Literature update week 19 (2019)

[1] *Hou ZH, Lu B, Li ZN et al.* **Coronary Atherosclerotic Plaque Volume Quantified by Computed Tomographic Angiography in Smokers Compared to Nonsmokers**. Academic radiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31072767

ABSTRACT

RATIONALE AND OBJECTIVES: We sought to compare the prevalence and volume of lipid plaque, fibrous plaque, and calcified plaque in patients with smokers versus nonsmokers. MATERIALS AND METHODS: We studied consecutive patients suspected of coronary artery disease and who underwent coronary computed tomography angiography. A structured interview and review of existing clinical data was conducted before computed tomography angiography to collect information on demographic characteristics, the presence of cardiovascular risk factors. The volume of lipid, fibrous, and calcified plaque were automatically calculated and marked in different colors according to predefined Hounsfield unit thresholds. The prevalence and volume of plaques were compared between smokers and nonsmokers. RESULTS: Overall 6380 patients (3351 men and 3029 women, mean age 55.35 years) were finally analyzed, of whom 2075 (32.5%) were smokers, and 4305 (67.5%) were never smokers. The prevalence of any plaque in smokers was significantly higher compared to never smokers (47.7% vs. 32.3%, $p < 0.001$). Smoking was an independent risk factor of the presence of any plaque after correcting for age, gender, body mass index, hypertension, dyslipidemia, diabetes, and family history in a multivariate model (odds ratio=1.250 (1.088-1.437), $p = 0.002$). The volume of lipid plaque, fibrous plaque, calcified plaque, and total plaque in smokers was significantly greater than nonsmokers ($p < 0.001$). CONCLUSION: The prevalence and volume of lipid plaque, fibrous plaque, and calcified plaque were significantly higher in smokers versus never smokers.

[2] *Lacin N, Izol BS, Ozkorkmaz EG et al.* **The effect of graft application and simvastatin treatment on tibial bone defect in rats. A histological and immunohistochemical study**. Acta Cir Bras 2019; 34:e201900408.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31066788

ABSTRACT

PURPOSE: To evaluate histologically and immunohistochemically the bone regeneration after application of simvastatin on tibial bone defects in rats. METHODS: Sixty Wistar albino rats were divided into 3 groups as control (6 mm tibial bone defect), defect + graft (allograft treatment), and defect + graft + simvastatin (10 mg/kg/day) for 28 days. RESULTS: Histopathological examination revealed inflammation in control group (defect group), congestion in blood vessels, and an increase in osteoclast cells. In defect + graft group, osteoclastic activity was observed and osteocyte cells were continued to develop. In defect + graft + simvastatin group, osteocytes and matrix formation were increased in the new bone trabeculae. Osteopontin and osteonectin expression were positive in the osteclast cells in the control group. Osteoblasts and some osteocytes showed a positive reaction of osteopontin and osteopontin. In defect + graft + simvastatin group, osteonectin and osteopontin expression were positive in osteoblast and osteocyte cells, and a positive expression in osteon formation was also seen in new bone trabeculae. CONCLUSION: The simvastatin application was thought to increase bone turnover by increasing the osteoinductive effect with graft and significantly affect the formation of new bone.

[3] *Nafrialdi N, Hudyono J, Suyatna FD, Setiawati A*. **Safety and Efficacy of NC120 for Improving Lipid Profile: A Double Blind Randomized Controlled Trial**. Acta medica Indonesiana 2019; 51:19-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31073102
ABSTRACT
BACKGROUND: the use of statin to lower blood cholesterol is often associated with bothersome adverse effects such as myopathy and liver dysfunction. NC120 is herbal lipid lowering drug containing red yeast rice (RYR) extract, guggulipid, and chromium picolinate, and expected to have better safety profile. The aim of this study was to evaluate the efficacy and safety profiles of NC120 in lowering blood lipid. METHODS: this was a double blind randomized clinical trial comparing NC120 with placebo in subjects with hypercholesterolemia. Two capsules of NC120 or placebo were administered twice a day for 28 days. Blood total-cholesterol, LDL-cholesterol, and triglyceride were measured on day-0, day-7, and day-28. Unpaired t-test was used to compare study parameter between groups, and one-way ANOVA was used to compare within group. RESULTS: 25 subjects received NC120 and 24 subjects received placebo. Significant decrease of total cholesterol and LDL-cholesterol were observed since day-7 in NC120 group, while the changes in placebo group were not significant at all time of observation. No significant decrease of triglyceride was observed in NC120 group and in placebo group. Side effects were minor and comparable between the two groups. CONCLUSION: NC120 is effective in reducing total cholesterol and LDL-cholesterol, but not triglyceride. This drug shows a good safety profile, and thus can be considered for patients who can not tolerate statin drugs.

[4] *Linden K, McQuillan C, Brennan P, Menown IBA*. **Advances in Clinical Cardiology 2018: A Summary of Key Clinical Trials**. Adv Ther 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31065993
ABSTRACT
INTRODUCTION: Many important clinical trials in cardiology were published or presented at major international meetings throughout 2018. This paper aims to offer a concise overview of these significant advances and to put them into clinical context. METHODS: Trials presented at the major international cardiology meetings during 2018 were reviewed including The American College of Cardiology, EuroPCR, The European Society of Cardiology, PCR London Valves, Transcatheter Cardiovascular Therapeutics, and the American Heart Association. In addition to this a literature search identified several other publications eligible for inclusion based on their relevance to clinical cardiology, their potential impact on clinical practice and on future guidelines. RESULTS: A total of 78 trials met the inclusion criteria. New interventional and structural data include trials examining novel stent designs (Biofreedom, COMBO), use of drug-coated balloons in patients with high bleeding risk, intervention in stable coronary artery disease, revascularisation strategy in ST elevation myocardial infarction, transcatheter aortic valve replacement in low-risk patients, and percutaneous mitral or tricuspid valve interventions. Preventative cardiology data included the use of sodium glucose cotransporter-2 inhibitors (empagliflozin, dapagliflozin, canagliflozin), proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (alirocumab) and approaches of hypertension management. Antiplatelet data included trials evaluating both the optimal length of course and combination

of antiplatelet agents. Heart failure data included trials of sacubitril-valsartan during acute hospital admission and the management of chemotherapy-induced cardiotoxicity. Electrophysiology data included trials examining atrial fibrillation ablation, wearable cardiac defibrillators (LifeVest) and His-bundle pacing. CONCLUSION: This article presents key clinical trials completed during 2018 and should be valuable to both cardiology clinicians and researchers.

[5] *Tummala R, Ghosh RK, Jain V et al.* **Fish Oil And Cardiometabolic Diseases: Recent Updates And Controversies**. The American journal of medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31077653
ABSTRACT
Fatty acids derived from fish oil are long chain omega-3 (n-3) polyunsaturated fatty acids. The important polyunsaturated fatty acids of fish oil are eicosapentaenoic acid, and docosahexaenoic acid. For decades, there has been a debate about the use of omega-3 fatty acid supplements and their benefits on cardiovascular health. The more recent trials including the JELIS, REDUCE-IT, VITAL, STRENGTH, and the ASCEND trials addressed the paucity of data of omega-3 Fatty acids on primary as well as secondary prevention of cardiovascular events and risk-benefit balance of these supplements. Prior to these studies, many large randomized controlled trials have shown conflicting results on the effect of polyunsaturated fatty acids in patients with prior coronary artery disease, stroke or major vascular events. These inconsistent results warrant a better understanding of the effects of omega-3 fatty acids on the subtypes of cardiovascular diseases, and their use in primary and secondary prevention. More recently, the REDUCE-IT study showed a possible protective benefit of fish oil supplements (in purified form and higher than normal doses) in the reduction of Triglyceride levels. It is also noteworthy that omega-3 fatty acids have found their mention in the most recent American College of Cardiology guidelines for the management of hypertriglyceridemia as an adjunct to statins and fibrates. The aim of this review is to discuss these recent updates on use of fish oil in cardiometabolic diseases, and their surrounding controversies.

[6] *Venturini G, Malagrino PA, Padilha K et al.* **Integrated Proteomics and Metabolomics Analysis Reveals Differential Lipid Metabolism in HUVEC under high and low shear stress**. Am J Physiol Cell Physiol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31067084
ABSTRACT
OBJECTIVE: Atherosclerotic plaque development is closely associated with the hemodynamic forces applied to endothelial cells (EC). Among these, shear stress (SS) plays a key role in disease development since changes in flow intensity and direction could stimulate an atheroprone or atheroprotective phenotype. EC under low or oscillatory SS (LSS) shows upregulation of inflammatory, adhesion and cellular permeability molecules. On the contrary, cells under high or laminar SS (HSS) increase their expression of protective and anti-inflammatory factors. The mechanism behind SS regulation of an atheroprotective phenotype is not completely elucidated. Approach and Results: Here we used proteomics and metabolomics to better understand the changes in endothelial cells (HUVECs) under in vitro LSS and HSS that promote an atheroprone or atheroprotective profile and how these modifications can be

connected to atherosclerosis development. Our data showed that lipid metabolism, in special cholesterol metabolism, was downregulated in cells under LSS. The LDLR showed significant alterations both at the quantitative expression level, as well as regarding post-translational modifications. Under LSS, LDLR was seen at lower concentrations and with a different glycosylation profile. Finally, modulating LDLR with atorvastatin led to the recapitulation of a HSS metabolic phenotype in EC under LSS. CONCLUSIONS: Altogether, our data suggest that there is significant modulation of lipid metabolism in endothelial cells under different SS intensities and that this could contribute to the atheroprone phenotype of LSS. Statin treatment was able to partially recover the protective profile of these cells.

[7] *Akinkuolie AO, Lawler PR, Chu AY et al.* **Group IIA Secretory Phospholipase A2 and Incident Cardiovascular Disease**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118311894.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31070471
ABSTRACT
Objective- Inflammation is a causal risk factor for cardiovascular disease (CVD). sPLA2-IIA (group IIA secretory phospholipase A2) plays an integral role in regulating vascular inflammation. Although studies investigated sPLA2-IIA in secondary prevention, we prospectively evaluated sPLA2-IIA mass and genetic variants with CVD events in a primary prevention population with chronic inflammation. Approach and Results- The JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) randomized participants with LDLc <130 mg/dL and hsCRP (high-sensitivity C-reactive protein) >/=2 mg/L to high-intensity rosuvastatin versus placebo. Baseline and 1-year plasma sPLA2-IIA mass was measured (N=11 269 baseline; N=9620 1 year). We also identified genetic variants influencing sPLA2-IIA using genome-wide association and examined them with CVD. Three hundred thirteen incident CVD events occurred during follow-up. Baseline sPLA2-IIA mass (median, 25th-75th percentile: 3.81, 2.49-6.03 ng/mL) was associated with increased risk of CVD: risk factor-adjusted hazard ratio (95% CI; P) per SD increment: 1.22 (1.08-1.38; P=0.002). This remained significant (1.18; 1.04-1.35; P=0.01) after incrementally adjusting for hsCRP. Similar estimates were observed in rosuvastatin and placebo groups (Ptreatment interaction>0.05). The rs11573156C variant in PLA2G2A (encoding sPLA2-IIA) had the strongest effect on sPLA2-II: median (25th-75th percentile, ng/mL) for CC and GG genotypes: 2.79 (1.97-4.01) and 7.38 (5.38-10.19), respectively; and had nonsignificant trend for higher CVD risk (hazard ratio, 1.11; 95% CI, 0.89-1.38; P=0.34). Conclusions- In the JUPITER population recruited on chronic inflammation, sPLA2-IIA mass was associated with CVD risk relating to vascular inflammation not fully reflected by hsCRP. Additional studies, including larger functional genetic and clinical studies, are needed to determine whether sPLA2-IIA may be a potential pharmacological target for primary prevention of CVD. Clinical Trial Registration- URL: http://www.clinicaltrials.gov . Unique identifier: NCT00239681.

[8] *Gao X, Song J, Watase H et al.* **Differences in Carotid Plaques Between Symptomatic Patients With and Without Diabetes Mellitus**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118312092.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31070472

ABSTRACT
Objective-- Diabetes mellitus is associated with high-risk atherosclerotic plaques. This study aimed to compare characteristics of carotid atherosclerotic plaques in symptomatic Chinese diabetic and nondiabetic patients using vessel wall magnetic resonance imaging. Approach and Results-- Patients with cerebral ischemic symptoms in the anterior circulation and carotid atherosclerotic plaque determined by ultrasound were recruited from a cross-sectional, observational, multicenter study of CARE-II (Chinese Atherosclerosis Risk Evaluation). All patients underwent magnetic resonance imaging for carotid arteries. The morphological and compositional characteristics of carotid plaques were compared between diabetic and nondiabetic patients using linear (continuous variables) and logistic regression (binary variables). In a total of 584 recruited patients, 182 (31.2%) had diabetes mellitus. From the univariate analysis, diabetic patients had a significantly greater mean wall area (33.7 versus 31.1 mm(2); P=0.002), maximum wall thickness (3.2 versus 2.8 mm; P<0.001), and mean normalized wall index (43.8% versus 41.0%; P<0.001) and had a significantly higher prevalence of calcification (51.6% versus 36.6%; P=0.001), lipid-rich necrotic core (77.5% versus 58.5%; P<0.001), and high-risk plaque (29.7% versus 19.9%; P=0.011) than nondiabetic patients. After adjusting for clinical characteristics, differences in presence of calcification (P=0.018) and lipid-rich necrotic core (P=0.001) remained statistically significant. Conclusions-- Symptomatic Chinese diabetic patients are more likely to have carotid plaque with calcification and lipid-rich necrotic core than nondiabetic patients, suggesting that diabetic patients may develop more severe atherosclerotic disease that should be accounted for in their clinical management.

[9] *Shih DM, Zhu W, Schugar RC et al.* **Genetic Deficiency of Flavin-Containing Monooxygenase-3 (Fmo3) Protects Against Thrombosis but Has Only a Minor Effect on Plasma Lipid Levels**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119312592.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31070450

ABSTRACT
Objective- FMO (flavin-containing monooxygenase)-3 converts bacterial-derived trimethylamine to trimethylamine N-oxide (TMAO), an independent risk factor for cardiovascular disease. We generated FMO-3 knockout (FMO3KO) mouse to study its effects on plasma TMAO, lipids, glucose/insulin metabolism, thrombosis, and atherosclerosis. Approach and Results- Previous studies with an antisense oligonucleotide (ASO) knockdown strategy targeting FMO-3 in LDLRKO (low-density lipoprotein receptor knockout) mice resulted in major reductions in TMAO levels and atherosclerosis, but also showed effects on plasma lipids, insulin, and glucose. Although FMO3KO mice generated via CRISPR/Cas9 technology bred onto the LDLRKO background did exhibit similar effects on TMAO levels, the effects on lipid metabolism were not as pronounced as with the ASO knockdown model. These differences could result from either off-target effects of the ASO or from a developmental adaptation to the FMO-3 deficiency. To distinguish these possibilities, we treated wild-type and FMO3KO mice with control or FMO-3 ASOs. FMO-3-ASO treatment led to the same extent of lipid-lowering effects in the FMO3KO mice as the wild-type mice, indicating off-target effects. The levels of TMAO in LDLRKO mice fed an atherogenic diet are very low in both wild-type and FMO3KO mice, and no significant effect was observed on atherosclerosis. When FMO3KO and

wild-type mice were maintained on a 0.5% choline diet, FMO3KO showed a marked reduction in both TMAO and in vivo thrombosis potential. Conclusions- FMO3KO markedly reduces systemic TMAO levels and thrombosis potential. However, the previously observed large effects of an FMO-3 ASO on plasma lipid levels appear to be due partly to off-target effects.

[10] *Tiniakou E, Rivera E, Mammen AL, Christopher-Stine L*. **Use of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors in statin-associated immune mediated necrotizing myopathy: a case-series**. Arthritis & rheumatology (Hoboken, N.J.) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31058470
ABSTRACT
OBJECTIVES: To report the safety of Protein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors in patients with statin-associated anti-HMG-CoA reductase (HMGCR) immune mediated necrotizing myopathy (IMNM). METHODS: Muscle strength was assessed in anti-HMGCR positive patients at each visit before and after the initiation of PCSK9 inhibitors. The trend over time of available creatine kinase (CK) and serum anti-HMGCR antibody titers were followed. RESULTS: Among 122 anti-HMGCR positive patients, we identified 8 patients placed on PCSK9 inhibitors for hyperlipidemia. These were followed for an average of 1.5 years (3-37months) and none exhibited reduction in muscle strength. The mean CK level prior to the initiation of PCSK9 inhibitors was 956+/-1137 IU/L and this declined to at 419+/-393 IU/L at their last visit. Anti-HMGCR antibody titers followed similar trend. Notably, in 2 patients the initiation of the lipid-lowering medication was followed by an unanticipated spontaneous clinical improvement and reduction in immunosuppression. CONCLUSIONS: PCSK9 inhibitors are safe to our experience for long term use in statin-associated IMNM patients as a cholesterol-lowering agent.

[11] *Wang T, Sun C, Hu L et al.* **Sirt6 stabilizes atherosclerosis plaques by promoting macrophage autophagy and reducing contact with endothelial cells**. Biochemistry and cell biology = Biochimie et biologie cellulaire 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31063699
ABSTRACT
Sirt6 has been reported to play a protective role in macrophage foam cell formation, but whether Sirt6 controls atherosclerosis plaque stability and whether it can reduce the interaction between endothelial cells and macrophages remains obscure. The aim of this study was to investigate the effect of Sirt6 on atherosclerosis plaque stability and the underlying mechanisms. We used Tie2-Cre transgenic mice as a Cre-lox tool to delete Sirt6 floxed sequences in endothelial cells during adulthood to establish Sirt6-/- mice. ApoE-/-:Sirt6-/- and ApoE-/-:Sirt6Tg mice were used in our investigation. After a 16-week high-fat diet, the mice developed markedly atherosclerotic plaques. Sirt6 knockout exacerbated atherosclerotic plaque progression in both size and stability. In vitro, murine macrophage RAW264.7 cells were treated with ox-low density lipoproteins for 24 h to simulate atherosclerosis. Furthermore, Sirt6 overexpression remarkably increased autophagic flux in macrophages and inhibited macrophage apoptosis. Moreover, Sirt6 overexpression inhibited the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and platelet selectin (P-selectin), leading to reduced infiltration of macrophages and foam cells. In

conclusion, our study indicates a new mechanism-based strategy to therapeutically stimulate atherosclerosis plaque stability.

[12] *Kozakova M, Morizzo C, Goncalves I et al.* **Cardiovascular organ damage in type 2 diabetes mellitus: the role of lipids and inflammation**. Cardiovascular diabetology 2019; 18:61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31077210

ABSTRACT

BACKGROUND: The relationship between dyslipidemia, inflammation and CV organ damage in type 2 diabetes mellitus (T2DM) is complex. Insulin resistance and inflammatory cytokines interleukins (ILs) increase plasma triglycerides (TG). ILs also up-regulate expression of matrix-metalloproteinases (MMPs) that, together with TG, decrease high density lipoprotein cholesterol (HDL) levels. High TG, low HDL, increased ILs and MMPs trigger structural and functional changes in different parts of cardiovascular (CV) system. To understand better the role of lipids and inflammation in CV organ damage, the present study investigated the inter-relationships between lipids, ILs and MMPs, as well as the associations of lipids, ILs and MMPs with various CV measures, both in diabetic and non-diabetic population (nonT2DM). METHODS: In T2DM patients (N = 191) and nonT2DM subjects (N = 94) were assessed carotid intima-media thickness (cIMT) and inter-adventitial diameter (IADiam), carotid wave speed (ccaWS), carotid-femoral pulse wave velocity (cfPWV), left ventricular (LV) mass, LV systolic (s') and early diastolic (e') longitudinal velocities of mitral annulus, together with glycemic control, lipid profile, IL-6, IL-18 and MMP-12. RESULTS: T2DM patients, as compared to nonT2DM subjects, had significantly higher plasma levels of IL-6, IL-18, MMP-12 and lower HDL ($P < 0.05$-0.0001). They had also higher cIMT, IADiam, ccaWS, cfPWV and LV mass, and lower e' velocity ($P < 0.005$-0.0001). Both in T2DM patients and nonT2DM subjects, MMP-12 increased with IL-6 ($r = 0.43$ and 0.39; $P < 0.0001$) and IL-18 ($r = 0.32$ and 0.42; $P < 0.0001$), and HDL decreased with MMP-12 ($r = -0.29$ and -0.42; $P < 0.0001$). In both populations, MMP-12 was directly associated with IADiam, ccaWS, cfPWV and LV mass ($r = 0.42$, 0.32, 0.26 and 0.29; $P < 0.0001$ in T2DM patients, and $r = 0.39$, 0.28, 0.32 and 0.27; $P < 0.01$-0.0001 in nonT2DM subjects). In multivariate analysis, MMP-12 remained independently related to IADiam, ccaWS, cfPWV and LV mass in T2DM patients, and to IADiam only in nonT2DM subjects. CONCLUSIONS: This cross-sectional study demonstrated a direct association between ILs and MMP-12, as well as an inverse association between MMP-12 and HDL, both in T2DM patients and in nonT2DM subjects. In T2DM patients, who had higher levels of ILs and MMP-12, the latter was independently related to several structural and functional markers of preclinical CV organ damage.

[13] *Huang Z, Li Q, Ye W et al.* **Efficacy and Safety of Ezetimibe in Combination with Atorvastatin for Acute Coronary Syndrome Patients Accompanied with Type 2 Diabetes: A Single-Center, Non-randomized Cohort Study**. Chemical & pharmaceutical bulletin 2019; 67:419-425.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31061366

ABSTRACT

Patients with type 2 diabetes (T2DM) and hyperlipidemia are with high risk of myocardial infarction (MI) or coronary death events. The combined use of ezetimibe and atorvastatin could

improve treatment efficacy and safety. To explore the efficacy and safety of ezetimibe in combination with atorvastatin for the treatment of patients with T2DM and acute coronary syndrome (ACS). This was a non-randomized cohort study of 95 consecutive, treatment-naive patients with T2DM and ACS treated at the Quanzhou First Hospital of Fujian Province between February 2014 and March 2016. According to the treatment strategy they selected, the patients were categorized into the atorvastatin (n = 46) and atorvastatin + ezetimibe (n = 49) groups. The patients were followed up at 2 weeks and 12 months. The primary endpoints included the incidence of adverse cardiovascular events and changed in blood lipids and high-sensitivity C-reactive protein (hs-CRP). At 12 months, serum total cholesterol (TC), triglycerides, and low-density lipoprotein cholesterol (LDL-C) levels were significantly lower, and high-density lipoprotein cholesterol (HDL-C) levels were significantly higher in the atorvastatin + ezetimibe (EZ) group than in the atorvastatin group (all $p < 0.05$). The LDL-C control rate at 12 months was significantly higher in the atorvastatin + EZ group compared with the atorvastatin group ($p = 0.006$). Seven patients in the atorvastatin group were re-hospitalized for angina pectoris, while only one patient in the atorvastatin + EZ group was re-hospitalized for angina pectoris ($p = 0.02$). The efficacy of atorvastatin + EZ in treating T2DM patients accompanied with ACS was significantly higher than using atorvastatin alone. This combined strategy has good safety profile, and could be recommended for clinical application.

[14] *Xiao J, Deng YM, Liu XR et al.* **PCSK9: A new participant in lipophagy in regulating atherosclerosis?** Clinica chimica acta; international journal of clinical chemistry 2019; 495:358-364.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31075236
ABSTRACT
Proprotein convertase subtilisin kexin 9 (PCSK9) regulates lipid metabolism by degrading low-density lipoprotein receptor on the surface of hepatocytes. PCSK9-mediated lipid degradation is associated with lipophagy. Lipophagy is a process by which autophagosomes selectively sequester lipid-droplet-stored lipids and are delivered to lysosomes for degradation. Lipophagy was first discovered in hepatocytes, and its occurrence provides important fundamental insights into how lipid metabolism regulates cellular physiology and pathophysiology. Furthermore, PCSK9 may regulate lipid levels by affecting lipophagy. This review will discuss recent advances by which PCSK9 mediates lipid degradation via the lipophagy pathway and present lipophagy as a potential therapeutic target for atherosclerosis.

[15] *Sands BE, Taub PR, Armuzzi A et al.* **Tofacitinib Treatment is Associated with Modest and Reversible Increases in Serum Lipids in Patients with Ulcerative Colitis**. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31077827
ABSTRACT
BACKGROUND & AIMS: Tofacitinib is an oral, small-molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We analyzed inflammation, lipid concentrations, and incidence rates of major adverse cardiovascular (CV) events (MACEs) in patients who received tofacitinib in worldwide studies. METHODS: We collected data from 1157 patients who

participated in 3 8-week induction studies (1 phase-2 study and 2 phase-3 studies; patients received tofacitinib 10 mg twice daily or placebo), a 52-week phase-3 maintenance study of responders (patients received tofacitinib 5 or 10 mg twice daily or placebo), and an ongoing long-term extension study of patients who did and did not respond to induction or maintenance therapy (patients received tofacitinib 5 or 10 mg twice daily). Lipid concentrations were assessed from induction baseline to week 61 (week 52 of maintenance therapy). We calculated MACE incidence rates (patients with >/=1 event per 100 patient-years of exposure) and Reynolds risk score (RRS; a composite score used to determine CV risk) for patients given tofacitinib vs placebo. RESULTS: The mean RRS was <5% at baseline and week 8 of treatment with tofacitinib. At week 8, there were greater increases from baseline in total cholesterol, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol in patients given tofacitinib compared with placebo. There were correlations between reduced levels of high-sensitivity C-reactive protein and increased serum concentrations of lipid in patients given tofacitinib or placebo (P<.001). Lipid concentrations were increased in patients given tofacitinib vs patients given placebo through week 61. Overall, ratios of low-density lipoprotein cholesterol to HDL-c and total cholesterol to HDL-c did not change significantly over the 61-week period. Four MACEs were reported; the incidence rate was 0.24 (95% CI, 0.07-0.62) and 3 of these patients had 4 or more CV risk factors. CONCLUSIONS: In an analysis of data from 5 trials of patients with UC who received tofacitinib, we found reversible increases in lipids with treatment and inverse correlations with reduced levels of high-sensitivity C-reactive protein. We did not find clinically meaningful changes in lipid ratios or RRS. MACEs were infrequent and not dose-related.

[16] *Tomic-Smiljanic M, Vasiljevic D, Lucic-Tomic A et al.* **Influence of different supplementation on platelet aggregation in patients with rheumatoid arthritis**. Clinical rheumatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31076942
ABSTRACT
INTRODUCTION: Long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) have been reported to reduce platelet aggregation. Our aim was to prospectively assess the potential influence of different supplementation omega-3 PUFA on the antiplatelet effects in rheumatoid arthritis (RA) patients. METHODS: The study included 60 patients with RA at the Department of Rheumatology, Clinical Center Kragujevac. Patients were divided into three groups depending on who used concentrated fish oil only or concentrated fish oil in combination with evening primrose oil or control group without supplementation in a period of 3 months. Platelet aggregation was measured using the multiplate analyzer and expressed through the value of adenosine diphosphate (ADP) test, aranchidonic acid-induced aggregation (ASPI) test, thrombin receptor-activating peptide (TRAP) test (to assess baseline platelet aggregation), and the ratio of ADP/TRAP and ASPI/TRAP representing the degree of inhibition of platelet aggregation compared to the basal value. The platelet function analysis in whole blood was performed 18-24 h before starting supplementation and after 90 days. Considerations were taken in the representation of demographic, clinical characteristics, and laboratory parameters between the groups. RESULTS: Patients who used concentrated fish oil only had a significantly lower value of the ratio of

ADP/TRAP (0.68 +/- 0.20) compared to patients without supplementation (0.83 +/- 0.12; p = 0.008), while there was no statistically significant difference in values of other laboratory parameters of platelet function between other groups. CONCLUSIONS: Co-administration of supplementation-concentrated fish oil may reduce platelet aggregation in adults with RA. KEY POINTS: * Omega-3 PUFAs are essential for health and are known to possess anti-inflammatory properties, improving cardiovascular health as well as benefiting inflammatory diseases.. * In this paper, we report on anti-aggregation effects n-3 PUFAs and -linolenic acid in RA. * The risk of cardiovascular morbidity and mortality is increased in RA, and dietary supplementation of n-3 PUFA may have preventive potential for the cardiovascular management in rheumatoid arthritis.

[17] *Agustini B, Mohebbi M, Woods RL et al.* **Association Between Statin Use and Depressive Symptoms in a Large Community-Dwelling Older Population Living in Australia and the USA: A Cross-Sectional Study**. CNS drugs 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31062260

ABSTRACT
BACKGROUND: Statin use has been frequently associated with depressive symptoms in an older population. However, the nature of this association is uncertain in the literature. In this study, we aimed to investigate the association of statin intake and the prevalence of depressive symptoms in healthy community-dwelling older adults living in Australia and the USA. METHODS: We analysed baseline data from 19,114 participants, over 70 years of age (over 65 years of age, if from an ethnic minority). The association of self-reported statin use and prevalence of depressive symptoms, as measured by a validated depression scale [Center for Epidemiological Studies Depression Scale (CES-D 10)], was determined using logistic regression models. Multivariable logistic models were implemented to account for important demographics and other lifestyle and socioeconomic factors, such as sex, age, living status, education and smoking history. RESULTS: A total of 5987 individuals were statin users. Of those, 633 (10.6%) had depressive symptoms (CES-D 10 cut-off >/= 8), compared with 1246 (9.5%) of the non-statin users. In the unadjusted model, statin use was associated with an increase in prevalence of depressive symptoms (odds ratio 1.13, confidence interval 1.02-1.25, p = 0.02). However, after adjusting for important demographic and socioeconomic factors, the use of statins was not significantly associated with depressive symptoms (odds ratio 1.09, confidence interval 0.98-1.20, p = 0.11). In secondary analyses, only simvastatin was marginally associated with an increased prevalence of depressive symptoms. Statins were associated with a decreased prevalence of depressive symptoms in individuals with severe obesity (body mass index > 35 kg/m(2)) and an increased prevalence in participants between 75 and 84 years of age. CONCLUSION: This study in a large community-dwelling older population did not show any association of statins with late-life depressive symptoms, after accounting for important socioeconomic and demographic factors. Confounding by indication is an important issue to be addressed in future pharmacoepidemiologic studies of statins.

[18] *Kolovou GD, Watts GF, Mikhailidis DP et al.* **Postprandial Hypertriglyceridaemia Revisited In The Era Of Non-Fasting Lipid Profile Testing: A 2019 Expert Panel Statement**. Current vascular pharmacology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31060488

ABSTRACT

Residual vascular risk exists despite aggressive lowering of low density lipoprotein cholesterol (LDL-C). A contributor to this residual risk may be elevated fasting, or non-fasting, levels of triglyceride (TG)-rich lipoproteins. Therefore, there is a need to establish whether a standardised oral fat tolerance test (OFTT) can improve atherosclerotic cardiovascular (CV) disease (ASCVD) risk prediction in addition to a fasting or non-fasting lipid profile. An expert panel considered the role of postprandial hypertriglyceridaemia (as represented by an OFTT) in predicting ASCVD. The panel updated its 2011 statement by considering new studies and various patient categories. The recommendations are based on expert opinion since no hard endpoint trials have been performed, Table 1. Individuals with fasting TG concentration <1 mmol/L (89 mg/dL) commonly do not have an abnormal response to an OFTT. In contrast, those with fasting TG concentration >/=2 mmol/L (175 mg/dL) or non-fasting >/=2.3 mmol/L (200 mg/dL) will usually have an abnormal response. We recommend considering postprandial hypertriglyceridaemia testing when fasting TG concentrations and non-fasting TG concentrations are 1-2 mmol/L (89-175 mg/dL) and 1.3-2.3 mmol/L (115-200 mg/dL), respectively as an additional investigation for metabolic risk prediction along with other risk factors (obesity, current tobacco abuse, metabolic syndrome, hypertension, and diabetes mellitus). The panel proposes that an abnormal TG response to an OFTT (consisting of 75 g fat, 25 g carbohydrate and 10 g proteins) is >2.5 mmol/L (220 mg/dL). Postprandial hypertriglyceridaemia is an emerging factor that may contribute to residual CV risk. This possibility requires further research. A standardised OFTT will allow comparisons between investigational studies. We acknowledge that the OFTT will be mainly used for research to further clarify the role of TG in relation to CV risk. For routine practice, there is a considerable support for the use of a single non-fasting sample.

[19] *Jujic A, Ostling G, Persson M et al.* **Skin autofluorescence as a measure of advanced glycation end product levels is associated with carotid atherosclerotic plaque burden in an elderly population**. Diabetes & vascular disease research 2019:1479164119845319.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31064217

ABSTRACT

BACKGROUND: Advanced glycation end product is an established risk marker in diabetic vascular disease, but its possible associations with atherosclerosis in a general population are yet to be investigated. We studied the degree of carotid atherosclerosis and its association with skin autofluorescence in an elderly population. METHODS: Carotid ultrasound and skin autofluorescence measurements were performed in a subpopulation within the 'Malmo Diet and Cancer Cardiovascular Cohort' re-examination study (n = 523). Total plaque area including all prevalent plaques in the right carotid artery was calculated. Complete data on all variables were available for 496 subjects (mean age 72 years). RESULTS: Each 1 standard deviation increment of skin autofluorescence was associated with increased risk of prevalent large plaques (odds ratio, 1.32; 95% confidence interval, 1.05-1.66; p = 0.018) independently of diabetes and cardiovascular risk factors. The top versus bottom tertile of the skin autofluorescence was associated with an approximately twofold risk of being in the population with the highest plaque burden [top quartile with total plaque area 35 mm(2) (odds ratio, 1.88;

95% confidence interval, 1.05-3.39; p for trend = 0.027)] in fully adjusted analysis. CONCLUSION: In an elderly population, skin autofluorescence was associated with increasing degree of carotid atherosclerosis measured as total plaque area, independently of diabetes and cardiovascular risk factors.

[20] *Sirtori CR, Yamashita S, Francesca Greco M et al.* **Recent advances in synthetic pharmacotherapies for dyslipidaemias**. European journal of preventive cardiology 2019:2047487319845314.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31060364
ABSTRACT
Despite the demonstrated benefits of statins and injectable biologics, there is a need for new and safe oral agents for addressing classical lipid targets, low-density lipoprotein cholesterol (LDL-C), triglycerides and high-density lipoprotein cholesterol (HDL-C). LDL-C is unquestionably causal in the development of atherogenesis and atherosclerotic cardiovascular disease, but new options are required to address triglyceride-rich lipoproteins and lipoprotein(a). For hypercholesterolaemia, pitavastatin provides a very low dose and potent statin that does not adversely affect glucose metabolism; bempedoic acid acts at a biochemical step preceding hydroxymethylglutaryl-CoA reductase and is not associated with muscular side effects. For hypertriglyceridaemia, pemafibrate displays a unique and selective agonist activity on peroxisomal proliferator activated receptor-alpha that does not elevate homocysteine or creatinine. Although omega-3 fatty acids supplementation is not effective in secondary prevention, high dose eicosapentaenoic ethyl ester can lead to a remarkable fall in first and recurrent events in high risk patients with hypertriglyceridaemia/low HDL-C. Gemcabene, a dicarboxylic acid regulating apolipoprotein B-100, is effective in reducing both cholesterol and triglycerides. Among cholesteryl ester transfer protein antagonists that elevate HDL-C, only anacetrapib reduces cardiovascular events. Probucol stimulates reverse cholesteryl ester transport, lowers LDL-C stabilizing plaques and may lower incidence of cardiovascular events. These agents, which act through novel mechanisms, afford good and potentially safe treatment choices that may increase adherence and the attainment of therapeutic targets.

[21] *Cicero AFG, Landolfo M, Ventura F, Borghi C*. **Current pharmacotherapeutic options for primary dyslipidemia in adults**. Expert opinion on pharmacotherapy 2019:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31059312
ABSTRACT
INTRODUCTION: Atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, remain a leading cause of death and disability worldwide. One of the major risk factors of ASCVD is dyslipidemia and all the available guidelines suggest the importance of strategies for lipid control in a remarkable proportion of the general population. Areas covered: This review focuses on the therapeutic options available for the management of lipid disorders in adults. Expert opinion: A large body of evidence supports that statins are still the first-line option for the management of hypercholesterolemia in a large percentage of patients. Statins should be given at the appropriate dose and considering the differences in lipid-lowering potency across the different medications. The main current challenge in the treatment of lipid disorders is the need of improving patient adherence and persistence to lipid-lowering treatments beyond the

drug choice and the target lipid component. To achieve this goal, the best strategy would be to treat the patients by using the appropriate drugs given at adequate doses to reach the treatment target. We should also avoid drug interactions, monitor possible untoward side effects and promote adherence to treatment by tailoring treatment strategies to each patient.

[22] *Joshita S, Umemura T, Yamashita Y et al.* **Biochemical and Plasma Lipids Responses to Pemafibrate in Patients with Primary Biliary Cholangitis**. Hepatology research : the official journal of the Japan Society of Hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31077509
ABSTRACT
BACKGROUND AND AIMS: Fibrate addition to ursodeoxycholic acid (UDCA) therapy has been shown to improve both liver biochemistry and long-term prognosis in PBC patients showing an incomplete biochemical response to UDCA alone. We herein describe the clinical outcome of 7 cases of PBC that received the new selective peroxisome proliferator-activated receptor alpha modulator pemafibrate in combination with UDCA therapy to investigate the biochemical and plasma lipid responses to the drug. METHODS: Of 124 initially enrolled PBC patients, 12 treated with UDCA alone and 7 receiving UDCA plus bezafibrate displayed alkaline phosphatase (ALP) levels above the upper limit of normal (330 U/L). Ultimately, 7 patients with PBC and dyslipidemia who had agreed to bi-weekly visits at our hospital for UDCA plus pemafibrate combination therapy were retrospectively analyzed. RESULTS: In the 4 cases that switched from bezafibrate to pemafibrate, ALP became significantly decreased (0.031) and gamma-glutamyltransferase tended to decrease (0.063) over the 3 months following pemafibrate addition. Two patients exhibited a greater than 50% reduction in ALP. No remarkable differences were observed for plasma lipid levels, alanine aminotransferase, aspartate aminotransferase, or the liver fibrosis marker Mac-2 binding protein glycosylation isomer between these time points. No adverse drug reactions were recorded. CONCLUSIONS: Pemafibrate might be another option for PBC patients displaying an incomplete response to UDCA therapy.

[23] *Asenjo Mota A, Caamano Selma O, Sanchez-Aquino Gonzalez R*. **[Are there different responses to different PCSK9 inhibitors?]**. Hipertens Riesgo Vasc 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31064717
ABSTRACT
The case is presented of a 62-year-old patient who required lipid-lowering therapy with proprotein convertase subtilisin/kexin type9 (PCSK9). It was empirically decided to change one drug to another of the two currently available, obtaining a different response. Our objective is to present our experience and to consider a possible therapeutic option in patients in whom, exceptionally, this could happen.

[24] *Straube R, Voit-Bak K, Gor A et al.* **Lipid Profiles in Lyme Borreliosis: A Potential Role for Apheresis?** Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2019; 51:326-329.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31071737
ABSTRACT

Dyslipidemia and dyslipoproteinemia are common causes of metabolic and cardiovascular diseases. On the other hand, intracellular bacteria, such as Borrelia burgdorferi, utilize host lipids to survive and disseminate within the host. Recent data suggest that elevated lipids are a contributing factor to the maintenance and severity of Lyme disease and its complications. Here we review and discuss the role of lipids in Borreliosis and report on a pilot trial to examine the potential roles of circulating lipids and lipoproteins in patients with Borrelia infection. In this analysis we assessed the clinical and lipid profiles of 519 patients (319 women, 200 men) with a proven history of Lyme disease, before and after an extracorporeal double membrane filtration. Lipid profiles pre- and post-apheresis were analyzed in conjunction with clinical symptoms and parameters of inflammation. Circulating cholesterol, triglycerides, LDL, LP(a), and other inflammatory lipids were significantly reduced after the apheresis, while symptoms of the disorder and bioindexes of inflammation such as CRP improved. Further studies should be initiated to investigate the possibly causal relation between Lyme disease and circulating lipids and to design appropriate therapeutic strategies.

[25] *Tada H, Takamura M, Kawashiri MA*. **Lipoprotein(a) as an Old and New Causal Risk Factor of Atherosclerotic Cardiovascular Disease**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31061262
ABSTRACT
Lipoprotein(a) [Lp(a)], discovered in 1963, has been associated with atherosclerotic cardiovascular disease (ASCVD) independent of other traditional risk factors, including LDL cholesterol. Lp(a) is an apolipoprotein B (apoB)-containing lipoprotein, which contains an LDL-like particle. Unlike LDL, which is a primary therapeutic target to decrease ASCVD, current guidelines recommend measuring Lp(a) for risk assessments because there is no clear evidence demonstrating the clinical benefit of decreasing Lp(a) using classical drugs such as niacin. However, recent Mendelian randomization studies indicate that Lp(a) causally correlates with ASCVD. In addition, novel drugs, including PCSK9 inhibitors, as well as antisense oligonucleotide for apo(a), have exhibited efficacy in decreasing Lp(a) substantially, invigorating a discussion whether Lp(a) could be a novel therapeutic target for further ASCVD risk reduction. This review aims to provide current understanding, and future perspectives, of Lp(a), which is currently considered a mere biomarker but may emerge as a novel therapeutic target in future clinical settings.

[26] *Olivetti CE, Alvarez Echazu MI, Perna O et al.* **Dodecenylsuccinic anhydride modified collagen hydrogels loaded with simvastatin as skin wound dressings**. Journal of biomedical materials research. Part A 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31071230
ABSTRACT
DDSA modification of collagen hydrogel to achieve an increment in wound dressing hydrophobicity for the delivery of non-water soluble drugs with antimicrobial and anti-inflammatory activity.

[27] *Mondragon-Garcia A, Luna-Luna M, Flores-Castillo C et al.* **Atorvastatin and Fenofibrate Exert Opposite Effects on the Vascularization and Characteristics of Visceral Adipose Tissue in**

New Zealand White Rabbits. Journal of cardiovascular pharmacology and therapeutics 2019:1074248419838517.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31056933
ABSTRACT
Statins may precipitate the onset of type 2 diabetes (T2D) in high-risk patients. In contrast, only the subset of individuals with insulin resistance and/or diabetes receives cardiovascular benefits with fibrates. In this context, previous observations from our laboratory suggested that atorvastatin induced an increase in visceral adipose tissue (VAT), whereas fenofibrate had the opposite effects in rabbits. Therefore, we determined the mass, morphology, and vascularization of VAT in New Zealand white rabbits (n = 6/group) that received 0.33 or 2.6 mg/kg/d of atorvastatin or fenofibrate, respectively, during 2 months. As expected, the cholesterol from the atorvastatin group was lower after treatment, while triglycerides decreased in the fenofibrate group. The mass of VAT from the fenofibrate group was 46% lower compared to the controls, meanwhile atorvastatin was associated with a larger diameter of adipocytes (+65%) than that of the control and fenofibrate groups. Fibroblast growth factor 2 (FGF2) gene expression was lower in the fenofibrate group than in the control group (-54%). By contrast, vascular endothelial growth factor A (VEGF-A) gene expression in fenofibrate-treated rabbits was 110% higher than in the control group. In agreement with the gene expression, the marker of angiogenesis platelet endothelial cell adhesion molecule 1 was slightly but significantly higher (+10%) in rabbits treated with fenofibrate than in controls, as determined by immunohistochemistry. These results suggest that fenofibrate is associated with a favorable remodeling of VAT, that is, reduced mass and increased vascularization in normolipemic rabbits; in contrast, atorvastatin induced a nonfavorable remodeling of VAT. These results may be related to the cardiovascular benefits of fenofibrate and the increased risk of T2D in high-risk patients induced by atorvastatin.

[28] *Bruckert E, Kereiakes DJ, Koren MJ et al.* **PCSK9 inhibition in patients with and without prior myocardial infarction or ischemic stroke: A pooled analysis of nine randomized-controlled studies of alirocumab**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31076261
ABSTRACT
BACKGROUND: Patients with prior cardiovascular events are at very high risk of recurrent events and may benefit from low-density lipoprotein cholesterol (LDL-C) lowering beyond that achieved with maximally tolerated statins. OBJECTIVE: To assess potential differences between the efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor, alirocumab, in patients with vs without prior myocardial infarction (MI)/ischemic stroke. METHODS: Data (n = 4880) were pooled from nine ODYSSEY phase 3 trials of alirocumab 75/150 mg or 150 mg every 2 weeks, mostly on background statins +/- other lipid-lowering therapies. Analyses were performed according to statin status, alirocumab dose, and control (placebo or ezetimibe). RESULTS: Baseline LDL-C, non-high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and apolipoprotein B levels were lower and lipoprotein(a) higher in patients with than without prior MI/ischemic stroke. LDL-C levels were reduced from baseline to week 24 in patients with (51.1%-62.9%) and without (43.6%-58.3%) prior MI/ischemic stroke, with no significant interaction between prior MI/ischemic stroke status and LDL-C-lowering

efficacy of alirocumab vs controls. Alirocumab significantly reduced other lipid/lipoproteins (including lipoprotein[a]) similarly in patients with/without MI/ischemic stroke. Week 24 LDL-C goal attainment rates for subgroups with/without prior MI/ischemic stroke on background statins were 74.1%-84.8% and 63.7%-74.7%, respectively. The safety profile of alirocumab was generally similar regardless of prior MI/ischemic stroke status. CONCLUSIONS: Alirocumab significantly reduced LDL-C and other atherogenic lipids/lipoproteins in patients with prior MI/ischemic stroke, and the majority of this very high cardiovascular risk population achieved LDL-C goals; efficacy and safety results were similar in patients without prior MI/ischemic stroke.

[29] *Tang K, Lin J, Ji X et al.* **Non-alcoholic fatty liver disease with reduced myocardial FDG uptake is associated with coronary atherosclerosis**. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31077075

ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) has a significant role in the development of coronary atherosclerosis, independent of traditional cardiovascular and metabolic risk factors. However, the role of myocardial glucose uptake in NAFLD patients who develop coronary atherosclerosis was unclear. The aim of the present study thus was to investigate the association between NAFLD with characteristic of coronary atherosclerotic plaque and myocardial glucose uptake measured by using (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG PET). METHODS AND RESULTS: A total of 418 consecutive subjects who had undergone FDG PET/computed tomography (CT) and coronary computed tomography angiography (CCTA) were retrospectively investigated. Fatty liver was assessed by unenhanced CT. Coronary atherosclerotic plaques and stenosis on CCTA were evaluated. The metabolic parameters were measured on PET images. The ratio of the maximum myocardium FDG value to the mean standardized uptake value of liver (SUVratio) was calculated to estimate myocardial glucose uptake. The association of myocardial glucose uptake with NAFLD and coronary atherosclerosis was determined by multivariate logistic regression analysis. The proportion of low SUVratio in patients with NAFLD was significantly higher compared to those without NAFLD (45.00% vs 19.82%, P < .001). There was a significantly negative correlation between myocardial FDG uptake and hepatic steatosis in association trend analysis (P < .001). When the proportion of individuals with non-calcified plaque on CCTA is stratified by quartiles of SUVratio, patients with low quartiles of SUVratio were more likely to have higher proportion of non-calcified plaque than those with high quartiles of SUVratio (Q1 and Q2 vs Q3 and Q4, P = .003). The trend analysis presented correlated inversely relationship between non-calcified plaque and myocardial SUVratio (P = .001). Moreover, multivariate regression analysis showed that the low SUVratio was independently associated with NAFLD, non-calcified plaque, and significant stenosis after adjusting for clinically important factors. CONCLUSION: We demonstrated that the presence of reduced myocardial glucose uptake in patients with NAFLD was independently associated with non-calcified plaque and significant stenosis, suggesting an increased risk of coronary atherosclerosis and future cardiovascular events.

Literature update week 19 (2019)

[30] *Li S, Shi CH, Liu XJ et al.* **Association of CYP3A4*1G and CYP3A5*3 With the 1-year Outcome of Acute Ischemic Stroke in the Han Chinese Population**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31064695
ABSTRACT
BACKGROUND AND PURPOSE: Previous studies have shown that common variants within CYP3A4 and CYP3A5 are associated with statin pharmacokinetics and the risk of cardiovascular disease. However, the association of variants in CYP3A4 and CYP3A5 with the prognosis of ischemic stroke remains undetermined. Therefore, we investigated this herein. METHODS: Four hundred thirty-three consecutive patients with acute ischemic stroke were recruited. The outcome at the 1-year follow-up was assessed using the modified Rankin Scale (mRS). Two variants, CYP3A4*1G and CYP3A5*3, were genotyped by the improved Multiple Ligase Detection Reaction platform. RESULTS: Binary logistic regression analysis showed that the CYP3A4*1G/*1G homozygote was associated with poor outcome at 1 year (mRS score >/=2) after adjustment for conventional factors in the additive model (odds ratio [OR] = 2.92; 95% confidence interval, 1.07-7.98; P=.037) and recessive model (OR=3.37; 95% confidence interval, 1.26-9.04; P=.016). Subgroup analysis indicated that the CYP3A4*1G/*1G homozygote was associated with poor prognosis at 1 year among patients with stable high-intensity atorvastatin therapy (40-80 mg/d) after adjustment for conventional factors in the additive model (OR=8.16; 95% confidence interval, 1.50-44.44; P=.015) and recessive model (OR=9.06; 95% confidence interval, 1.72-47.64; P=.009). No significant association was identified between CYP3A5*3 and the 1-year outcome of patients with ischemic stroke. CONCLUSIONS: Our study findings suggest that the CYP3A4*1G/CYP3A4*1G genotype may be associated with poor prognosis at 1 year after acute ischemic stroke in the Han Chinese population.

[31] *Teng MS, Wu S, Hsu LA et al.* **Pleiotropic association of LIPC variants with lipid and urinary 8-hydroxy deoxyguanosine levels in a Taiwanese population**. Lipids in health and disease 2019; 18:111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31077211
ABSTRACT
BACKGROUND: Hepatic lipase (HL, encoded by LIPC) is a glycoprotein primarily synthesized and secreted by hepatocytes. Previous studies had demonstrated that HL is crucial for reverse cholesterol transport and affects the metabolism, composition, and level of several lipoproteins. In current study, we investigated the association of LIPC (Lipase C, Hepatic Type) variants with circulating and urinary biomarker levels by using subgroup and mediation analyses. METHODS: A total of 572 participants from Taiwan were genotyped for three LIPC single nucleotide polymorphisms (SNPs) by using TaqMan assay. Fasting levels of glucose, lipid profile, inflammation markers, urine creatinine and 8-hydroxy deoxyguanosine (8-OHdG) were measured. The chi-square test, 2-sample t test and Analysis of variance (ANOVA) were used to examine differences among variables and genotype frequencies. RESULTS: SNPs rs2043085 and rs1532085 were significantly associated with urinary 8-OHdG levels, whereas all three SNPs were more significantly associated with Triglycerides (TG) or HDL-cholesterol (HDL-C) levels after additional adjustment for HDL-C or TG levels, respectively. Subgroup analyses revealed that the association of the LIPC SNPs with the levels of serum TG, HDL-C, and urinary 8-OHdG

were predominantly observed in the men but not in the women. Differential associations of the LIPC SNPs with various lipid levels were observed in participants with different adiposity statuses. Mediation analyses indicated that TG levels acted as a suppressor masking the association of the LIPC genotypes with HDL-C levels, particularly in the men (Sobel test, all P < 0.01). CONCLUSION: Our data revealed that interaction and suppression effects mediated the pleiotropic association of the LIPC variants. The effects of the LIPC SNPs depended on sex, adiposity status, and TG levels. Thus, our findings can provide a method for identifying high-risk populations of cardiovascular diseases for clinical diagnosis.

[32] *Wang MX, Wong CH, Kim JE*. **Impact of whole egg intake on blood pressure, lipids and lipoproteins in middle-aged and older population: A systematic review and meta-analysis of randomized controlled trials**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31076323

ABSTRACT

BACKGROUND AND AIM: Effects of whole egg consumption on cardiovascular diseases (CVD) risk in the middle-aged and older population remain unclear due to inconsistent findings from observational and randomized controlled trials (RCTs). This meta-analysis aimed to assess the impacts of whole egg and egg category (whole eggs versus egg substitutes) intake quantity on CVD risk factors from systematically searched RCTs. Egg substitutes were hypothesized to have minimal effects of the blood lipid and lipoprotein profile as they are void of dietary cholesterol. METHODS AND RESULTS: As many as 434 studies identified from PubMed, Cochrane Library, CINAHL and Medline (Ovid) databases were screened and data were extracted from 8 selected RCTs. Quality of the selected studies were assessed and the overall effect sizes of weighted mean differences (WMD) were calculated using a random effects model. Non-differential effects in blood pressures, lipids and lipoproteins were observed when >4 whole eggs/week compared to </=4 whole eggs/week were consumed. Intake of >4 whole eggs/week compared to equivalent amounts of egg substitutes caused greater elevations in blood total cholesterol (WMD: 0.198 mmol/L; 95% CIs: 0.056, 0.339), HDL cholesterol (WMD: 0.068 mmol/L; 95% CIs: 0.006, 0.130) and LDL cholesterol (WMD: 0.171 mmol/L; 95% CIs: 0.028, 0.315) but did not differentially affect triglycerides concentration. CONCLUSION: Overall, the results support the notion that quantity of whole egg intake does not affect CVD risk factors and consuming egg substitutes may also be beneficial compared to whole eggs on lowering CVD risk in the middle-aged and older population.

[33] *Huang J, Li L, Zhang J et al.* **Treatment of Relapsed Chronic Subdural Hematoma in Four Young Children with Atorvastatin and Low-dose Dexamethasone**. Pharmacotherapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31069819

ABSTRACT

Chronic subdural hematoma (CSDH) can develop in children in rare cases. Burr-hole drainage (BHD) is the treatment of choice, but it is associated with a high rate of recurrence. This report describes 4 cases of pediatric patients (1-7 years old) with post-BHD relapsed CSDH, who were successfully treated with a drug regimen that included 2.5 to 5 mg of atorvastatin daily combined with dexamethasone with stepwise-decreasing dosing for a total of 4 weeks. After 4 weeks of treatment, hematoma was completely resolved in 3 patients and significantly reduced

in 1 patient. During the treatment, no patient reported clinically significant adverse events. No patient experienced hematoma relapse during the follow-up period, which lasted for up to 4 years. This case report suggests the need for a randomized, placebo-controlled trial to evaluate this drug regimen for non-surgical treatment of patients with relapsed CSDH.

[34] *Eshaghi A, Kievit RA, Prados F et al.* **Applying causal models to explore the mechanism of action of simvastatin in progressive multiple sclerosis**. Proceedings of the National Academy of Sciences of the United States of America 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31072935
ABSTRACT
Understanding the mode of action of drugs is a challenge with conventional methods in clinical trials. Here, we aimed to explore whether simvastatin effects on brain atrophy and disability in secondary progressive multiple sclerosis (SPMS) are mediated by reducing cholesterol or are independent of cholesterol. We applied structural equation models to the MS-STAT trial in which 140 patients with SPMS were randomized to receive placebo or simvastatin. At baseline, after 1 and 2 years, patients underwent brain magnetic resonance imaging; their cognitive and physical disability were assessed on the block design test and Expanded Disability Status Scale (EDSS), and serum total cholesterol levels were measured. We calculated the percentage brain volume change (brain atrophy). We compared two models to select the most likely one: a cholesterol-dependent model with a cholesterol-independent model. The cholesterol-independent model was the most likely option. When we deconstructed the total treatment effect into indirect effects, which were mediated by brain atrophy, and direct effects, simvastatin had a direct effect (independent of serum cholesterol) on both the EDSS, which explained 69% of the overall treatment effect on EDSS, and brain atrophy, which, in turn, was responsible for 31% of the total treatment effect on EDSS [beta = -0.037; 95% credible interval (CI) = -0.075, -0.010]. This suggests that simvastatin's beneficial effects in MS are independent of its effect on lowering peripheral cholesterol levels, implicating a role for upstream intermediate metabolites of the cholesterol synthesis pathway. Importantly, it demonstrates that computational models can elucidate the causal architecture underlying treatment effects in clinical trials of progressive MS.

[35] *Sudhakaran S, Bottiglieri T, Tecson KM et al.* **Alteration of lipid metabolism in chronic kidney disease, the role of novel antihyperlipidemic agents, and future directions**. Reviews in cardiovascular medicine 2018; 19:77-88.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31054556
ABSTRACT
The role of anti-hyperlipidemic therapy remains of key importance in the treatment of atherosclerotic disease. Moreover, given an already exaggerated predisposition for vascular disease at baseline, there is a preponderance of data that show management of hyperlipidemia is especially important in patients with chronic kidney disease. This is a concise, up-to-date review of lipid physiology, alterations in lipid concentrations with progressive renal failure, and currently available and emerging hyperlipidemic treatment options. Specifically, the roles of these therapies in patients with chronic kidney disease are reviewed.

[36] *Atia NN, Tawfeek HM, Rageh AH et al.* **Novel sublingual tablets of Atorvastatin calcium/Trimetazidine hydrochloride combination; HPTLC quantification, in vitro formulation and characterization**. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 2019; 27:540-549.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31061623
ABSTRACT
Background: Ischemic heart disorders and accumulation of lipids in blood vessels could contribute to angina pectoris. Therefore, the aim of this study was to formulate sublingual tablets containing a novel combination of Atorvastatin calcium (ATOR) and Trimetazidine HCl (TMZ) for efficient treatment of coronary heart disorders. Methods: The dissolution rate of water-insoluble ATOR was enhanced via complexation with sulfobutyl ether-beta-cyclodextrin (SBE-beta-CD) and addition of soluplus as a polymeric solubilizer excipient. The solubilized ATOR and TMZ were compressed into a sublingual tablets by direct compression technique and evaluated for their tableting characteristics. In addition, a new validated method based on High Performance Thin Layer Chromatography (HPTLC) was developed for simultaneous determination of both drugs in pure forms and sublingual tablets. Results: The developed HPTLC method showed LODs of 0.056 and 0.013mug/band and LOQs of 0.17, 0.040mug/band for TMZ and ATOR, respectively and proved to be linear, accurate, precise and robust. The optimum formulation containing mixture of superdisintegrants; Ac-Di-Sol and crospovidone (4.8% w/w, each) showed the shortest disintegration time (65s) and enhanced release profiles of both drugs. Conclusions: The prepared sublingual tablets combining ATOR and TMZ will be a promising dosage form for coronary heart disease patients with an instant action and improved patient compliance.

[37] *Cao LJ, Yu ZJ, Jiang M et al.* **[Clinical features of 20 patients with phytosterolemia causing hematologic abnormalities]**. Zhonghua yi xue za zhi 2019; 99:1226-1231.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31060161
ABSTRACT
Objective: To investigate the clinical and laboratory features of Phytosterolemia with hematological abnormalities. Methods: A retrospective study was performed on 20 patients with phytosterolemia admitted to the hematology department of the First Affiliated Hospital of Suzhou University during 2004-2017. History of patients was collected and the platelet counts, lipidomic analysis of plasma and osmotic fragility of erythrocytes were carried out. The erythrocyte and platelet morphology was examined by light microscope. Phytosterol levels in serum were measured by high performance liquid chromatography method. All of ABCG5/8 exons and intron-exon boundaries were amplified by PCR and directly sequenced to identify mutations. Results: All patients had been misdiagnosed as immune thrombocytopenia (ITP), or Evans syndrome with a mean delay of 21 years between symptom onset and accuracy diagnosis. The clinical manifestations of the patients were variable, but most of them presented with thrombocytopenia, anemia, splenomegaly from early ages, and xanthomas. Other major features were also observed, such as impaired liver functions (9 cases), premature atherosclerosis (5 cases) and/or arthritis (4 cases). Interestingly, all patients displayed an increased osmotic fragility of red cells and unique blood film features: large unequal platelets

surrounded by a circle of vacuoles and various abnormal erythrocyte shapes, especially stomatocyte. Serum levels of the sitosterol and stigmasterol in the patients were remarkably elevated up to 331.05(276.00, 670.20)mg/L and 244.60(193.78,399.40)mg/L, about 10 and 24 times higher than those of normal subjects. There were 14 mutations in ABCG5/8 genes found in the patients. Among them, 2/3 of the mutations were in ABCG5 gene, including p.(E22X), p.(R446X),g.ISV7+3G>A, p.(R446X), p.(R419H), g.ISV7+3G>A, p.(G90E), p.(R389H) and g.7+2G>A), and 1/3 in ABCG8 gene involving p.(M614-K628del), p.(E25X), p.(L86P fs X185), p.(R263Q), p.(E500D fs X604) and p.(G674R) mutation. The ABCG5 p.(R446X) mutation was found in 3 separate families. Conclusions: The phenomena of thrombocytopenia/ stomatocyte/splenomegaly represents a special clinical manifestations of phytosterolemia, and distinct changes of blood cell morphology are the typical characters. Plasma plant sterols and ABCG5/ABCG8 genes should be analyzed when such hematologic abnormalities are unexplained.