides insights on the molecular targets for therapeutic intervention of atherosclerosis, their effect at various stages of atherosclerosis development, and the therapies that have been designed and currently being evaluated in clinical trials.

Literature update week 06 (2018)

[65] *Pokrywka GS*. **PCSK9 inhibitors: a non-statin cholesterol-lowering treatment option**. Postgraduate medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29411675
ABSTRACT
Elevated low-density lipoprotein cholesterol (LDL-C) plays a major role in the development of atherosclerotic cardiovascular disease. Statins are the first-line treatment to lower LDL-C in patients with hypercholesterolemia; however, some high cardiovascular risk patients may have inadequate responses to statin therapy or are intolerant to statins, and may need additional and/or alternative non-statin therapies to further reduce their LDL-C levels. Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of circulating LDL-C levels, have received considerable attention as promising non-statin therapeutic options for the management of hypercholesterolemia. This review provides a brief overview of the history and science of PCSK9 inhibitors, focusing on two PCSK9 monoclonal antibodies that have been approved by the US Food and Drug Administration: alirocumab and evolocumab. Recently released and forthcoming clinical trial data will be discussed, as well as the practical application of patient populations that may benefit from PCSK9 inhibitors. Finally, the recent expert recommendations regarding the use of PCSK9 inhibitors and other non-statin therapies to treat patients with inadequate LDL-C-lowering on statin therapy will be summarized.

[66] *Shen H, Li R, Yan R et al.* **Adjunctive therapy with statins in schizophrenia patients: A meta-analysis and implications**. Psychiatry research 2018; 262:84-93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29427912
ABSTRACT
There are some conflicting results regarding the benefit of adjunctive therapy with statins for severity of negative symptoms in schizophrenia. This study aimed to verify whether statins use for adjunctive therapy was indeed beneficial to improve psychiatric symptoms in schizophrenia. The data were from CENTRAL, PubMed, Embase and MEDLINE. The Boolean search term used for the electronic database search was (statin OR simvastatin OR atorvastatin OR fluvastatin OR lovastatin OR mevastatin OR pitavastatin OR pravastatin OR rosuvastatin OR cerivastatin) and (schizophrenia OR schizoaffective disorder OR psychosis). Inclusion criteria were the following: RCTs, the adult schizophrenia patients, received antipsychotics plus statins or placebo, and the PANSS or SANS scores. Exclusion criteria were as follows: no data reported and multiple reports of the same study. A meta-analysis was used to compare psychiatric symptoms in schizophrenia patients with or without statins adjunctive therapy. The 6 RCTs included in the analysis represented 339 participants (169 in treatment group versus 170 in placebo group). A test for overall effect demonstrated that the PANSS positive scale and negative scale significantly reduced in participants receiving compliant with statins. Our meta-analyses first clarified that adjunctive therapy with statins could improve psychiatric symptoms, either negative symptoms or positive symptoms.

[67] McAuley DF, Laffey JG, O'Kane CM *et al.* Efficacy and Mechanism Evaluation. In: Simvastatin to reduce pulmonary dysfunction in patients with acute respiratory distress syndrome: the HARP-2 RCT. Southampton (UK): NIHR Journals Library

[68] *Fomin VV, Svistunov AA, Napalkov DA et al.* **[The new 2017 European society of cardiology (ESC) guidelines: important changes for introduction into clinical practice]**. Terapevticheskii arkhiv 2017; 89:4-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29411754
ABSTRACT
The paper gives an overview of the European Society of Cardiology (ESC) guidelines updated in 2017. The revised and amended guidelines for areas, such as dual antiplatelet therapy (DAT), treatment of patients with ST-segment elevation myocardial infarction (STEMI), and management of patients with valvular heart disease and peripheral artery disease, were presented in late summer of this year. The authors of this paper present an independent analysis and discussion of new data on the key issues of diagnosis and treatment in patients in the above areas. The recommendations on DAT pay special attention to the timing of the therapy and to the choice of its drugs. The updated data on the treatment of patients with STEMI accurately determine the time to percutaneous coronary interventions, approaches to revascularization; the updates touch upon fibrinolytic therapy and new approaches to lipid-lowering therapy too. Recommendations for the management of patients with peripheral artery atherosclerosis propose for the first time a section devoted to the choice of antiplatelet therapy (an antiaggregant and/or an anticoagulant) depending on the clinical situation.

[69] *Kobalava ZD, Villevalde SV, Vorobyeva MA*. **[Alirocoumab: new perspectives of lipid-lowering therapy]**. Terapevticheskii arkhiv 2017; 89:114-121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29411770
ABSTRACT
Alirocoumab (Praluent) is a fully human monoclonal antibody against proprotein covertase subtilisin/kexin type 9 (PCSK9). The data of ODYSSEY Phases II and III clinical trials demonstrate the high efficacy of alirocoumab in lowering the level of low-density lipoprotein (LDL) cholesterol in patients with primary hypercholesterolemia, with a considerable advantage over control groups (placebo, ezetimibe or modified statin therapy) in both monotherapy and combination therapy with statins and other lipid-lowering agents. Alirocoumab provides additional lipid-lowering effects against other atherogenic fractions of cholesterol, including non-high-density lipoprotein cholesterol, apolipoprotein B and lipoprotein (a). The agent show high safety and good tolerability and it can be considered as the drug of choice for patients who have not reached their target LDL cholesterol levels after statin therapy and have statin intolerance and familial heterozygous hypercholesterolemia. There are now the preliminary results of a secondary analysis of data from the ODYSSEY LONG TERM study, suggesting that

alirocoumab therapy may be accompanied by a lower risk of cardiovascular events. The final results will be provided after the data of a study of cardiovascular outcomes after therapy with alirocoumab versus placebo (ODYSSEY OUTCOMES) are published.

[70] *Podzolkov VI, Bragina AE, Osadchiy KK*. **[A fixed-dose lisinopril+amlodipine+rosuvastatin combination: prospects for its use in patients with hypertension and concomitant dyslipidemia]**. Terapevticheskii arkhiv 2017; 89:133-140.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29411773
ABSTRACT
In Russia, target blood pressure (BP) levels are achieved in only 14.4% of men and in 30.9% of women. The need for combination therapy of hypertension is as high as 70.7%. There are well-known benefits of combined antihypertensive therapy allowing for higher efficiency and better tolerability. One of the current combinations is a combination of an angiotensin-converting enzyme inhibitor and a calcium antagonist, which have pronounced protective activity and metabolic neutrality. Fixed-dose combinations have substantial advantages over free ones, contributing to improving patient compliance with the used treatment regimen. Dyslipidemia is present in 60.7% of the hypertensive patients. Nonetheless, only 9.7% of Russian patients with coronary heart disease take statins and control of lipid levels remains very poor. The review discusses whether the use of the triple combination lisinopril + amlodipine + rosuvastatin is reasonable from the standpoint of evidence-based medicine. There are literature data suggesting the high value of this fixed-dose combination in the context of organ protection and the reduced risk of cardiovascular events.

[71] *Lappegard KT, Kjellmo CA, Ljunggren S et al.* **Lipoprotein apheresis affects lipoprotein particle subclasses more efficiently compared to the PCSK9 inhibitor evolocumab, a 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=29398508
ABSTRACT
Lipoprotein apheresis and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are last therapeutic resorts in patients with familial hypercholesterolemia (FH). We explored changes in lipoprotein subclasses and high-density lipoprotein (HDL) function when changing treatment from lipoprotein apheresis to PCSK9 inhibition. We measured the levels of low-density lipoprotein (LDL) and HDL particle subclasses, serum amyloid A1 (SAA1), paraoxonase-1 (PON1) activity and cholesterol efflux capacity (CEC) in three heterozygous FH patients. Concentrations of all LDL particle subclasses were reduced during apheresis (large 68.0+/-17.5 to 16.3+/-2.1mg/dL, (p=0.03), intermediate 38.3+/-0.6 to 5.0+/-3.5mg/dL (p=0.004) and small 5.0+/-2.6 to 0.2+/-0.1mg/dL (p=0.08)). There were non-significant reductions in the LDL subclasses during evolocumab treatment. There were non-significant reductions in subclasses of HDL particles during apheresis, and no changes during evolocumab treatment. CEC was unchanged throughout the study, while the SAA1/PON1 ratio was unchanged during apheresis but decreased during evolocumab treatment. In conclusion, there were significant reductions in large and intermediate size LDL particles during apheresis, and a non-significant reduction in

small LDL particles. There were only non-significant reductions in the LDL subclasses during evolocumab treatment.

[72] *Yildizeli SO, Balcan B, Eryuksel E et al.* **Influence of Statin Therapy on Exacerbation Frequency in Patients with Chronic Obstructive Pulmonary Disease**. Turkish thoracic journal 2017; 18:29-32.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29404156
ABSTRACT
OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is an inflammatory disease, in which chronic and systemic inflammation plays an important role. By decreasing neutrophil infiltration and cytokine production, statins have anti-inflammatory mechanisms. MATERIALS AND METHODS: Fifty-seven patients who had diagnosis of chronic obstructive pulmonary disease according to GOLD guideline were included in the study; 20 of them were statin users. Statin users group were patients being under medication with regular simvastatin, atorvastatin or rosuvastatin 20 mg per day for at least the past 1 year. RESULTS: There was statistically no significant difference between patients with or without statin treatment with respect to; age, female-male ratio, COPD severity level, medication used for COPD, pulmonary function tests results and smoking habits. COPD exacerbation frequency in patients using statins was significantly less than patients not using statins ($p<0.05$). Patient number with COPD exacerbation, antibiotic treatment and outpatient clinic administration and outpatient clinic administration frequency was significantly lower in statin using patients ($p<0.05$). CONCLUSION: COPD patients receiving statins have a lower frequency of COPD exacarbations, hospital administration and antibiotic treatment compared to patients not receiving statins.

[73] *Cohen AJ, Adamsky MA, Nottingham CU et al.* **Impact of Statin Intake on Kidney Stone Formation**. Urology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29421299
ABSTRACT
OBJECTIVES: To determine whether statin intake affects nephrolithiasis risk, and whether higher lipid levels correlate with stone risk. Dyslipidemia is a known independent risk factor for urolithiasis, and emerging evidence suggests common biological pathways. Previous work has suggested that statins protect against new stone formation, but these findings have not been verified by other investigators. METHODS: We queried our Institution's Electronic Data Warehouse for all patients who were newly diagnosed with hyperlipidemia between 2009 and 2011, and had never taken a statin drug. These patients' clinical outcomes were followed until 2015, to assess whether they had been newly prescribed statins and whether they had developed symptomatic urolithiasis. Patient demographics, stone risk factors, prescription data, and serum lipid values were collected. RESULTS: 101,259 patients met inclusion criteria, 47.8% of whom received a statin prescription during the study period. Patients prescribed statins were significantly older, had a greater likelihood of osteoporosis, hemiplegia, immobility, and more likely to take a thiazide diuretic. Patients without a history of urolithiasis who were started on statin therapy were significantly less likely to develop new stones than patients not taking statins. This protective effect was even greater in patients with a history of stone disease. Lipid parameters (LDL, TG, cholesterol) were lower in the statin-treated group, suggesting overall

compliance with these medications. CONCLUSIONS: Our data confirms previous work that statins protect against urinary stone formation, however the underlying mechanism seems to be distinct from statins' lipid-lowering effect.

[74] *Gebauer K, Reinecke H*. **PCSK9 inhibition for LDL lowering and beyond - implications for patients with peripheral artery disease**. VASA. Zeitschrift fur Gefasskrankheiten 2018:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29412075
ABSTRACT
Low-density lipoprotein cholesterol (LDL-C) has been proven to be a causal factor of atherosclerosis and, along with other triggers like inflammation, the most frequent reason for peripheral arterial disease. Moreover, a linear correlation between LDL-C concentration and cardiovascular outcome in high-risk patients could be established during the past century. After the development of statins, numerous randomized trials have shown the superiority for LDL-C reduction and hence the decrease in cardiovascular outcomes including mortality. Over the past decades it became evident that more intense LDL-C lowering, by either the use of highly potent statin supplements or by additional cholesterol absorption inhibitor application, accounted for an even more profound cardiovascular risk reduction. Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serin protease with effect on the LDL receptor cycle leading to its degradation and therefore preventing continuing LDL-C clearance from the blood, is the target of a newly developed monoclonal antibody facilitating astounding LDL-C reduction far below to what has been set as target level by recent ESC/EAS guidelines in management of dyslipidaemias. Large randomized outcome trials including subjects with PAD so far have been able to prove significant and even more intense cardiovascular risk reduction via further LDL-C debasement on top of high-intensity statin medication. Another approach for LDL-C reduction is a silencing interfering RNA muting the translation of PCSK9 intracellularly. Moreover, PCSK9 concentrations are elevated in cells involved in plaque composition, so the potency of intracellular PCSK9 inhibition and therefore prevention or reversal of plaques may provide this mechanism of action on PCSK9 with additional beneficial effects on cells involved in plaque formation. Thus, simultaneous application of statins and PCSK9 inhibitors promise to reduce cardiovascular event burden by both LDL-C reduction and pleiotropic effects of both agents.

[75] *Madonna R, Pieragostino D, Balistreri CR et al.* **Diabetic macroangiopathy: Pathogenetic insights and novel therapeutic approaches with focus on high glucose-mediated vascular damage**. Vascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29425894
ABSTRACT
Diabetic macroangiopathy - a specific form of accelerated atherosclerosis - is characterized by intra-plaque new vessel formation due to excessive/abnormal neovasculogenesis and angiogenesis, increased vascular permeability of the capillary vessels, and tissue edema, resulting in frequent atherosclerotic plaque hemorrhage and plaque rupture. Mechanisms that may explain the premature and rapidly progressive nature of atherosclerosis in diabetes are multiple, and to a large extent still unclear. However, mechanisms related to hyperglycemia certainly play an important role. These include a dysregulated vascular regeneration. In addition, oxidative and hyperosmolar stresses, as well as the activation of inflammatory

pathways triggered by a dysregulated activation of membrane channel proteins aquaporins, have been recognized as key events. Here, we review recent knowledge of cellular and molecular pathways of macrovascular disease related to hyperglycemia in diabetes. We also here highlight how new insights into pathogenic mechanisms of vascular damage in diabetes may indicate new targets for prevention and treatment.

[76] *To MS, Prakash S, Poonnoose SI, Bihari S*. **Dose-dependent effects of statins for patients with aneurysmal subarachnoid hemorrhage: meta-regression analysis**. World neurosurgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29425980
ABSTRACT
OBJECTIVE: The study utilizes meta-regression analysis to quantify the dose-dependent effects of statin pharmacotherapy on vasospasm, delayed ischemic neurologic deficits (DINDs) and mortality in aneurysmal subarachnoid hemorrhage (aSAH). METHODS: Prospective, retrospective observational studies and randomized controlled trials (RCTs) were retrieved by a systematic database search. Summary estimates were expressed as absolute risk (AR) for a given statin dose or control (placebo). Meta-regression using inverse variance weighting and robust variance estimation was performed to assess the effect of statin dose on transformed AR in a random effects model. Dose-dependence of predicted AR with 95% confidence interval (CI) was recovered using Miller's Freeman-Tukey inverse. RESULTS: The database search and study selection criteria yielded 18 studies (2594 patients) for analysis. These included twelve RCTs, four retrospective observational studies and two prospective observational studies. Twelve studies investigated simvastatin, while the remaining studies investigated atorvastatin, pravastatin or pitavastatin, with simvastatin equivalent doses ranging from 20 mg to 80 mg. Meta-regression revealed dose-dependent reductions in Freeman-Tukey transformed absolute risk of vasospasm (slope coefficient -0.00404, 95% CI -0.00720 to -0.00087; p = 0.0321), DINDs (slope coefficient -0.00316, 95% CI -0.00586 to -0.00047; p = 0.0392), and mortality (slope coefficient -0.00345, 95% CI -0.00623 to -0.00067; p = 0.0352). CONCLUSIONS: The present meta-regression provides weak evidence for dose-dependent reductions in vasospasm, DINDs and mortality associated with acute statin use following aSAH. However, the analysis was limited by substantial heterogeneity among individual studies. Higher dosing strategies are a potential consideration for future RCTs.