Literature update week 27 (2019)

[1] *Roh JW, Chun KH, Kang M et al.* **PRavastatin versus FlUVastatin after Statin Intolerance: The PRUV-Intolerance Study with Propensity Score Matching**. The American journal of medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31278931
ABSTRACT
BACKGROUND: Limited data are available on the relapse of statin intolerance after resumption of statins. We aimed to evaluate the relapse rates of statin intolerance in patients who subsequently received pravastatin or fluvastatin and to identify associated factors. METHODS: This retrospective, propensity score-matched cohort study screened data obtained from a tertiary university hospital between 2006 and 2015. Of 8073 patients screened, 488 with statin intolerance who received pravastatin or fluvastatin with regular follow-up were enrolled. After propensity score matching of patients, 384 were finally analyzed. The primary outcome variables were relapse of statin intolerance and stopping (discontinuation or switching to other statins) rate for the two statins. RESULTS: During the median follow-up period of 37 months, the rate of relapse of intolerance was 10.4% and 18.2% among users of pravastatin and fluvastatin, respectively (p=0.04). However, the log-rank test showed no difference in the relapse-free rates between the two groups (p=0.34). The stopping rates of the two statins were 36.5% and 42.2% (p=0.30), respectively, for various reasons, including low efficacy of the drugs. After adjustment, chronic kidney disease (hazard ratio [HR] 1.83, p=0.03) and previous creatine kinase elevation (HR 3.13, p=0.001) were identified as independent determinants of relapse. Older age (HR 1.03, p=0.057) and female sex (HR 1.70, p=0.059) were associated, but not significantly, with relapse. CONCLUSION: Although small proportion of patients taking pravastatin or fluvastatin experienced a relapse of intolerance, many patients eventually discontinued or changed these agents. Chronic kidney disease and history of creatine kinase elevation were independent determinants of relapse.

[2] *Lou PH, Lucchinetti E, Hersberger M et al.* **Lipid Emulsion Containing High Amounts of n3 Fatty Acids (Omegaven) as Opposed to n6 Fatty Acids (Intralipid) Preserves Insulin Signaling and Glucose Uptake in Perfused Rat Hearts**. Anesthesia and analgesia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31274599
ABSTRACT
BACKGROUND: It is currently unknown whether acute exposure to n3 fatty acid-containing fish oil-based lipid emulsion Omegaven as opposed to the n6 fatty acid-containing soybean oil-based lipid emulsion Intralipid is more favorable in terms of insulin signaling and glucose uptake in the intact beating heart. METHODS: Sprague-Dawley rat hearts were perfused in the working mode for 90 minutes in the presence of 11 mM glucose and 1.2 mM palmitate bound to albumin, the first 30 minutes without insulin followed by 60 minutes with insulin (50 mU/L). Hearts were randomly allocated to 100 microM Intralipid, 100 microM Omegaven, or no emulsion (insulin treatment alone) for 60 minutes. Glycolysis and glycogen synthesis were measured with the radioactive tracer [5-H]glucose, and glucose uptake was calculated. Phosphorylation of protein phosphatase 2A (PP2A), protein kinase Akt, and phosphofructokinase (PFK)-2 was measured by immunoblotting. Glycolytic metabolites were determined by enzymatic assays. Mass spectrometry was used to establish acylcarnitine profiles. Nuclear factor kappaB (NFkappaB) nuclear translocation served as reactive oxygen

species (ROS) biosensor. RESULTS: Insulin-mediated glucose uptake was decreased by Intralipid (4.9 +/- 0.4 vs 3.7 +/- 0.3 mumol/gram dry heart weight [gdw].min; P = .047) due to both reduced glycolysis and glycogen synthesis. In contrast, Omegaven treatment did not affect insulin-mediated glycolysis or glycogen synthesis and thus preserved glucose uptake (5.1 +/- 0.3 vs 4.9 +/- 0.4 mumol/gdw.min; P = .94). While Intralipid did not affect PP2A phosphorylation status, Omegaven resulted in significantly enhanced tyrosine phosphorylation and inhibition of PP2A. This was accompanied by increased selective threonine phosphorylation of Akt and the downstream target PFK-2 at S483. PFK-1 activity was increased when compared with Intralipid as measured by the ratio of fructose 1,6-bisphosphate to fructose 6-phosphate (Omegaven 0.60 +/- 0.11 versus Intralipid 0.47 +/- 0.09; P = .023), consistent with increased formation of fructose 2,6-bisphosphate by PFK2, its main allosteric activator. Omegaven lead to accumulation of acylcarnitines and fostered a prooxidant response as evidenced by NFkappaB nuclear translocation and activation. CONCLUSIONS: Omegaven as opposed to Intralipid preserves glucose uptake via the PP2A-Akt-PFK pathway in intact beating hearts. n3 fatty acids decelerate beta-oxidation causing accumulation of acylcarnitine species and a prooxidant response, which likely inhibits redox-sensitive PP2A and thus preserves insulin signaling and glucose uptake.

[3] *Malo J, Parajuli A, Walker S*. **ANNALS EXPRESS: PCSK9: from molecular biology to clinical applications**. Annals of clinical biochemistry 2019:4563219864379.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31257903
ABSTRACT
Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease with a key role in regulating plasma low-density lipoprotein (LDL) concentration. Since its discovery via parallel molecular biology and clinical genetics studies in 2003, work to characterise PCSK9 has shed new light on the life-cycle of the LDL receptor and the molecular basis of Familial Hypercholesterolaemia (FH). These discoveries have also led to the advent of the PCSK9 inhibitors, a new generation of LDL cholesterol (LDL-C) lowering drugs. Clinical trials have shown these agents to be both safe and capable of unprecedented reductions in LDL-C, and it is hoped they may herald a new era of cardiovascular disease prevention. As such, the still evolving PCSK9 story serves as a particularly successful example of translational medicine. This review provides a summary of the principal PCSK9 research findings, which underpin our current understanding of its function and clinical relevance. Keywords: cardiovascular disease, Familial Hypercholesterolaemia, lipids, LDL-C, PCSK9, PCSK9 inhibitor.

[4] *Breuninger TA, Wawro N, Meisinger C et al.* **Associations between fecal bile acids, neutral sterols, and serum lipids in the KORA FF4 study**. Atherosclerosis 2019; 288:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31277007
ABSTRACT
BACKGROUND AND AIMS: Dyslipidemia is a major risk factor for cardiovascular disease, the leading cause of preventable death worldwide. As a result, a full understanding of the factors influencing dyslipidemia is urgently necessary. Bile acids have been recognized as regulators of lipid metabolism, and neutral sterols may influence serum lipid levels. Therefore, this analysis was conducted to better understand the relationship between bile acids, neutral sterols, and

dyslipidemia. METHODS: We examined cross-sectional associations between selected fecal metabolites and serum lipids or markers of dyslipidemia in 1387 participants of the KORA FF4 study using linear and logistic regression models. RESULTS: We found positive associations between fecal bile acids and serum high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-c), total cholesterol, triglycerides and markers of dyslipidemia, though associations were seen most consistently with triglycerides and hypertriglyceridemia. We also found positive associations between fecal cholesterol and serum LDL-c, total cholesterol, triglycerides, hypertriglyceridemia and high serum total cholesterol, though only associations with triglycerides or hypertriglyceridemia remained significant after applying the Bonferroni correction. Unexpectedly, several fecal plant sterols were positively associated with serum lipids and the associated markers of dyslipidemia. However, many of these associations were no longer statistically significant after adjusting for multiple testing. CONCLUSIONS: Our results provide insight into the role that bile acids may play in the development or progression of dyslipidemia. However, further confirmation of these results is warranted. Longitudinal and experimental studies are necessary to clarify the mechanisms behind these associations and to determine causality.

[5] *Liu X, Sun C, Gu X et al.* **Intraplaque neovascularization attenuated statin benefit on atherosclerotic plaque in CAD patients: A follow-up study with combined imaging modalities**. Atherosclerosis 2019; 287:134-139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272069
ABSTRACT
BACKGROUND AND AIMS: Plaque progression increases the risk of a cardiovascular event. This study aims to determine whether intraplaque neovascularization (NV) associates with a greater risk of plaque progression. METHODS: Baseline and 12-month follow-up IVUS was used in combination with baseline OCT to assess 164 non-culprit plaques in 118 CAD patients. A generalized estimating equation approach with exchangeable correlation structure was used to correct for the dependency of repeated measurements. RESULTS: Patients were divided into two groups according to NV (52 patients with 62 NV plaques, 66 patients with 102 non-NV plaques). Non-culprit plaques in the NV group exhibited a more frequent occurrence of TCFA (p=0.004), macrophage (p=0.005), cholesterol crystal (p=0.012), calcification (p=0.030), thinner fibrous cap thickness (FCT) [(86.8+/-55.1) vs. (127.4+/-70.1) mum, p=0.015], larger lipid arc [(219.5+/-66.9) vs. (179.8+/-61.4), p=0.002] compared to the non-NV group. A large change in percent atheroma volume (PAV), plaque plus media cross-sectional area (P&M CSA), plaque volume, and plaque burden was observed from baseline to follow-up in the NV group. Changes in P&M CSA, plaque volume, and plaque burden showed significant differences in fibroatheroma with NV. Intraplaque NV could predict a high risk of plaque progression despite statin therapy [OR 6.521 (95% CI 2.457-17.308), p<0.001]. CONCLUSIONS: NV might attenuate the benefits of statin therapy in plaque progression. This study may provide a new basis for anti-angiogenic strategies to prevent atherosclerotic plaque progression.

[6] *Lee MC, Cheng KJ, Chen SM et al.* **A novel preventive mechanism of gentamicin-induced nephrotoxicity by atorvastatin**. Biomedical chromatography : BMC 2019:e4639.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31256419

ABSTRACT
Atorvastatin (ATO) inhibited the synthesis of non-steroidal isoprenoid compounds and possessed pleiotropic effect. However, the detailed mechanism of ATO in preventing gentamicin (GM)-induced renal injury remained obscure. Although underlying multifaceted mechanisms involving in GM-induced nephrotoxicity were well known, further work on elucidating the essential mechanism was needed. By using fluorogenic derivatization-liquid chromatography tandem mass spectrometry proteomic method (FD-LC-MS/MS method), we investigated the effects and mechanisms of ATO treatment on GM-induced nephrotoxicity rats. Consequently, 49 differentially expressed proteins were identified. The most significant mechanisms of nephrotoxicity caused by GM were mitochondrial dysfunction, fatty acid metabolism and oxidative stress. Their upstream regulator was also found to be PPARalpha. The proteins involving in GM nephrotoxicity were sodium-hydrogen exchanger regulatory factor (SLC9A3R1), cathepsin V (CTSV), macrophage Migration Inhibitory Factor (MIF) and RhoGDP dissociation inhibitor alpha (ARHGDIA). After ATO intervention, we observed a reverse enrichment pattern of the expression of them, especially in CTSV and SLC9A3R1 (p-value<0.05). We predicted ATO may improve abnormal phospholipid metabolism and phospholipidosis caused by GM and also alleviate cell volume homeostasis and reverse the interference of GM to the transporter. Furthermore, proteomic results also provided clues for GM-induced nephrotoxicity biomarkers such as CTSV and transthyretin.

[7] *Ellul S, Wake M, Clifford SA et al.* **Metabolomics: population epidemiology and concordance in Australian children aged 11-12 years and their parents**. BMJ open 2019; 9:106-117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31273021

ABSTRACT
OBJECTIVES: Nuclear magnetic resonance (NMR) metabolomics is high throughput and cost-effective, with the potential to improve the understanding of disease and risk. We examine the circulating metabolic profile by quantitative NMR metabolomics of a sample of Australian 11-12 year olds children and their parents, describe differences by age and sex, and explore the correlation of metabolites in parent-child dyads. DESIGN: The population-based cross-sectional Child Health CheckPoint study nested within the Longitudinal Study of Australian Children. SETTING: Blood samples collected from CheckPoint participants at assessment centres in seven Australian cities and eight regional towns; February 2015-March 2016. PARTICIPANTS: 1180 children and 1325 parents provided a blood sample and had metabolomics data available. This included 1133 parent-child dyads (518 mother-daughter, 469 mother-son, 68 father-daughter and 78 father-son). OUTCOME MEASURES: 228 metabolic measures were obtained for each participant. We focused on 74 biomarkers including amino acid species, lipoprotein subclass measures, lipids, fatty acids, measures related to fatty acid saturation, and composite markers of inflammation and energy homeostasis. RESULTS: We identified differences in the concentration of specific metabolites between childhood and adulthood and in metabolic profiles in children and adults by sex. In general, metabolite concentrations were higher in adults than children and sex differences were larger in adults than in children. Positive correlations were observed for the majority of metabolites including isoleucine (CC 0.33, 95% CI 0.27 to 0.38), total cholesterol (CC 0.30, 95% CI 0.24 to 0.35) and omega 6 fatty acids (CC 0.28, 95% CI 0.23 to 0.34) in parent-child comparisons. CONCLUSIONS: We describe the serum

metabolite profiles from mid-childhood and adulthood in a population-based sample, together with a parent-child concordance. Differences in profiles by age and sex were observed. These data will be informative for investigation of the childhood origins of adult non-communicable diseases and for comparative studies in other populations.

[8] *Dai W, Tham YC, Chee ML et al.* **Systemic medications and cortical cataract: the Singapore Epidemiology of Eye Diseases Study**. The British journal of ophthalmology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272959
ABSTRACT
BACKGROUND/AIMS: To evaluate the association between systemic medications and cortical cataract prevalence in an Asian population. METHODS: The Singapore Epidemiology of Eye Diseases Study recruited 10 033 Chinese, Malay and Indian residents aged 40+ years living in Singapore. Information on medication use was collected at interview using questionnaires. The presence and severity of cortical cataract were assessed from lens photographs using the modified Wisconsin Cataract Grading System. Associations between medications and the presence of cortical cataract were assessed using logistic regression. Associations between medications and greater severity of cortical cataract (none, minimal, early and late) were assessed using ordinal logistic regression. RESULTS: A total of 8965 participants were included, the mean age was 57.6 (SD=9.8) years, and 4555 (50.8%) were women. After adjusting for age, gender, ethnicity, body mass index, smoking status, socioeconomic status, hypertension, hyperlipidaemia, diabetes, duration of diabetes and cardiovascular disease, ACE inhibitors (OR=1.27; 95% CI 1.05 to 1.55), fibrates (OR=1.57; 95% CI 1.05 to 2.35), alpha-glucosidase inhibitors (AGIs) (OR=1.85; 95% CI 1.13 to 3.02) and insulin (OR=1.80; 95% CI 1.11 to 2.93) were significantly associated with the presence of cortical cataract. Further adjusting for concurrent medication use did not alter these associations. Consistently, the four medications were also associated with a greater severity level of cortical cataract. CONCLUSION: ACE inhibitors, fibrates and AGIs were associated with increased prevalence of cortical cataract in this Asian population, independent of the presence of hypertension, hyperlipidaemia and diabetes, respectively. Whether they contribute to the risk of cortical cataract needs confirmation in longitudinal studies.

[9] *Hsieh CC, Li CY, Hsu CH et al.* **Mitochondrial protection by simvastatin against Angiotensin II-mediated heart failure**. Br J Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31265743
ABSTRACT
BACKGROUND AND PURPOSE: Mitochondrial dysfunction plays a role in the progression of cardiovascular diseases including heart failure. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), which inhibit reactive oxygen species (ROS) synthesis, show cardioprotective effects in chronic heart failure. However, the beneficial role of statins in mitochondrial protection in heart failure remains unclear. EXPERIMENTAL APPROACH: Rats were treated with Angiotensin II (Ang II) (1.5 mg/kg/day) or co-administered simvastatin (oral, 10 mg/kg) for 14 days; and then administration was stopped for the following 14 days. Cardiac structure/function was examined by wheat germ agglutinin staining and echocardiography. Mitochondrial morphology and the numbers of lipid droplets, lysosomes, autophagosomes, and

mitophagosomes were determined by transmission electron microscopy. Human cardiomyocytes were stimulated and intracellular ROS and mitochondrial membrane potential (DeltaPsim) changes were measured by flow cytometry and JC-1 staining, respectively. Autophagy and mitophagy-related and mitochondria-regulated apoptotic proteins were identified by immunohistochemistry and western blotting. KEY RESULTS: Simvastatin significantly reduced ROS production and attenuated the disruption of DeltaPsim. Simvastatin induced the accumulation of lipid droplets to provide energy for maintaining mitochondrial function, promoted autophagy and mitophagy, and inhibited mitochondria-mediated apoptosis. These findings suggest that mitochondrial protection mediated by simvastatin plays a therapeutic role in heart failure prevention by modulating antioxidant status, and promoting energy supplies for autophagy and mitophagy to inhibit mitochondrial damage and cardiomyocyte apoptosis. CONCLUSION AND IMPLICATIONS: Mitochondria play a key role in mediating heart failure progression. Simvastatin attenuated Ang II-induced heart failure via mitochondrial protection and might provide a new therapy for heart failure prevention.

[10] *Harborg S, Cronin-Fenton DP, Borgquist S*. **RE.: Impact of long-term lipid-lowering therapy on clinical outcomes in breast cancer**. Breast cancer research and treatment 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31270762
ABSTRACT

[11] *Devuyst S, Gigase A, Spapen J et al.* **Impact of non-invasive anatomical testing on optimal medical prescription in patients with suspected coronary artery disease**. Cardiovascular diagnosis and therapy 2019; 9:221-228.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31275812
ABSTRACT
Background: Compared to functional testing, coronary computed tomography angiography (CTA) improves clinical outcomes in patients with suspected coronary artery disease (CAD). This is thought to be the result of an increased prescription of preventive medical therapy (statins and aspirin) when relying on a CTA imaging strategy. We compared the rate of statins prescription in a patient cohort assessed either with coronary CTA or exercise testing, and evaluated the agreement on medication prescriptions. Methods: Consecutive patients who underwent coronary CTA and exercise test for suspected CAD were included. Four clinical cardiologists independently analysed each case based on clinical information and the result of either coronary CTA or exercise test. For each case, treatment strategy and prescription were recorded while blinded to the results of the other cardiac test. Treatment strategy was reassessed using the alternative imaging modality three weeks after the first evaluation. Results: A total of 113 patients were included. Mean age was 56.7+/-11.5 years, 52% were males and diabetes were present in 6%. Coronary CTA showed an obstructive epicardial stenosis in 21.4% and any type of atherosclerotic plaque in 54.2%. Functional testing identified ischemia in 9.1%. The use of coronary CTA resulted in higher number of statin (64.9% vs. 44.5%, P<0.001) and aspirin (21.4% vs. 4.3%, P<0.001) prescriptions. There was a substantial agreement on the prescription of statins (mean Cohen's kappa coefficient of 0.79+/-0.07). Conclusions: Epicardial atherosclerotic disease was found in half of patients with suspected CAD

as assessed by coronary CTA. Compared to functional testing, coronary CTA evaluation by coronary was associated with an increase in the rate preventive therapy prescription.

[12] *Su X, Luo M, Tang X et al.* **Goals of non-high density lipoprotein cholesterol need to be adjusted in Chinese acute coronary syndrome patients: Findings from the CCC-ACS project**. Clinica chimica acta; international journal of clinical chemistry 2019; 496:48-54.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31255567
ABSTRACT
BACKGROUND: Guidelines recommended non-high density lipoprotein cholesterol (non-HDL-C) as a co-primary target, and set non-HDL-C goals as 30mg/dl higher than low-density lipoprotein cholesterol (LDL-C) goals. However, the value is largely uncertain in Chinese patients. METHODS: We assigned non-HDL-C values at the same percentiles correspondent to LDL-C goals for patients from the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) Project. We calculated the differences between non-HDL-C and LDL-C and proposed appropriate adding values according to LDL-C and TG concentrations. RESULTS: Among 73,495 patients, 17.7% used lipid-lowering agents before admission. Of these, 27.2% achieved LDL-C <70mg/dl while 39.4% achieved non-HDL-C <100mg/dl. The mean difference between non-HDL-C and LDL-C was 23.2mg/dl, which could be affected by LDL-C and TG concentrations. Importantly, of patients with LDL-C concentrations </=100mg/dl, the mean differences were 19.1mg/dl in patients with TG </=150mg/dl and 24.6mg/dl in patients with TG >150mg/dl. CONCLUSIONS: There are significant differences between LDL-C and non-HDL-C in Chinese ACS patients. For secondary prevention, on average, the adding values should be 20mg/dl for patients with TG </=150mg/dl and 25mg/dl for patients with TG >150mg/dl when LDL-C goals of 70mg/dl is achieved.

[13] *Olson EJ, Mahar KM, Haws TF et al.* **A Randomized, Placebo-Controlled Trial to Assess the Effects of 8 Weeks of Administration of GSK256073, a Selective GPR109A Agonist, on High-Density Lipoprotein Cholesterol in Subjects With Dyslipidemia**. Clinical pharmacology in drug development 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31268250
ABSTRACT
GPR109A (HM74A), a G-protein-coupled receptor, is hypothesized to mediate lipid and lipoprotein changes and dermal flushing associated with niacin administration. GSK256073 (8-chloro-3-pentyl-1H-purine-2,6[3H,7H]-dione) is a selective GPR109A agonist shown to suppress fatty acid levels and produce mild flushing in short-term clinical studies. This study evaluated the effects of GSK256073 on lipids in subjects with low high-density lipoprotein cholesterol (HDLc). Subjects (n = 80) were randomized (1:1:1:1) to receive GSK256073 5, 50, or 150 mg/day or matching placebo for 8 weeks. The primary end point was determining the GSK256073 exposure-response relationship for change from baseline in HDLc. No significant exposure response was observed between GSK256073 and HDLc levels. GSK256073 did not significantly alter HDLc levels versus placebo, but rather revealed a trend at the 150-mg dose for a nonsignificant decrease in HDLc (-6.31%; P = .12) and an increase in triglycerides (median, 24.4%; 95% confidence interval, 7.3%-41.6%). Flushing was reported in 21%, 25%, and 60% of subjects (5, 50, and 150 mg, respectively) versus 24% for placebo. Results indicated that

selective activation of the GPR109A receptor with GSK256073 did not produce niacin-like lipid effects. These findings add to the increasing evidence that niacin-mediated lipoprotein changes occur predominantly via GPR109A-independent pathways.

[14] *Kelion AD*. **Commentary on myocardial CT perfusion imaging and atherosclerotic plaque characteristics on coronary CT angiography for the identification of myocardial ischaemia**. Clinical radiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272600
ABSTRACT

[15] *Lushington GH, Barnes AC*. **Protein glycation: An old villain is shedding secrets**. Combinatorial chemistry & high throughput screening 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272349
ABSTRACT
The glycation of proteins is a non-physiological post-translational incorporation of carbohydrates onto the free amines or guanidines of proteins and some lipids. Although the existence of glycated proteins has been known for forty years, a full understanding of their pathogenic nature has been slow in accruing. In recent years, however, glycation has gained wide-spread acceptance as a contributing factor in numerous metabolic, autoimmune and neurological disorders, tying together several confounding aspects of disease etiology. From diabetes, arthritis and lupus, to multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases, an emerging glycation / inflammation paradigm now offers significant new insight into a physiologically important toxicological phenomenon. It exposes novel drug targets and treatment options, and may even lay foundations for long-awaited breakthroughs. This 'current frontier' article briefly profiles current knowledge regarding the underlying causes of glycation, the structural biology implications of such modifications and their pathological consequences. Although several emerging therapeutic strategies for addressing glycation pathologies are introduced, the primary purpose of this mini-review is to raise awareness of the challenges and opportunities inherent in this emerging new medicinal target area.

[16] *Liu L, Huo C, Sun H et al.* **Vascular morphology has no direct relationship to atherosclerotic plaque burden in patients with symptomatic middle cerebral artery stenosis**. Current neurovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31258086
ABSTRACT
BACKGROUND: The vascular morphology and the characteristics of atherosclerotic plaques in the middle cerebral artery (MCA) have not been fully studied with high-resolution magnetic resonance imaging (HR-MRI). PURPOSE: HR-MRI was applied to investigate vascular morphology and atherosclerotic plaque in patients with symptomatic MCA stenosis. MATERIALS AND METHODS: A total of 343 patients with symptomatic MCA stenosis were enrolled in this study. All patients were examined by HR-MRI to analyze the morphology of MCA and the M1 segment (MCA-M1), the characteristics and the location of the plaques. RESULTS: The proportion of L-shaped MCA-M1 decreased, and the proportion of S-shaped MCA-M1 increased with age. The anterior plaques were the most common in all patients. The superior plaques

were relatively common in patients with L-shaped and U-shaped MCA-M1, while the inferior plaques were relatively common in patients with inverted U-shaped and S-shaped MCA-M1. Among all the plaques, the majority were isointense or heterogeneous. The MCA-M1 morphology had no direct relationship with the common risk factors of atherosclerosis and the clinical outcomes of the patients after 12 months of follow up. CONCLUSION: The morphology of MCA-M1 is not directly related to the plaque burden or the degree of stenosis in patients with symptomatic MCA stenosis. The morphology of MCA-M1 is not associated with the risk factors of atherosclerosis, or the clinical outcomes of the patients.

[17] *Lee YK, Kwak HS, Chung GH, Hwang SB*. **Lipid-Rich Necrotic Core of Basilar Artery Atherosclerotic Plaque: Contrast-Enhanced Black Blood Imaging on Vessel Wall Imaging**. Diagnostics (Basel, Switzerland) 2019; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31269676
ABSTRACT
PURPOSE: We wished to evaluate the lipid-rich necrotic core (LRNC) using contrast-enhanced T1-weighted (CE-T1W) black-blood (BB) imaging for vessel walls. METHODS: Ninety-five patients with basilar artery (BA) stenosis who underwent magnetic resonance angiography between January 2016 and August 2018 were enrolled into this present study. CE-T1W BB imaging was considered as a reference method for identifying an LRNC. RESULTS: Ten (10.5%) patients were identified as having an LRNC on CE-T1W BB imaging. Of these patients, 9 had acute symptoms. The extent of stenosis in patients with an LRNC on CE-T1W BB imaging was significantly greater than that of patients without an LRNC ($p < 0.001$). The maximum wall thickness in patients with an LRNC on CE-T1W imaging was significantly thicker than that of patients without an LRNC ($p = 0.008$). CONCLUSIONS: Identification of an LRNC on CE-T1W BB imaging was associated with high-grade stenosis and massive plaque burden from BA atherosclerosis.

[18] *Wawruch M, Wimmer G, Jr., Murin J et al.* **Patient-Associated Characteristics Influencing the Risk for Non-Persistence with Statins in Older Patients with Peripheral Arterial Disease**. Drugs Aging 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31256366
ABSTRACT
BACKGROUND AND OBJECTIVES: Secondary prevention of peripheral arterial disease includes administration of statins regardless of the patient's serum cholesterol level. Our study aimed to identify patient-associated risk factors for statin non-persistence and comparison of the explanatory power of models based on clusters of patient-associated characteristics. METHODS: Our study cohort (n = 8330) was assembled from the database of the largest health insurance provider in the Slovak Republic. Statin users aged >/= 65 years in whom peripheral arterial disease was diagnosed during 2012 were included. Patients were followed for 5 years; those with a treatment gap period of at least 6 months without statin prescription were classified as "non-persistent". The risk factors for non-persistence were identified within six models (sociodemographic, cardiovascular events, comorbid conditions, statin-related characteristics, cardiovascular co-medication and full model) using Cox regression. The explanatory power of models was assessed using Harrell's C-index. RESULTS: At the end of the

follow-up, 35.7% of patients were found to be non-persistent. The full model had the highest explanatory power (C = 0.632). Female sex, atorvastatin and rosuvastatin as initially administered statins, being a new statin user and an increasing co-payment were associated with an increased risk for non-persistence. Increasing age, history of ischaemic stroke, diabetes mellitus, general practitioner as index prescriber, increasing overall number of medications and co-administration of certain cardiovascular co-medications were associated with a lower likelihood for non-persistence. CONCLUSIONS: Patients identified as high risk for non-persistence require special attention aimed at the improvement of their persistence with statin treatment.

[19] *Guedeney P, Giustino G, Sorrentino S et al.* **Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31270529
ABSTRACT
AIMS: The effect of low-density lipoprotein cholesterol-lowering therapy with alirocumab or evolocumab on individual clinical efficacy and safety endpoints remains unclear. We aimed to evaluate the efficacy and safety of alirocumab and evolocumab in patients with dyslipidaemia or atherosclerotic cardiovascular disease. METHODS AND RESULTS: We performed a review of randomized controlled trials (RCTs) comparing treatment with alirocumab or evolocumab vs. placebo or other lipid-lowering therapies up to March 2018. Primary efficacy endpoints were all-cause death, cardiovascular death, myocardial infarction (MI), and stroke. We estimated risk ratios (RR) and 95% confidence intervals (CI) using random effect models. We included 39 RCTs comprising 66 478 patients of whom 35 896 were treated with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (14 639 with alirocumab and 21 257 with evolocumab) and 30 582 with controls. Mean weighted follow-up time across trials was 2.3 years with an exposure time of 150 617 patient-years. Overall, the effects of PCSK9 inhibition on all-cause death and cardiovascular death were not statistically significant (P = 0.15 and P = 0.34, respectively). Proprotein convertase subtilisin-kexin type 9 inhibitors were associated with lower risk of MI (1.49 vs. 1.93 per 100 patient-year; RR 0.80, 95% CI 0.74-0.86; I2 = 0%; P < 0.0001), ischaemic stroke (0.44 vs. 0.58 per 100 patient-year; RR 0.78, 95% CI 0.67-0.89; I2 = 0%; P = 0.0005), and coronary revascularization (2.16 vs. 2.64 per 100 patient-year; RR 0.83, 95% CI 0.78-0.89; I2 = 0%; P < 0.0001), compared with the control group. Use of these PCSK9 inhibitors was not associated with increased risk of neurocognitive adverse events (P = 0.91), liver enzymes elevations (P = 0.34), rhabdomyolysis (P = 0.58), or new-onset diabetes mellitus (P = 0.97). CONCLUSION: Proprotein convertase subtilisin-kexin type 9 inhibition with alirocumab or evolocumab was associated with lower risk of MI, stroke, and coronary revascularization, with favourable safety profile.

[20] *Liu W, Yu J, Tian T et al.* **Meta-analysis of the efficacy of liraglutide in patients with type 2 diabetes accompanied by incipient nephropathy**. Experimental and therapeutic medicine 2019; 18:342-351.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31258671
ABSTRACT

The efficacy of liraglutide in patients with type 2 diabetes accompanied by early-stage nephropathy has remained to be fully elucidated. The present meta-analysis was performed to determine the clinical outcomes associated with liraglutide treatment. The PubMed, Ovid, Cochrane Library, Chinese National Knowledge Infrastructure and Wanfang databases were searched in October 2018 to identify randomized controlled trials of liraglutide for diabetes patients with early-stage nephropathy. The treatment effect was estimated by calculating the mean difference (MD). Heterogeneity was assessed using chi(2) and I(2) tests. In addition, risk of bias graphs and summaries were used to assess the quality of the trials included. A total of 13 randomized controlled trials were included in the present meta-analysis. In subjects with stage I-II diabetic nephropathy (DN), liraglutide had obvious advantages in lowering the urinary albumin-to-creatinine ratio [UACR; MD=-90.96, 95% confidence interval (CI)=-94.12 to -87.80, P<0.00001], urinary albumin excretion rate (UAER; MD=-64.86, 95% CI=-66.63 to -63.08, P<0.00001), serum creatinine (Scr; MD=-13.67, 95% CI=-17.88 to -9.46, P<0.00001). In subjects with stage-III DN, liraglutide had favorable effects on renal function (UACR: MD=-11.23, 95% CI=-13.14 to -9.32, P<0.00001; UAER: MD=-14.06; 95% CI=-6.93 to -11.18; P<0.00001; Scr: MD=-9.17, 95% CI=-14.61 to -3.72, P=0.0010) and exhibited anti-inflammatory effects (transforming growth factor-beta1: P<0.00001; tumor necrosis factor-alpha: P=0.006; interleukin-6: P<0.00001). Furthermore, liraglutide also reduced the blood lipid levels, body mass index and post-prandial blood glucose. The most common adverse effects of liraglutide were gastrointestinal tract reactions and hypoglycemia, but these symptoms resolved quickly. Liraglutide appears to be effective in reducing proteinuria, improving renal function, producing an anti-inflammatory effect and ameliorating glucose and lipid metabolism in diabetic patients with early-stage nephropathy.

[21] *Hafez M, Musa N, Abdel Atty S et al.* **Effect of Vitamin D Supplementation on Lipid Profile in Vitamin D-Deficient Children with Type 1 Diabetes and Dyslipidemia**. Hormone research in paediatrics 2019:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31266036
ABSTRACT
BACKGROUND: Vitamin D (VD) was suggested to have both direct and indirect effects on modifying lipid profile in patients with diabetes through its regulatory action that increases the activity of lipoprotein lipase in adiposity. OBJECTIVES: To detect the relationship between serum 25-hydroxyvitamin D (25OHD) and lipid profiles in dyslipidemic T1D patients and study the effect of VD supplementation on lipid profiles of VD-deficient T1D patients. METHODS: Fifty patients with T1D (for >2 years) and dyslipidemia were included. 25OHD was assessed and patients were divided accordingly into 2 groups: VD sufficiency (>30 ng/mL) and VD deficiency (VDD) or insufficiency (<29 ng/mL) who were allocated to VD3 supplementation for 4 months, then lipid profile was reevaluated in both groups. RESULTS: Thirty patients had VDD, while 20 patients had VD sufficiency. There was no significant correlation between 25OHD and different study parameters (p > 0.05). A significant difference was found among both groups in the family history of coronary heart disease (p = 0.036) and free tetraiodothyronine 4 (p = 0.035). After 4 months of VD supplementation in VDD group, the mean difference (at 0 and 4 months) in low-density lipoproteins (LDL) and hemoglobin A1c (HbA1c) was statistically significant (p = 0.02 and 0.04 respectively) between both groups. The mean basal LDL was 126.91 mg/dL in VDD group

that improved to 117.13 mg/dL after 4 months of VD therapy with a mean difference of -9.7 mg/dL compared to a mean difference of -2 mg/dL in VD sufficiency group. CONCLUSIONS: VDD was highly prevalent in patients with T1D. There was no significant correlation between 25OHD levels and lipid profile in patients with T1D. VD supplementation for 4 months had a significant lowering effect on LDL and HbA1c.

[22] *Ha D, Lee YJ, Chun Y, Shin JY*. **Comparison of signal detection between statin and statin/ezetimibe fixed-dose combination using the Korea Adverse Events Reporting System Database, 2005 - 2016**. International journal of clinical pharmacology and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272527
ABSTRACT
BACKGROUND AND OBJECTIVES: Statin/ezetimibe fixed-dose combination is often used as statin monotherapy; however, no study has analyzed its adverse effect (AE) signals. We comparatively analyzed the AE status of statin and statin/ezetimibe fixed-dose combination and compared the signal information using a 12-year AE reporting database. MATERIALS AND METHODS: We used data from the Korea Adverse Events Reporting System database from 2005 to 2016. Drug-AE pairs corresponded to drugs and AEs for analysis of demographic characteristics, causality, number, and type of serious AEs. Metrics, including proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC) were used to detect signals. Signals were compared with drug labels in the USA and Korea. RESULTS: Of the 4,569 AE cases identified, 4,130 and 442 were of statin and statin/ezetimibe fixed-dose combination, respectively. There were no statistically significant differences in AE report characterization for statin and the statin/ezetimibe fixed-dose combination. The number of AE signal detections for statin, statin/ezetimibe fixed-dose combination, and both, based on PRR and ROR, was 16, 4, and 2, respectively, and the number of cases not included on the label was 3, 2, and 0, respectively. The number of AE signals that only met IC indicators was greater in statin/ezetimibe fixed-dose combination (33) than in statin (4), and 12 of the 33 cases in statin/ezetimibe fixed-dose combination were not included on the drug label. CONCLUSION: The combination of statin and ezetimibe exhibited greater AE signal detection than statin alone, and the inclusion of AEs on the drug label was insufficient..

[23] *Taghizadeh E, Esfehani RJ, Sahebkar A et al.* **Familial combined hyperlipidemia: An overview of the underlying molecular mechanisms and therapeutic strategies**. IUBMB life 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31271707
ABSTRACT
Among different types of dyslipidemia, familial combined hyperlipidemia (FCHL) is the most common genetic disorder, which is characterized by at least two different forms of lipid abnormalities: hypercholesterolemia and hypertriglyceridemia. FCHL is an important cause of cardiovascular diseases. FCHL is a heterogeneous condition linked with some metabolic defects that are closely associated with FCHL. These metabolic features include dysfunctional adipose tissue, delayed clearance of triglyceride-rich lipoproteins, overproduction of very low-density lipoprotein and hepatic lipids, and defect in the clearance of low-density lipoprotein particles. There are also some genes associated with FCHL such as those affecting the metabolism and

clearance of plasma lipoprotein particles. Due to the high prevalence of FCHL especially in cardiovascular patients, targeted treatment is ideal but this necessitates identification of the genetic background of patients. This review describes the metabolic pathways and associated genes that are implicated in FCHL pathogenesis. We also review existing and novel treatment options for FCHL. (c) 2019 IUBMB Life, 2019.

[24] *Chandra S, Pahan K*. **Gemfibrozil, a Lipid-Lowering Drug, Lowers Amyloid Plaque Pathology and Enhances Memory in a Mouse Model of Alzheimer's Disease via Peroxisome Proliferator-Activated Receptor alpha**. Journal of Alzheimer's disease reports 2019; 3:149-168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31259309
ABSTRACT
Deposition of extracellular senile plaques containing amyloid-beta is one of the major neuropathological characteristics of Alzheimer's disease (AD). Therefore, targeting amyloid-beta dyshomeostasis is an important therapeutic strategy for treatment of AD. In this study, we demonstrate that gemfibrozil, an FDA-approved drug for hyperlipidemia, can lower the amyloid plaque burden in the hippocampus and cortex of the 5XFAD model of AD. Additionally, gemfibrozil reduced microgliosis and astrogliosis associated with plaque in these mice. Administration of gemfibrozil also improved spatial learning and memory of the 5XFAD mice. Finally, we delineate that gemfibrozil requires the transcription factor peroxisome proliferator-activated receptor alpha (PPARalpha) to exhibit its amyloid lowering and memory enhancing effects in 5XFAD mice. These results highlight a new therapeutic property of gemfibrozil and suggest that this drug may be repurposed for treatment of AD.

[25] *Pencina KM, Thanassoulis G, Wilkins JT et al.* **Trajectories of Non-HDL Cholesterol Across Midlife: Implications for Cardiovascular Prevention**. Journal of the American College of Cardiology 2019; 74:70-79.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272554
ABSTRACT
BACKGROUND: Extended elevations of non-high-density lipoprotein cholesterol (non-HDL-C) across a lifespan are associated with increased risk of cardiovascular disease (CVD). However, optimal testing intervals to identify individuals with high lipid-related CVD risk are unknown. OBJECTIVES: This study determined the extent to which lipid levels in young adulthood predict future lipid trajectories and associated long-term CVD risk. METHODS: A sample of 2,516 Framingham Offspring study participants 25 to 40 years of age free of CVD and diabetes had their non-HDL-C progression modeled over 8 study examinations (mean follow-up 32.6 years) using group-based methods. CVD risk based on 25 to 30 years of follow-up was evaluated using Kaplan-Meier analyses for those with mean non-HDL-C >/=160 mg/dl ("high") and <130 mg/dl ("low") at the first 2 examinations. Levels of non-HDL-C for participants on lipid treatment were adjusted by nonparametric algorithm. RESULTS: The trajectories of the lipid levels were generally stable over the 30-year life course; mean non-HDL-C measured in young adulthood were highly predictive of levels later in life. Individuals could be reliably assigned to high and low non-HDL-C groups based on 2 measurements collected between 25 to 40 years of age. Overall, 80% of those with non-HDL-C >/=160 mg/dl at the first 2 exams remained in the high group on subsequent 25-year testing, whereas 88% of those with non-HDL-C <130 mg/dl

remained below 160 mg/dl. Those with high non-HDL-C in young adulthood had a 22.6% risk of CVD in the next 25 years as compared with a 6.4% risk in those with low non-HDL-C. CONCLUSIONS: Most adults with elevated non-HDL-C early in life continue to have high non-HDL-C over their life course, leading to significantly increased risk of CVD. The results demonstrate that early lipid monitoring before 40 years of age would identify a majority of those with a high likelihood for lifetime elevated lipid levels who also have a high long-term risk for CVD. This information could facilitate informed patient-provider discussion about the potential benefits of preventive lipid-lowering efforts during the early midlife period.

[26] *Ramo JT, Ripatti P, Tabassum R et al.* **Coronary Artery Disease Risk and Lipidomic Profiles Are Similar in Hyperlipidemias With Family History and Population-Ascertained Hyperlipidemias**. Journal of the American Heart Association 2019; 8:e012415.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31256696
ABSTRACT
Background We asked whether, after excluding familial hypercholesterolemia, individuals with high low-density lipoprotein cholesterol (LDL -C) or triacylglyceride levels and a family history of the same hyperlipidemia have greater coronary artery disease risk or different lipidomic profiles compared with population-based hyperlipidemias. Methods and Results We determined incident coronary artery disease risk for 755 members of 66 hyperlipidemic families (>/=2 first-degree relatives with similar hyperlipidemia) and 19 644 Finnish FINRISK population study participants. We quantified 151 circulating lipid species from 550 members of 73 hyperlipidemic families and 897 FINRISK participants using mass spectrometric shotgun lipidomics. Familial hypercholesterolemia was excluded using functional LDL receptor testing and genotyping. Hyperlipidemias (LDL -C or triacylglycerides >90th population percentile) associated with increased coronary artery disease risk in meta-analysis of the hyperlipidemic families and the population cohort (high LDL -C: hazard ratio, 1.74 [95% CI, 1.48-2.04]; high triacylglycerides: hazard ratio, 1.38 [95% CI, 1.09-1.74]). Risk estimates were similar in the family and population cohorts also after adjusting for lipid-lowering medication. In lipidomic profiling, high LDL -C associated with 108 lipid species, and high triacylglycerides associated with 131 lipid species in either cohort (at 5% false discovery rate; P-value range 0.038-2.3x10(-56)). Lipidomic profiles were highly similar for hyperlipidemic individuals in the families and the population (LDL -C: r=0.80; triacylglycerides: r=0.96; no lipid species deviated between the cohorts). Conclusions Hyperlipidemias with family history conferred similar coronary artery disease risk as population-based hyperlipidemias. We identified distinct lipidomic profiles associated with high LDL -C and triacylglycerides. Lipidomic profiles were similar between hyperlipidemias with family history and population-ascertained hyperlipidemias, providing evidence of similar and overlapping underlying mechanisms.

[27] *Liu Y, Wang M, Zhang B et al.* **Size of carotid artery intraplaque hemorrhage and acute ischemic stroke: a cardiovascular magnetic resonance Chinese atherosclerosis risk evaluation study**. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2019; 21:36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31262337
ABSTRACT

BACKGROUND: To determine the usefulness of the size of carotid artery intraplaque hemorrhage (IPH) in discriminating the risk of acute ischemic stroke using cardiovascular magnetic resonance (CMR) vessel wall imaging. METHODS: Symptomatic patients with carotid atherosclerotic plaque who participated in a cross-sectional, multicenter study of CARE-II (NCT02017756) were included. All patients underwent carotid and brain CMR imaging. Carotid plaque burden and the size of plaque compositions including calcification, lipid-rich necrotic core (LRNC), and IPH were measured. Presence of acute cerebral infarct (ACI) in ipsilateral hemisphere of carotid plaque was determined. The relationship between carotid plaque features and presence of ipsilateral ACI was then analyzed. RESULTS: Of 687 recruited patients (62.7 +/- 10.1 years; 69.4% males) with carotid plaque, 28.5% had ACI in ipsilateral hemispheres. Logistic regression revealed that carotid plaque burden was significantly associated with the presence of ACI before and after adjusted for clinical confounding factors. The volume of LRNC, %LRNC volume, volume of IPH, and %IPH volume were significantly associated with ACI before (volume of LRNC: OR = 1.297, p = 0.005; %LRNC volume: OR = 1.119, p = 0.018; volume of IPH: OR = 2.514, p = 0.003; %IPH volume: OR = 2.202, p = 0.003) and after (volume of LRNC: OR = 1.312, p = 0.006; %LRNC volume: OR = 1.90, p = 0.034; volume of IPH: OR = 2.907, p = 0.007; % IPH volume: OR = 2.374, p = 0.004) adjusted for clinical confounding factors. The association between volume of IPH and ACI remained statistically significant after further adjusted for plaque volume (OR = 2.813, p = 0.016) or both plaque volume and volume of LRNC (OR = 4.044, p = 0.024). CONCLUSIONS: In symptomatic patients with carotid atherosclerotic plaques, the size of IPH is independently associated with ipsilateral ACI, suggesting the size of IPH might be a useful indicator for the risk of ACI. TRIAL REGISTRATION: Clinical Trial Registration-URL: http://www.clinicaltrials.gov . Unique Identifier: NCT02017756.

[28] *Khan SU, Riaz H, Rahman H et al.* **Association of baseline LDL-C with total and cardiovascular mortality in patients using proprotein convertase subtilisin-kexin type 9 inhibitors: A systematic review and meta-analysis**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31278046

ABSTRACT

BACKGROUND: The objective of this study was to investigate whether baseline low-density lipoprotein cholesterol (LDL-C) levels influence total and cardiovascular mortality reduction associated with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor therapy. METHODS: In this meta-analysis, 9 randomized controlled trials were selected using Medline, Embase, and CENTRAL until November 2018. Analyses were stratified by mean baseline LDL-C (<100 mg/dL and >/= 100 mg/dL). Stepwise prespecified sensitivity analyses were performed after excluding the SPIRE trials and by regrouping ODYSSEY OUTCOME mortality data according to the baseline LDL-C (< and >/=100 mg/dL). RESULTS: In 83,321 patients, PCSK9 inhibitor therapy was not associated with a reduction in the risk of all-cause mortality (relative risk [RR], 0.94, 95% confidence interval [CI], 0.81-1.09, P = .41). These results remained consistent after excluding the SPIRE trials (RR, 0.89, 95% CI, 0.75-1.05, P = .18). However, the RR varied by baseline LDL-C, with significant RR reduction only in patients with LDL-C >/= 100 mg/dL (RR, 0.39, 95% CI, 0.20-0.76) (P-interaction = .01). Meta-regression showed RR of 0.97 for all-cause mortality per 1 mg/dL higher baseline LDL-C (95% CI, 0.94-0.99). PCSK9 inhibitor therapy showed no significant effect on cardiovascular mortality, with no effect when excluding the

SPIRE trials. However, after regrouping ODYSSEY OUTCOME estimates, there was a significant reduction in cardiovascular mortality restricted to patients with LDL-C >/= 100 mg/dL (RR, 0.67, 95% CI, 0.51-0.87) (P-interaction = .006). CONCLUSION: PCSK9 inhibitor therapy on a background statin treatment may reduce the risk of total and cardiovascular mortality in patients with baseline LDL-C >/= 100 mg/dL. These results support current guidelines reserving PCSK9 inhibitors for high-risk patients with residually high LDL-C.

[29] *Stefanutti C, Pang J, Di Giacomo S et al.* **A cross-national investigation of cardiovascular survival in homozygous familial hypercholesterolemia: The Sino-Roman Study**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31255589
ABSTRACT
BACKGROUND: Homozygous familial hypercholesterolemia (hoFH) is a rare inherited disorder characterized by extreme elevation of low-density lipoprotein (LDL) cholesterol, accelerated coronary artery disease, and premature death. Aggressive LDL-lowering therapies are important for survival, but these are not available worldwide. OBJECTIVE: The aim of the study was to compare and contrast cardiovascular outcomes and mortality of hoFH patients in 2 countries with disparate use of lipoprotein apheresis (LA) and modern therapies for lowering LDL cholesterol. METHODS: A retrospective study was undertaken comparing cardiovascular disease (CVD)-free survival and mortality in 44 hoFH patients who were treated with statins but not LA, from a center in Beijing, China, and 18 hoFH patients who were treated with LA and novel therapies from an early age, from a center in Rome, Italy. RESULTS: CVD-free survival and survival were significantly reduced in Chinese patients compared with the Italian patients after 30 years of follow-up (log-rank P < .01). In a pooled analysis, cardiovascular survival was significantly increased with earlier age at treatment, longer duration of treatment, and lower on-treatment LDL cholesterol concentrations (P < .05). In addition, the probability of a CVD event and death were increased in patients that carried a null mutation in the LDLR or had elevated lipoprotein(a). CONCLUSIONS: We show that coronary artery disease outcomes in patients with hoFH can be significantly improved with earlier and potent LDL cholesterol lowering with pharmacotherapies and LA. This has major implications for countries, such as China, where the models of care for hoFH remains underdeveloped.

[30] *Lammi C, Sgrignani J, Arnoldi A et al.* **Computationally Driven Structure Optimization, Synthesis, and Biological Evaluation of Imidazole-Based Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) Inhibitors**. Journal of medicinal chemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31260298
ABSTRACT
Proprotein convertase subtilisin/kexin 9 (PCSK9) is responsible for the degradation of the hepatic low-density lipoprotein receptor (LDLR), which in turn regulates the circulating low-density lipoprotein cholesterol (LDL-C) level. For this reason, the PCSK9 inhibition, by small molecules or peptides, is a validated therapeutic approach for fighting hypercholesterolemia and cardiovascular diseases. In this field, we have recently reported an imidazole-based peptidomimetic that has shown PCSK9 inhibitory activity in the micromolar range. Here, by applying advanced computational techniques, the binding mechanism of that imidazole

peptidomimetic was predicted. Then, among a small set of poly-imidazole analogs, compounds showing the highest theoretical affinity were suitably synthesized, relying on a van Leusen reaction based multicomponent strategy. One compound (named RIm13) displayed a PCSK9 inhibitory activity 10-fold lower than the template compound, and, remarkably, at a concentration of 1 muM, it successfully prevented the LDLR degradation mediated by PCSK9 on HepG2 cells. As well as increasing the LDL uptake at the same concentration, RIm13 represents currently one of the most potent small molecules targeting the PCSK9/LDLR protein-protein interaction.

[31] *Lin L, Burke J, Venkatesh S, Sadana P*. **AMPK-SIRT1-independent inhibition of ANGPTL3 gene expression is a potential lipid-lowering mechanism of metformin**. The Journal of pharmacy and pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31273790
ABSTRACT
OBJECTIVES: Hypertriglyceridaemia enhances cardiovascular disease risk in patients with diabetes. Lipoprotein lipase (LPL) regulates plasma triglyceride levels by hydrolysing chylomicrons and very-low-density lipoprotein (VLDL). Metformin, an antidiabetic drug, improves plasma lipids including triglycerides. We examined metformin's regulation of angiopoietin-like 3 (ANGPTL3), a liver-derived secretory protein with LPL inhibitory property. METHODS: Using HepG2 cells, a human hepatocyte cell line, the effects of metformin on ANGPTL3 gene and protein expression were determined. The role of AMPK-SIRT1 pathway in metformin regulation of ANGPTL3 was determined using pharmacological, RNAi and reporter assays. Metformin regulation of ANGPTL3 expression was also examined in sodium palmitate-induced insulin resistance. KEY FINDINGS: Metformin and pharmacological activators of AMPK and SIRT1 inhibited the expression of ANGPTL3 in HepG2 cells. Pharmacological or RNAi-based antagonism of AMPK or SIRT1 failed to affect metformin inhibition of ANGPTL3. AMPK-SIRT1 activators and metformin exhibited distinct effects on the expression of ANGPTL3 gene luciferase reporter. Sodium palmitate-induced insulin resistance in cells resulted in increased ANGPTL3 gene expression which was suppressed by pretreatment with metformin. CONCLUSIONS: Metformin inhibits ANGPTL3 expression in the liver in an AMPK-SIRT1-independent manner as a potential mechanism to regulate LPL and lower plasma lipids.

[32] *Bravata DM, Myers LJ, Reeves M et al.* **Processes of Care Associated With Risk of Mortality and Recurrent Stroke Among Patients With Transient Ischemic Attack and Nonsevere Ischemic Stroke**. JAMA network open 2019; 2:e196716.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31268543
ABSTRACT
Importance: Early evaluation and management of patients with transient ischemic attack (TIA) and nonsevere ischemic stroke improves outcomes. Objective: To identify processes of care associated with reduced risk of death or recurrent stroke among patients with TIA or nonsevere ischemic stroke. Design, Setting, and Participants: This cohort study included all patients with TIA or nonsevere ischemic stroke at Department of Veterans Affairs emergency department or inpatient settings from October 2010 to September 2011. Multivariable logistic regression was used to model associations of processes of care and without-fail care, defined as receiving all

guideline-concordant processes of care for which patients are eligible, with risk of death and recurrent stroke. Data were analyzed from March 2018 to April 2019. Main Outcomes and Measures: Risk of all-cause mortality and recurrent ischemic stroke at 90 days and 1 year was calculated. Overall, 28 processes of care were examined. Without-fail care was assessed for 6 processes: brain imaging, carotid artery imaging, hypertension medication intensification, high- or moderate-potency statin therapy, antithrombotics, and anticoagulation for atrial fibrillation. Results: Among 8076 patients, the mean (SD) age was 67.8 (11.6) years, 7752 patients (96.0%) were men, 5929 (73.4%) were white, 474 (6.1%) had a recurrent ischemic stroke within 90 days, 793 (10.7%) had a recurrent ischemic stroke within 1 year, 320 (4.0%) died within 90 days, and 814 (10.1%) died within 1 year. Overall, 9 processes were independently associated with lower odds of both 90-day and 1-year mortality after adjustment for multiple comparisons: carotid artery imaging (90-day adjusted odds ratio [aOR], 0.49; 95% CI, 0.38-0.63; 1-year aOR, 0.61; 95% CI, 0.52-0.72), antihypertensive medication class (90-day aOR, 0.58; 95% CI, 0.45-0.74; 1-year aOR, 0.70; 95% CI, 0.60-0.83), lipid measurement (90-day aOR, 0.68; 95% CI, 0.51-0.90; 1-year aOR, 0.64; 95% CI, 0.53-0.78), lipid management (90-day aOR, 0.46; 95% CI, 0.33-0.65; 1-year aOR, 0.67; 95% CI, 0.53-0.85), discharged receiving statin medication (90-day aOR, 0.51; 95% CI, 0.36-0.73; 1-year aOR, 0.70; 95% CI, 0.55-0.88), cholesterol-lowering medication intensification (90-day aOR, 0.47; 95% CI, 0.26-0.83; 1-year aOR, 0.56; 95% CI, 0.41-0.77), antithrombotics by day 2 (90-day aOR, 0.56; 95% CI, 0.40-0.79; 1-year aOR, 0.69; 95% CI, 0.55-0.87) or at discharge (90-day aOR, 0.59; 95% CI, 0.41-0.86; 1-year aOR, 0.69; 95% CI, 0.54-0.88), and neurology consultation (90-day aOR, 0.67; 95% CI, 0.52-0.87; 1-year aOR, 0.74; 95% CI, 0.63-0.87). Anticoagulation for atrial fibrillation was associated with lower odds of 1-year mortality only (aOR, 0.59; 95% CI, 0.40-0.85). No processes were associated with reduced risk of recurrent stroke after adjustment for multiple comparisons. The rate of without-fail care was 15.3%; 1216 patients received all guideline-concordant processes of care for which they were eligible. Without-fail care was associated with a 31.2% lower odds of 1-year mortality (aOR, 0.69; 95% CI, 0.55-0.87) but was not independently associated with stroke risk. Conclusions and Relevance: Patients who received 6 readily available processes of care had lower adjusted mortality 1 year after TIA or nonsevere ischemic stroke. Clinicians caring for patients with TIA and nonsevere ischemic stroke should seek to ensure that patients receive all guideline-concordant processes of care for which they are eligible.

[33] *Raal FJ, Mohamed F*. **More aggressive lipid lowering in people with diabetes?** The lancet. Diabetes & endocrinology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272929
ABSTRACT

[34] *Ray KK, Colhoun HM, Szarek M et al.* **Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial**. The lancet. Diabetes & endocrinology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272931
ABSTRACT

Literature update week 27 (2019)

BACKGROUND: After acute coronary syndrome, diabetes conveys an excess risk of ischaemic cardiovascular events. A reduction in mean LDL cholesterol to 1.4-1.8 mmol/L with ezetimibe or statins reduces cardiovascular events in patients with an acute coronary syndrome and diabetes. However, the efficacy and safety of further reduction in LDL cholesterol with an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) after acute coronary syndrome is unknown. We aimed to explore this issue in a prespecified analysis of the ODYSSEY OUTCOMES trial of the PCSK9 inhibitor alirocumab, assessing its effects on cardiovascular outcomes by baseline glycaemic status, while also assessing its effects on glycaemic measures including risk of new-onset diabetes. METHODS: ODYSSEY OUTCOMES was a randomised, double-blind, placebo-controlled trial, done at 1315 sites in 57 countries, that compared alirocumab with placebo in patients who had been admitted to hospital with an acute coronary syndrome (myocardial infarction or unstable angina) 1-12 months before randomisation and who had raised concentrations of atherogenic lipoproteins despite use of high-intensity statins. Patients were randomly assigned (1:1) to receive alirocumab or placebo every 2 weeks; randomisation was stratified by country and was done centrally with an interactive voice-response or web-response system. Alirocumab was titrated to target LDL cholesterol concentrations of 0.65-1.30 mmol/L. In this prespecified analysis, we investigated the effect of alirocumab on cardiovascular events by glycaemic status at baseline (diabetes, prediabetes, or normoglycaemia)-defined on the basis of patient history, review of medical records, or baseline HbA1c or fasting serum glucose-and risk of new-onset diabetes among those without diabetes at baseline. The primary endpoint was a composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospital admission. ODYSSEY OUTCOMES is registered with ClinicalTrials.gov, number NCT01663402. FINDINGS: At study baseline, 5444 patients (28.8%) had diabetes, 8246 (43.6%) had prediabetes, and 5234 (27.7%) had normoglycaemia. There were no significant differences across glycaemic categories in median LDL cholesterol at baseline (2.20-2.28 mmol/L), after 4 months' treatment with alirocumab (0.80 mmol/L), or after 4 months' treatment with placebo (2.25-2.28 mmol/L). In the placebo group, the incidence of the primary endpoint over a median of 2.8 years was greater in patients with diabetes (16.4%) than in those with prediabetes (9.2%) or normoglycaemia (8.5%); hazard ratio (HR) for diabetes versus normoglycaemia 2.09 (95% CI 1.78-2.46, p<0.0001) and for diabetes versus prediabetes 1.90 (1.65-2.17, p<0.0001). Alirocumab resulted in similar relative reductions in the incidence of the primary endpoint in each glycaemic category, but a greater absolute reduction in the incidence of the primary endpoint in patients with diabetes (2.3%, 95% CI 0.4 to 4.2) than in those with prediabetes (1.2%, 0.0 to 2.4) or normoglycaemia (1.2%, -0.3 to 2.7; absolute risk reduction pinteraction=0.0019). Among patients without diabetes at baseline, 676 (10.1%) developed diabetes in the placebo group, compared with 648 (9.6%) in the alirocumab group; alirocumab did not increase the risk of new-onset diabetes (HR 1.00, 95% CI 0.89-1.11). HRs were 0.97 (95% CI 0.87-1.09) for patients with prediabetes and 1.30 (95% CI 0.93-1.81) for those with normoglycaemia (pinteraction=0.11). INTERPRETATION: After a recent acute coronary syndrome, alirocumab treatment targeting an LDL cholesterol concentration of 0.65-1.30 mmol/L produced about twice the absolute reduction in cardiovascular events among patients with diabetes as in those without diabetes. Alirocumab treatment did not increase the risk of new-onset diabetes. FUNDING: Sanofi and Regeneron Pharmaceuticals.

[35] *Arshad MS, Batool SM, Khan MK et al.* **Bio-evaluation of functional date bars using rats as model organism against hypercholesterolemia**. Lipids in health and disease 2019; 18:148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272450

ABSTRACT

BACKGROUND: The present research project was designed to evaluate the cholesterol lowering potential of different date varieties including one exotic (Ajwa) and three Pakistani varieties (Aseel, Khudravi, Hallawi). METHODS: The albino rats were divided into six groups on the basis of different diets which includes, control having basal diet, high cholesterol high sucrose diet, high cholesterol high sucrose diet plus Khudravi dates, high cholesterol high sucrose diet plus Hallawi dates, high cholesterol high sucrose diet plus Aseel dates, high cholesterol high sucrose diet plus Ajwa dates to evaluate maximum cholesterol lowering potential of each date variety. RESULTS: The results showed that Hallawi and Ajwa have lower crude fiber content as 2.02 +/- 0.03% and 2.43 +/- 0.04% however, lowest crude fat content (0.26 +/- 0.01%) was also observed in ajwa. Mineral profile depicted that sodium (9.50-18.00 mg/100 g) was found to be in lesser amount among all varieties whereas, higher amount of potassium (465.00 to 887.20 mg/100 g) depicted that it is suitable for people having hypertension. Higher amount of reducing sugar was also observed in ajwa (79.45 +/- 1.22%) followed by Hallawi (77.68 +/- 1.42%). Total phenolic contents were found higher in Aseel (291.36 mg/100 g) whereas, minimum was observed in Khudravi (232.64 mg/100 g). Furthermore, date varieties were also examined rat modeling to evaluate their maximum cholesterol lowering efficiency. Ajwa and Hallawi were observed to suppress the cholesterol efficiently as 110 mg/dL and 103 mg/dL respectively. On the basis of chemical profiling and other parameters, two date varieties Ajwa and Hallawi showed almost similar results and found to have maximum serum cholesterol, LDL and triglyceride reduction potential with good kidney and liver functions. Functional date bar was also developed by using Hallawi variety andsubjected to sensory evaluation. CONCLUSION: In nutshell, Hallawi date variety was considered as better cholesterol lowering potential among other indigenous varieties and very close to Ajwa variety. So that Hallawi can be used to suppress the deadly effects of obesity and allied discrepancies particularly hypercholesterolemia.

[36] *Qian M, Lyu Q, Liu Y et al.* **Chitosan Oligosaccharide Ameliorates Nonalcoholic Fatty Liver Disease (NAFLD) in Diet-Induced Obese Mice**. Marine drugs 2019; 17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31269758

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a global epidemic, and there is no standard and efficient therapy for it. Chitosan oligosaccharide (COS) is widely known to have various biological effects, and in this study we aimed to evaluate the liver-protective effect in diet-induced obese mice for an enzymatically digested product of COS called COS23 which is mainly composed of dimers and trimers. An integrated analysis of the lipidome and gut microbiome were performed to assess the effects of COS23 on lipids in plasma and the liver as well as on intestinal microbiota. Our results revealed that COS23 obviously attenuated hepatic steatosis and ameliorated liver injury in diet-induced obese mice. The hepatic toxic lipids-especially triglycerides (TGs) and free fatty acids (FFAs)-were decreased dramatically after COS23

treatment. COS23 regulated lipid-related pathways, especially inhibiting the expressions of FFA-synthesis-related genes and inflammation-related genes. Furthermore, COS23 could alter lipid profiles in plasma. More importantly, COS23 also decreased the abundance of Mucispirillum and increased the abundance of Coprococcus in gut microbiota and protected the intestinal barrier by up-regulating the expression of tight-junction-related genes. In conclusion, COS23, an enzymatically digested product of COS, might serve as a promising candidate in the clinical treatment of NAFLD.

[37] *Iakobishvili Z, Hasin T, Klempfner R et al.* **Association of Bezafibrate Treatment With Reduced Risk of Cancer in Patients With Coronary Artery Disease**. Mayo Clinic proceedings 2019; 94:1171-1179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31272567
ABSTRACT
OBJECTIVE: To evaluate the association between bezafibrate, a drug used to treat hypertriglyceridemia, and long-term cancer incidence in patients with coronary artery disease (CAD). PATIENTS AND METHODS: The study comprised 2980 patients with CAD (mean age, 60 years; 2729 [91.6%] men) who were free of cancer and were enrolled in the Bezafibrate Infarction Prevention study, a double-blind trial conducted between May 1, 1990, and January 31, 1993, in 18 cardiology departments in Israel. Patients randomized to receive 400 mg of bezafibrate (n=1486) or placebo (n=1494) daily for a median of 6.2 years (range, 4.7-7.6 years) were followed up for incidence of cancer through the Israeli National Cancer Registry and all-cause death through the Population Registry of the State of Israel until December 31, 2013. Cox proportional hazards and Fine and Gray survival models were used to assess the bezafibrate-cancer association. RESULTS: Clinical characteristics and laboratory values were well balanced between the 2 groups at the study entry. Over a median follow-up of 22.5 years (range, 21.2-23.9 years), cancer developed in 753 patients. With death considered a competing event, the cumulative incidence of cancer at the end of the follow-up was lower in the bezafibrate vs the placebo group (23.9%; 95 CI, 21.9%-26.1% vs 27.2%; 95 CI, 25.1%-29.4%; P=.04). The hazard ratio for cancer in the bezafibrate vs placebo groups was 0.86 (95% CI, 0.74-0.99). In mediation analysis, the association between bezafibrate treatment and cancer incidence was not sensitive to adjustment for on-trial lipid levels but was attenuated on adjustment for on-trial fibrinogen levels. CONCLUSION: Bezafibrate treatment is associated with reduced risk of cancer among patients with CAD. Fibrinogen, but not lipid lowering, is linked to this association.

[38] *Zhu J, Wu S, Hu S et al.* **NLRP3 inflammasome expression in peripheral blood monocytes of coronary heart disease patients and its modulation by rosuvastatin**. Molecular medicine reports 2019; 20:1826-1836.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31257469
ABSTRACT
Nucleotidebinding oligomerization domain, leucine rich repeat, and pyrin domaincontaining protein 3 (NLRP3) inflammasome has been implicated in a series of physiological and pathological processes. However, its correlation in coronary heart disease (CHD) still remains to be elucidated. The present study aimed to determine the expression of NLRP3 inflammasome in peripheral blood monocytes (PBMCs) of stable angina pectoris (SAP) and acute myocardial

infarction (AMI) patients. In addition, the effect of rosuvastatin on their activities was analyzed in vitro. A total of 60 participants with SAP (n=20), AMI (n=20) and nonCHD controls (n=20) were enrolled. Fluorescenceactivated cell sorting, realtime PCR, western blotting and enzymelinked immunosorbent assay were performed to reveal the role of NLRP3 inflammasome. NLRP3 inflammasome was expressed in the PBMCs, and revealed an increased expression along the downstream interleukin (IL)1beta and IL18 in both SAP and AMI groups, compared to the control group. Moreover, there was a more marked increase in the expression of these indicators in AMI patients when compared to SAP patients. Interference with rosuvastatin in vitro revealed that the expression of NLRP3 inflammasome and its downstream cytokines were significantly downregulated in both SAP and AMI groups in a timedependent manner. The activation of NLRP3 inflammasome may be involved in the development of CHD, and rosuvastatin could attenuate the inflammatory process of atherosclerosis by downregulating NLRP3 expression and its downstream mediators. These findings indicated a potential role of NLRP3 in the pathogenesis and management of CHD, and also provided new insights into the mechanistic framework of rosuvastatin activity.

[39] *Ma C, Gurol ME, Huang Z et al.* **Low-density lipoprotein cholesterol and risk of intracerebral hemorrhage: A prospective study**. Neurology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31266905
ABSTRACT
OBJECTIVE: To prospectively examine the association between low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations and intracerebral hemorrhage (ICH) risk. METHODS: The current cohort study included 96,043 participants (mean age 51.3 years) who were free of stroke, myocardial infarction, and cancer at baseline (2006). Serum LDL-C concentrations were assessed in 2006, 2008, 2010, and 2012. Cumulative average LDL-C concentrations were calculated from all available LDL-C data during that period. Incident ICH was confirmed by review of medical records. RESULTS: We identified 753 incident ICH cases during 9 years of follow-up. The ICH risk was similar among participants with LDL concentrations of 70 to 99 mg/dL and those with LDL-C concentrations >/=100 mg/dL. In contrast, participants with LDL-C concentrations <70 mg/dL had a significantly higher risk of developing ICH than those with LDL-C concentrations of 70 to 99 mg/dL; adjusted hazard ratios were 1.65 (95% confidence interval [CI] 1.32-2.05) for LDL-C concentrations of 50 to 69 mg/dL and 2.69 (95% CI 2.03-3.57) for LDL-C concentrations <50 mg/dL. CONCLUSIONS: We observed a significant association between lower LDL-C and higher risk of ICH when LDL-C was <70 mg/dL, and the association became nonsignificant when LDL-C >/=70 mg/dL. These data can help determination of the ideal LDL range in patients who are at increased risk of both atherosclerotic disease and hemorrhagic stroke and guide planning of future lipid-lowering studies.

[40] *Wang Q, Qu X, Zheng L, Yi X*. **Atorvastatin improves cardiac function of mice with acute myocardial infarction by interfering in macrophages to activate MAPK pathway**. Panminerva medica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31262147
ABSTRACT

Literature update week 27 (2019)

[41] *Seo KS, Han HK*. **Multilayer-Coated Tablet of Clopidogrel and Rosuvastatin: Preparation and In Vitro/In vivo Characterization**. Pharmaceutics 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31277408
ABSTRACT
The acid lability of rosuvastatin hinders the preparation of mixed combination formulations of rosuvastatin with acidic drugs such as clopidogrel. Therefore, the purpose of this study was to develop a multilayer-coated tablet that avoids physicochemical interactions between rosuvastatin and clopidogrel. Among the tested hydrophobic materials, glyceryl behenate was most effective at inhibiting the production of lactone, the acid degradation product of rosuvastatin. Therefore, the multilayer-coated tablet included a hydrophobic separation layer consisting of glyceryl behenate between the clopidogrel core tablet and the rosuvastatin coating layer. In order to prevent delayed dissolution by the stable hydrophobic separation layer, crospovidone was added into the clopidogrel core tablet as an effective disintegrant. Copovidone was also added to the coating layer of rosuvastatin, achieving a dissolution profile comparable to that of the reference drug, Crestor((R)). The resulting multilayer-coated tablet exhibited similar pharmacokinetic profiles to those of reference drugs (Plavix((R)) and Crestor((R))) in beagle dogs, and there was no statistically significant difference in the maximum plasma concentration (Cmax), the time to reach the maximum plasma concentration (Tmax), or the area under the plasma-concentration time curve (AUC) between the test and reference formulations. The storage stability tests showed that the amounts of acid degradation products and total impurities were comparable to that of the reference drug. In conclusion, the present study successfully developed a stable multilayer-coated tablet containing both clopidogrel and rosuvastatin that may improve the patient compliance in combination therapy for cardiovascular diseases.

[42] *Vella L, Markworth JF, Farnfield MM et al.* **Intramuscular inflammatory and resolving lipid profile responses to an acute bout of resistance exercise in men**. Physiological reports 2019; 7:e14108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31257737
ABSTRACT
Lipid mediators including classical arachidonic acid-derived eicosanoids (e.g. prostaglandins and leukotrienes) and more recently identified specialized pro-resolving-mediator metabolites of the omega-3 fatty acids play essential roles in initiation, self-limitation, and active resolution of acute inflammatory responses. In this study, we examined the bioactive lipid mediator profile of human skeletal muscle at rest and following acute resistance exercise. Twelve male subjects completed a single bout of maximal isokinetic unilateral knee extension exercise and muscle biopsies were taken from the m.vastus lateralis before and at 2, 4, and 24 h of recovery. Muscle tissue lipid mediator profile was analyzed via liquid chromatography-mass spectrometry (LC-MS)-based targeted lipidomics. At 2 h postexercise, there was an increased intramuscular abundance of cyclooxygenase (COX)-derived thromboxanes (TXB2 : 3.33 fold) and prostaglandins (PGE2 : 2.52 fold and PGF2alpha : 1.77 fold). Resistance exercise also transiently increased muscle concentrations of lipoxygenase (LOX) pathway-derived leukotrienes (12-Oxo LTB4 : 1.49 fold and 20-COOH LTB4 : 2.91 fold), monohydroxy-eicosatetraenoic acids (5-HETE: 2.66 fold, 12-HETE: 2.83 fold, and 15-HETE: 1.69 fold) and monohydroxy-docosahexaenoic acids

(4-HDoHE: 1.69 fold, 7-HDoHE: 1.58 fold and 14-HDoHE: 2.35 fold). Furthermore, the abundance of CYP pathway-derived epoxy- and dihydroxy-eicosatrienoic acids was increased in 2 h postexercise biopsies (5,6-EpETrE: 2.48 fold, 11,12-DiHETrE: 1.66 fold and 14,15-DiHETrE: 2.23 fold). These data reveal a range of bioactive lipid mediators as present within human skeletal muscle tissue and demonstrate that acute resistance exercise transiently stimulates the local production of both proinflammatory eicosanoids and pathway markers in specialized proresolving mediator biosynthesis circuits.

[43] *Li JJ*. **Relation of oxidized-low-density lipoprotein and high-density lipoprotein subfractions in non-treated patients with coronary artery disease**. Prostaglandins Other Lipid Mediat 2019:106345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31278984
ABSTRACT
BACKGROUND: Oxidized-low-density lipoprotein (ox-LDL), as well as high-density lipoprotein (HDL) and its subfractions play important role in the development of coronary artery disease (CAD). METHODS: A total of 1417 individuals who received selective coronary angiography (CAG) without lipids-lowering treatments were consecutively enrolled. Patients were divided into CAD (n = 942) and non-CAD group (n = 475). The severity of CAD was assessed by Gensini Scores (GS) system. The correlations of ox-LDL with HDL subfractions were analyzed. RESULTS: Compared with non-CAD subjects, CAD patients had higher ox-LDL but lower concentrations of HDL cholesterol ($p = 0.002$) and large HDL subfractions ($p = 0.004$). And ox-LDL was negatively correlated with large HDL subfractions in patients with severe CAD ($p < 0.05$). Moreover, ox-LDL was elevated and large HDL subfractions decreased with the increase of the number of stenotic coronary arteries and GS ($p < 0.05$,respectivelly). CONCLUSIONS: The correlations between ox-LDL and cholesterol level of large HDL particles varied among CAD and non-CAD, and CAD with different severities of atherosclerosis.

[44] *Abdullah MI, Abed MN, Khanim F, Richardson A*. **Screening a library of approved drugs reveals that prednisolone synergizes with pitavastatin to induce ovarian cancer cell death**. Scientific reports 2019; 9:9632.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31270377
ABSTRACT
The survival rate for patients with ovarian cancer has changed little in the past three decades since the introduction of platinum-based chemotherapy and new drugs are needed. Statins are drugs used for the treatment and prevention of cardiovascular diseases. Recent work from our laboratory has shown that pitavastatin has potential as a treatment for ovarian cancer if dietary geranylgeraniol is controlled. However, relatively high doses of statins are required to induce apoptosis in cancer cells, increasing the risk of myopathy, the most common adverse effect associated with statins. This makes it desirable to identify drugs which reduce the dose of pitavastatin necessary to treat cancer. A drug-repositioning strategy was employed to identify suitable candidates. Screening a custom library of 100 off-patent drugs for synergistic activity with pitavastatin identified prednisolone as the most prominent hit. Prednisolone potentiated the activity of pitavastatin in several assays measuring the growth, survival or apoptosis in several ovarian cancer cells lines. Prednisolone, alone or in some cases in combination with

pitavastatin, reduced the expression of genes encoding enzymes in the mevalonate pathway, providing a mechanistic explanation for the synergy.

[45] *Thompson PD*. **Editorial commentary: Using PCSK9 inhibitors to win at "cholesterol limbo"**. Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31255506
ABSTRACT

[46] *Russell KS, Yates DP, Kramer CM et al.* **A randomized, placebo-controlled trial of canakinumab in patients with peripheral artery disease**. Vascular medicine (London, England) 2019:1358863x19859072.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31277561
ABSTRACT
Extensive atherosclerotic plaque burden in the lower extremities often leads to symptomatic peripheral artery disease (PAD) including impaired walking performance and claudication. Interleukin-1beta (IL-1beta) may play an important pro-inflammatory role in the pathogenesis of this disease. Interruption of IL-1beta signaling was hypothesized to decrease plaque progression in the leg macrovasculature and improve the mobility of patients with PAD with intermittent claudication. Thirty-eight patients (mean age 65 years; 71% male) with symptomatic PAD (confirmed by ankle-brachial index) were randomized 1:1 to receive canakinumab (150 mg subcutaneously) or placebo monthly for up to 12 months. The mean vessel wall area (by 3.0 T black-blood magnetic resonance imaging (MRI)) of the superficial femoral artery (SFA) was used to measure plaque volume. Mobility was assessed using the 6-minute walk test. Canakinumab was safe and well tolerated. Markers of systemic inflammation (interleukin-6 and high-sensitivity C-reactive protein) fell as early as 1 month after treatment. MRI (32 patients at 3 months; 21 patients at 12 months) showed no evidence of plaque progression in the SFA in either placebo-treated or canakinumab-treated patients. Although an exploratory endpoint, placebo-adjusted maximum and pain-free walking distance (58 m) improved as early as 3 months after treatment with canakinumab when compared with placebo. Although canakinumab did not alter plaque progression in the SFA, there is an early signal that it may improve maximum and pain-free walking distance in patients with symptomatic PAD. Larger studies aimed at this endpoint will be required to definitively demonstrate this. ClinicalTrials.gov Identifier: NCT01731990.