[1] *Eid WE, Sapp EH, McCreless T et al.* **Prevalence and Characteristics of Patients With Primary Severe Hypercholesterolemia in a Multidisciplinary Healthcare System**. The American journal of cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32773228
ABSTRACT
Severe hypercholesterolemia (SH) includes individuals with LDL-C ≥ 190 mg/dl, regardless of cause. These individuals have a fivefold increased long-term risk for coronary artery disease. Although systematic SH screening can trigger early treatment, current treatment guidelines may not be fully implemented or followed by patients. To further understand this treatment gap, we used electronic health record data to retrospectively assess SH prevalence, characteristics, and treatment in a midwest US healthcare system, between 2009 and 2020. Comorbidities, tobacco exposure, and prescribed lipid-lowering therapies were assessed. Statistical analyses were conducted to identify differences between individuals with primary SH (LDL-C ≥ 190 mg/dl, group 1) and those without primary SH (LDL-C < 190 mg/dl, group 2). Of 265,220 records analyzed, 7.4% met the definition for primary SH. These group 1 cases had more comorbidities than group 2 cases, including premature coronary artery disease (5.8% vs 2.7%). Results showed most individuals in group 1 were treated by primary care providers (43.2% to 45.7%), than by specialty providers (2.5% to 3.3%), and these primary care providers prescribed mainly moderate-intensity statins. Seventy-seven percent of group 1 individuals were treated with a statin, 27% were treated with a high-intensity statin, and 4% were treated with ezetimibe. Fewer young patients (< 40 years) were treated with statins (50% to 58.3%) than older patients (74.0% to 76.3%). Although use of general statins, high-intensity statins, and ezetimibe was higher in individuals with SH than those without SH, treatment remains below guideline recommendations, especially in younger individuals.

[2] *Nelson AJ, Navar AM, Mulder H et al.* **Association Between Triglycerides and Residual Cardiovascular Risk in Patients With Type 2 Diabetes Mellitus and Established Cardiovascular Disease (From the Bypass Angioplasty Revascularization Investigation 2 Diabetes [BARI 2D] Trial)**. The American journal of cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32773223
ABSTRACT
Triglyceride (TG) levels encompass several lipoproteins that have been implicated in atherogenic pathways. Whether TG levels independently associate with cardiovascular disease both overall and, in particular among patients with established coronary artery disease (CAD) and type 2 diabetes (T2DM), remains controversial. Data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was used to evaluate patients with T2DM and CAD. Cox proportional hazards models were used to determine the association between TG levels and outcomes. Stepwise adjustment was performed for demographics, clinical factors, lipid profile and statin treatment. The primary composite outcome was time to CV death, myocardial infarction (MI), or stroke and secondary outcome was CV death. Among 2,307 patients with T2DM and CAD, the mean (±SD) TG levels were 181 (±136) with a median (Q1-Q3) 148mg/dL (104-219). Overall, 51% of patients had TG <150 mg/dL, 18% 150-199 mg/dL, 28% 200-499 mg/dL and 3% ≥500 mg/dL. Participants with elevated TG levels (≥150 mg/dL) were younger (61 vs 63 years, p <0.001), had higher BMI (32 vs 30 kg/m(2), p <0.001), more likely to have had prior MI (34.2 vs 30.1%, p = 0.033) and revascularization (25.8 vs 21.4%, p = 0.013), had lower HDL-C (34 vs 39 mg/dL, p <0.001) and higher HbA1c (8 vs 7%, p

<0.001). In unadjusted analyses, baseline TG levels were linearly associated with both the primary composite and secondary outcomes. In fully adjusted analyses, every 50 mg/dL increase in TG level was associated with a 3.8% (HR 1.038, 95%CI 1.004-1.072, p <0.001) increase in the primary composite outcome and a 6.4% (HR 1.064 95%CI 1.018-1.113, p <0.001) increase in the secondary outcome. There was no interaction between TG and outcomes within key subgroups including female sex, additional non-coronary atherosclerotic disease, CKD or low LDL (<100 mg/dL). In conclusion, among patients with T2DM and CAD, elevated TG were independently associated with adverse cardiovascular outcomes, even after adjustment for clinical and simple biochemical covariates.

[3] *Otsuki H, Arashi H, Yamaguchi J et al.* **Effect of Ezetimibe + Pitavastatin on Cardiovascular Outcomes in Patients with ST-Segment Elevation Myocardial Infarction (from the HIJ-PROPER Study)**. The American journal of cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32773226
ABSTRACT
Lipid-lowering therapy is necessary to reduce cardiovascular event rates in patients with ST-segment elevation myocardial infarction (STEMI). This study aimed to evaluate the effect of intensive lipid-lowering therapy, which comprised pitavastatin and ezetimibe, on patients with STEMI. We therefore undertook a post hoc subanalysis of the HIJ-PROPER study's data that examined the clinical outcomes of the patients with dyslipidemia and STEMI (n = 880) who received pitavastatin and ezetimibe therapy (intensive lipid-lowering therapy group) or pitavastatin monotherapy (standard lipid-lowering therapy group), and we evaluated their cardiovascular events. The primary end point was a composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina, and ischemia-driven revascularization. During the median 3.4-year follow-up period, the cumulative rates of the primary end point were 31.9% and 39.7% in the intensive lipid-lowering therapy and standard lipid-lowering therapy groups, respectively (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.62 to 0.97; p = 0.02). Compared with the standard lipid-lowering therapy group, the intensive lipid-lowering therapy group had significantly lower all-cause death (6.9% vs 3.2%; HR, 0.45; 95% CI, 0.23 to 1.84; p = 0.01) and nonfatal stroke (2.9% vs 1.6%; HR, 0.77; 95% CI, 0.62 to 0.97; p = 0.02) rates. Patients with pitavastatin and ezetimibe therapy, as compared with pitavastatin monotherapy, had a lower cardiovascular event in STEMI patients. In conclusion, adding ezetimibe to statin therapy may be beneficial for patients with dyslipidemia and STEMI.

[4] *Crimarco A, Springfield S, Petlura C et al.* **A randomized crossover trial on the effect of plant-based compared with animal-based meat on trimethylamine-N-oxide and cardiovascular disease risk factors in generally healthy adults: Study With Appetizing Plantfood-Meat Eating Alternative Trial (SWAP-MEAT)**. The American journal of clinical nutrition 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32780794
ABSTRACT
BACKGROUND: Despite the rising popularity of plant-based alternative meats, there is limited evidence of the health effects of these products. OBJECTIVES: We aimed to compare the effect of consuming plant-based alternative meat (Plant) as opposed to animal meat (Animal) on health factors. The primary outcome was fasting serum trimethylamine-N-oxide (TMAO). Secondary outcomes included fasting insulin-like growth factor 1, lipids, glucose, insulin, blood

pressure, and weight. METHODS: SWAP-MEAT (The Study With Appetizing Plantfood-Meat Eating Alternatives Trial) was a single-site, randomized crossover trial with no washout period. Participants received Plant and Animal products, dietary counseling, lab assessments, microbiome assessments (16S), and anthropometric measurements. Participants were instructed to consume ≥2 servings/d of Plant compared with Animal for 8 wk each, while keeping all other foods and beverages as similar as possible between the 2 phases. RESULTS: The 36 participants who provided complete data for both crossover phases included 67% women, were 69% Caucasian, had a mean ± SD age 50 ± 14 y, and BMI 28 ± 5 kg/m2. Mean ± SD servings per day were not different by intervention sequence: 2.5 ± 0.6 compared with 2.6 ± 0.7 for Plant and Animal, respectively (P = 0.76). Mean ± SEM TMAO concentrations were significantly lower overall for Plant (2.7 ± 0.3) than for Animal (4.7 ± 0.9) (P = 0.012), but a significant order effect was observed (P = 0.023). TMAO concentrations were significantly lower for Plant among the n = 18 who received Plant second (2.9 ± 0.4 compared with 6.4 ± 1.5, Plant compared with Animal, P = 0.007), but not for the n = 18 who received Plant first (2.5 ± 0.4 compared with 3.0 ± 0.6, Plant compared with Animal, P = 0.23). Exploratory analyses of the microbiome failed to reveal possible responder compared with nonresponder factors. Mean ± SEM LDL-cholesterol concentrations (109.9 ± 4.5 compared with 120.7 ± 4.5 mg/dL, P = 0.002) and weight (78.7 ± 3.0 compared with 79.6 ± 3.0 kg, P < 0.001) were lower during the Plant phase. CONCLUSIONS: Among generally healthy adults, contrasting Plant with Animal intake, while keeping all other dietary components similar, the Plant products improved several cardiovascular disease risk factors, including TMAO; there were no adverse effects on risk factors from the Plant products.This trial was registered at clinicaltrials.gov as NCT03718988.

[5] *Perak AM, Lancki N, Kuang A et al.* **Associations of Gestational Cardiovascular Health with Pregnancy Outcomes: The Hyperglycemia and Adverse Pregnancy Outcome Study**. American journal of obstetrics and gynecology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32768430

ABSTRACT

BACKGROUND: The American Heart Association's formal characterization of "cardiovascular health" combines several metrics in a health-oriented, rather than disease-oriented, framework. Although cardiovascular health assessment during pregnancy has been recommended, its significance for pregnancy outcomes is unknown. OBJECTIVE: The purpose of this study was to examine the association of gestational cardiovascular health-formally characterized by a combination of five metrics-with adverse maternal and newborn outcomes. STUDY DESIGN: We analyzed data from the Hyperglycemia and Adverse Pregnancy Outcome Study, including 2,230 mother-newborn dyads from six countries. Maternal cardiovascular health was defined by the combination of five metrics measured at a mean of 28 (24-32) weeks' gestation: body mass index, blood pressure, lipids, glucose, and smoking. Levels of each metric were categorized using pregnancy guidelines, and total cardiovascular health was scored (0-10 points; 10 most favorable). Cord blood was collected at delivery, newborn anthropometrics were measured within 72 hours, and medical records were abstracted for obstetric outcomes. Modified Poisson and multinomial logistic regression were utilized to test associations of gestational cardiovascular health with pregnancy outcomes, adjusted for center and maternal and newborn characteristics. RESULTS: Women averaged 29.6 years old and delivered at a mean gestational age of 39.8 weeks. The mean

total gestational cardiovascular health score was 8.5 (of 10); 35.7% had all ideal metrics and 7.8% had 2+ poor metrics. In fully adjusted models, each 1 point higher (more favorable) cardiovascular health score was associated with lower risks for preeclampsia (relative risk 0.67 [95% confidence interval, 0.61-0.74]), unplanned primary cesarean section (0.88 [0.82-0.95]), and newborn birthweight >90(th) percentile (0.81 [0.75-0.88]), sum of skinfolds >90(th) percentile (0.85 [0.77-0.93]), and insulin sensitivity <10(th) percentile (0.83 [0.77-0.90]). Cardiovascular health categories demonstrated graded associations with outcomes; for example, relative risks (95% confidence intervals) for preeclampsia were 3.05 (1.35-7.21), 5.07 (2.31-11.11), and 8.88 (3.79-20.81) for women with 1+ intermediate, 1 poor, or 2+ poor (versus all ideal) metrics, respectively. CONCLUSION: More favorable cardiovascular health at 24-32 weeks' gestation was associated with lower risks for several adverse pregnancy outcomes in a multinational cohort.

[6] *Mohammad Mirzaei N, Weintraub WS, Fok PW*. **An integrated approach to simulating the vulnerable atherosclerotic plaque**. American journal of physiology. Heart and circulatory physiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32795179
ABSTRACT
Analyses of individual atherosclerotic plaques are mostly descriptive, relying - for example - on histological classification by spectral analysis of ultrasound waves or staining and observing particular cellular components. Such passive methods have proved useful for characterizing the structure and vulnerability of plaques but have little quantitative predictive power. Our aim is to introduce and discuss a computational framework to provide insight to clinicians and help them visualize internal plaque dynamics. We use Partial Differential Equations (PDEs) with macrophages, necrotic cells, oxidized lipids, oxygen concentration and PDGF (Platelet Derived Growth Factor) as primary variables coupled to a biomechanical model to describe vessel growth. The model is deterministic, providing mechanical, morphological, and histological characteristics of an atherosclerotic vessel at any desired future time point. We use our model to create computer-generated animations of a plaque evolution that are in qualitative agreement with published serial ultrasound images and hypothesize possible atherogenic mechanisms. A systems-biology model consisting of 5 differential equations is able to capture the morphology of necrotic cores residing within vulnerable atherosclerotic plaque. In the context of the model, the distribution of Ox-LDL particles, endothelial inflammation, plaque oxygenation (via the presence of vasa vasora) and intimal oxygenation are four important factors that drive changes in core morphology.

[7] *Quevedo-Abeledo JC, Sánchez-Pérez H, Tejera-Segura B et al.* **Differences in HDL-Cholesterol Efflux Capacity Between Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis**. Arthritis care & research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32770725
ABSTRACT
OBJECTIVES: Cholesterol efflux capacity (CEC) is the ability of high-density lipoprotein (HDL)-cholesterol to accept cholesterol from macrophages. Lipid profiles and CEC appear to be altered in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) due to disease activity and inflammation. CEC has been linked to cardiovascular events in the general population and to subclinical atherosclerosis in SLE and RA patients. The aim of this

study was to establish whether CEC varies between patients with SLE and those with RA. METHODS: Study that encompassed 460 individuals; 195 SLE patients and 265 patients with RA. CEC, using an in vitro assay, and lipoprotein serum concentrations were assessed in both populations. A multivariable regression analysis was performed to study whether CEC differs between SLE and RA patients. RESULTS: Lipid patterns comparison revealed that patients with RA have lower HDL-cholesterol and higher apolipoprotein B serum levels than SLE patients. CEC was downregulated in SLE patients compared to patients with RA (beta coef. -12 [95%CI -13- -10] %, p=<0.001). It occurred independently of traditional cardiovascular risk factors, statin use, disease-related data and other variations in the lipid profile related to the diseases. CONCLUSION: RA patients have a more pro-atherogenic lipid pattern compared to those with SLE. However, CEC seems to be more damaged in SLE than in RA patients.

[8] *Hu W, Zhang P, Su Q et al.* **Peripheral leukocyte counts vary with lipid levels, age and sex in subjects from the healthy population**. Atherosclerosis 2020; 308:15-21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32795745
ABSTRACT
BACKGROUND AND AIMS: Disorders in blood lipid metabolism and leukocyte-mediated inflammation are considered the main mechanisms of the pathogenesis of atherosclerosis. This study aims to show whether and how peripheral leukocyte counts are associated with serum lipid levels. METHODS: This is a cross-sectional study of 175,079 subjects from the healthy population. RESULTS: Age and sex are two key factors dictating the relationship between peripheral leukocyte counts and serum lipid levels. The log-transformed level of triglycerides (LnTG) was positively associated with all leukocyte counts in males except monocyte count in younger subjects. LnTG was positively associated with total leukocyte count in females regardless of age, and it was positively associated with lymphocyte and monocyte counts and neutrophil count only in elderly and young women, respectively. Total cholesterol levels were positively associated with total leukocyte, neutrophil and lymphocyte counts only in young males and with lymphocyte counts only in elderly women. LDL-C was negatively associated with monocyte count in males regardless of age; by contrast, it was positively associated with total leukocyte and lymphocyte counts in females regardless of age range and neutrophil and LnEosinophil counts only in young women. HDL-C was negatively associated with total leukocyte, lymphocyte and monocyte counts in both young men and young women; was negatively associated with monocyte count in elderly men and women; and was negatively associated with LnEosinophil count only in older men. CONCLUSIONS: Peripheral leukocyte counts are extensively associated with serum lipid levels, with patterns differing by sex, age, lipid and leukocyte subset.

[9] *Pasta A, Cremonini AL, Formisano E et al.* **Long term follow-up of genetically confirmed patients with familial hypercholesterolemia treated with first and second-generation statins and then with PCSK9 monoclonal antibodies**. Atherosclerosis 2020; 308:6-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32771803
ABSTRACT
BACKGROUND AND AIMS: In Italy, the clinical and genetic characteristics of familial hypercholesterolemia (FH) have been extensively assessed in various lipid clinics, although no studies on long-term cardiovascular outcomes in heterozygous patients (He-FH) have been conducted. This study evaluated the incidence of atherosclerotic cardiovascular disease

(ASCVD) in He-FH before and after a long-term period of lipid-lowering treatments to ascertain the interference of other risk factors. METHODS: A total of 294 genetically characterised He-FH subjects from 1989 to 2019 were retrospectively analysed. General characteristics, lipid profiles, ASCVD prevalence, and ultrasound carotid atherosclerosis assessment were evaluated. Primary end points were ASCVD outcomes and the percentage of patients reaching recommended LDL-C targets. RESULTS: During follow-up, despite a significant improvement in plasma lipid profiles, the ESC/EAS 2016 and 2019 recommended LDL cholesterol (LDL-C) goals were attained in only a few patients treated with anti-PCSK9 monoclonal antibodies added to the maximum tolerated oral therapy with statins plus ezetimibe. Forty-seven subjects had an ASCVD event before starting lipid-lowering therapy (LLT). During follow-up (median 13 years) on LLT, 28 patients had a first ASCVD event and 16 had recurrent ASCVD. In basal conditions and during follow-up, higher LDL-C levels were associated with increased ASCVD risk ($p < 0.001$). Prevention of recurrent ASCVD events was recorded with a long-term reduction of LDL-C below 100 mg/dl with statins plus ezetimibe. CONCLUSIONS: PCSK9 inhibition is the only therapeutic option to achieve LDL-C goals as recommended for He-FH and can prevent ASCVD events as reported in large clinical trials. Long-term treatment with statins and ezetimibe seems to be effective at preventing ASCVD recurrence when LDL-C is maintained below 130 and 100 mg/dL for primary and secondary prevention, respectively.

[10] *Kirchhofer D, Burdick DJ, Skelton NJ et al.* **Regions of conformational flexibility in the proprotein convertase PCSK9 and design of antagonists for LDL cholesterol lowering**. Biochemical Society transactions 2020; 48:1323-1336.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32794575
ABSTRACT
The proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates plasma LDL cholesterol levels by binding to the liver LDL receptor (LDLR) and promoting its degradation. Therefore, PCSK9 has become a compelling new therapeutic target for lipid lowering and the prevention of cardiovascular disease. PCSK9 contains two regions of conformational flexibility, the N-terminal regions of the prodomain and of the catalytic domain. The recognition that the latter region, the so-called P' helix, is able to transition from an α-helical to a disordered state gave rise to new strategies to develop small molecule inhibitors of PCSK9 for lipid lowering. In the ordered state the P' helix is buried in a groove of the PCSK9 catalytic domain located next to the main LDLR binding site. The transition to a disordered state leaves the groove site vacated and accessible for compounds to antagonize LDLR binding. By use of a groove-directed phage display strategy we were able to identify several groove-binding peptides. Based on structural information of PCSK9-peptide complexes, a minimized groove-binding peptide was generated and utilized as an anchor to extend towards the adjacent main LDLR binding site, either by use of a phage-displayed peptide extension library, or by appending organic moieties to yield organo-peptides. Both strategies led to antagonists with pharmacologic activities in cell-based assays. The intricate bipartite mechanism of the potent organo-peptide inhibitors was revealed by structural studies, showing that the core peptide occupies the N-terminal groove, while the organic moiety interacts with the LDLR binding site to create antagonism. These findings validate the PCSK9 groove as an attractive target site and should inspire the development of a new class of small molecule antagonists of PCSK9.

[11] *Emma MR, Giannitrapani L, Cabibi D et al.* **Hepatic and circulating levels of PCSK9 in morbidly obese patients: Relation with severity of liver steatosis**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2020; 1865:158792.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32777481
ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is becoming the main cause of liver disease in Western countries, especially in morbidly obese patients (MOPs). The proprotein convertase subtilisin/kexin type 9 (PCSK9) has been recently studied because of its possible involvement in the pathogenesis of NAFLD, but its role, at least in MOPs, is still controversial. The aim of this study was to clarify the correlation between the circulating levels of the PCSK9 protein (cPCSK9) and its hepatic expression with the severity of liver damage in a population of MOPs with NAFLD undergoing bariatric surgery. PCSK9 mRNA was positively correlated with FASN, PPARγ and PPARα mRNAs, while no significant differences were found in PCSK9 mRNA expression in relation to the severity of liver steatosis, lobular inflammation and hepatocellular ballooning. In addition, hepatic PCSK9 protein expression levels were not related to histological parameters of lobular inflammation and hepatocyte ballooning, decreased significantly only in relation to the severity of hepatic steatosis, and were inversely correlated with ALT and AST serum levels. cPCSK9 levels in the whole population were associated with the severity of hepatic steatosis and were positively correlated to total cholesterol levels. In multivariate analysis, cPCSK9 levels were associated with age, total cholesterol and HbA1c. In conclusion, in MOPs our findings support a role for PCSK9 in liver fat accumulation, but not in liver damage progression, and confirm its role in the increase of blood cholesterol, which ultimately may contribute to increased cardiovascular risk in this population.

[12] *Lachkar F, Papaioannou A, Ferré P, Foufelle F.* **[ER stress and NAFLD]**. Biol Aujourdhui 2020; 214:15-23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32773026
ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent pathology associated with obesity. It encompasses a spectrum of hepatic disorders ranging from steatosis to non-alcoholic steatohepatitis (NASH), which may lead to cirrhosis and hepatocellular carcinoma (HCC). Endoplasmic reticulum (ER) stress has been widely involved to drive in NAFLD progression through the activation of the unfolded protein response (UPR). While transient UPR activation can boost hepatic ER functions, its continuous activation upon a chronic ER stress contributes to lipid accumulation, inflammation and hepatocyte death, which are determinant factors for the progression to more severe stages. The aim of this review is to describe the mechanisms through which the UPR can take part in the transition from a healthy to a diseased liver and to report on possible ways of pharmacological manipulation against these pathological mechanisms.

[13] *Wang M, Li J, Cai J et al.* **Overexpression of MicroRNA-16 Alleviates Atherosclerosis by Inhibition of Inflammatory Pathways**. BioMed research international 2020; 2020:8504238.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32775445
ABSTRACT

BACKGROUND: Our previous study demonstrated that the expression of miR-16 was downregulated in the cell and animal models of atherosclerosis (AS), a main contributor to coronary artery disease (CAD). Overexpression of miR-16 inhibited the formation of foam cells by exerting anti-inflammatory roles. These findings indicated miR-16 may be an anti-atherogenic and CAD miRNA. The goal of this study was to further validate the expression of miR-16 in CAD patients and explore its therapeutic roles in an AS animal model. METHODS: A total of 40 CAD patients and 40 non-CAD people were prospectively registered in our study. The AS model was established in ApoE-/- mice fed a high-fat diet. The model mice were randomly treated with miR-16 agomiR (n = 10) or miR-negative control (n = 10). Hematoxylin-eosin staining was conducted for histopathological examination in thoracic aorta samples. ELISA and immunohistochemistry were performed to determine the expression levels of inflammatory factors (IL-6, TNF-α, MCP-1, IL-1β, IL-10, and TGF-β). qRT-PCR and western blotting were carried out to detect the mRNA and protein expression levels of PDCD4, miR-16, and mitogen-activated protein kinase pathway-related genes. RESULTS: Compared with the normal control, miR-16 was downregulated in the plasma and peripheral blood mononuclear cell of CAD patients, and its expression level was negatively associated with IL-6 and the severity of CAD evaluated by the Gensini score, but positively related with IL-10. Injection of miR-16 agomiR in ApoE-/- mice reduced the formation of atherosclerotic plaque and suppressed the accumulation of proinflammatory factors (IL-6, TNF-α, MCP-1, and IL-1β) in the plasma and tissues but promoted the secretion of anti-inflammatory factors (IL-10 and TGF-β). Mechanism analysis showed overexpression of miR-16 might downregulate target mRNA PDCD4 and then activate p38 and ERK1/2, but inactivate the JNK pathway. CONCLUSIONS: Our findings suggest miR-16 may be a potential diagnostic biomarker and therapeutic target for atherosclerotic CAD.

[14] *Theusch E, Chen YI, Rotter JI et al.* **Genetic variants modulate gene expression statin response in human lymphoblastoid cell lines**. BMC Genomics 2020; 21:555.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32787775

ABSTRACT

BACKGROUND: Statins are widely prescribed to lower plasma low-density lipoprotein cholesterol levels. Though statins reduce cardiovascular disease risk overall, statin efficacy varies, and some people experience adverse side effects while on statin treatment. Statins also have pleiotropic effects not directly related to their cholesterol-lowering properties, but the mechanisms are not well understood. To identify potential genetic modulators of clinical statin response, we looked for genetic variants associated with statin-induced changes in gene expression (differential eQTLs or deQTLs) in lymphoblastoid cell lines (LCLs) derived from participants of the Cholesterol and Pharmacogenetics (CAP) 40 mg/day 6-week simvastatin clinical trial. We exposed CAP LCLs to 2 μM simvastatin or control buffer for 24 h and performed polyA-selected, strand-specific RNA-seq. Statin-induced changes in gene expression from 259 European ancestry or 153 African American ancestry LCLs were adjusted for potential confounders prior to association with genotyped and imputed genetic variants within 1 Mb of each gene's transcription start site. RESULTS: From the deQTL meta-analysis of the two ancestral populations, we identified significant cis-deQTLs for 15 genes (TBC1D4, MDGA1, CHI3L2, OAS1, GATM, ASNSD1, GLUL, TDRD12, PPIP5K2, OAS3, SERPINB1, ANKDD1A, DTD1, CYFIP2, and GSDME), eight of which were significant in at least one of the ancestry subsets alone. We also conducted eQTL analyses of the endogenous (control-

treated), statin-treated, and average of endogenous and statin-treated LCL gene expression levels. We identified eQTLs for approximately 6000 genes in each of the three (endogenous, statin-treated, and average) eQTL meta-analyses, with smaller numbers identified in the ancestral subsets alone. CONCLUSIONS: Several of the genes in which we identified deQTLs have functions in human health and disease, such as defense from viruses, glucose regulation, and response to chemotherapy drugs. This suggests that DNA variation may play a role in statin effects on various health outcomes. These findings could prove useful to future studies aiming to assess benefit versus risk of statin treatment using individual genetic profiles.

[15] *Chen M, Xiao J, Du Y et al.* **Elevated non-high-density lipoprotein cholesterol corresponds to a high risk of nephrolithiasis in children**. BMC Urol 2020; 20:120.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32778076
ABSTRACT
BACKGROUND: Dyslipidemia contributes to the development of nephrolithiasis in adults; however its relationship to urolithiasis in children remains debatable, and will be clarified in the present work. METHODS: A case-control study was performed involving 58 pediatric patients diagnosed with upper urinary tract stones as well as 351 controls. Age, gender, body mass index (BMI), serum calcium, serum uric acid, blood glucose, blood lipids, and compositions of stones were compared. RESULTS: According to the univariate analysis, uric acid was higher ($P < 0.01$) but serum calcium lower in the stone group than the control ($P < 0.05$). As for the blood lipids, non-high-density lipoprotein cholesterol (non-HDL-c) was significantly higher in the stone group as compared to the control ($P < 0.01$), while total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol did not show statistical difference between the two groups. In the multivariate analysis, only non-HDL-c and serum uric acid were increased in the stone group ($P = 0.003$ and $P = 0.008$). In the stone compositions' analysis, serum uric acid and non-HDL-c were associated with percentage of uric acid and pure calcium oxalate stones, respectively. CONCLUSION: Non-high-density lipoprotein cholesterol may act as a lipid risk factor for urolithiasis in children.

[16] *Sabeel S, Motaung B, Ozturk M et al.* **Protocol for systematic review and meta-analysis: impact of statins as immune-modulatory agents on inflammatory markers in adults with chronic diseases**. BMJ open 2020; 10:e039034.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32792452
ABSTRACT
INTRODUCTION: Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors, are lipid-lowering agents that are central in preventing or reducing the complications of atherosclerotic cardiovascular disease. Because statins have anti-inflammatory properties, there is considerable interest in their therapeutic potential in other chronic inflammatory conditions. We aim to identify the statin with the greatest ability to reduce systemic inflammation, independent of the underlying disease entity. METHODS AND ANALYSIS: We aim to conduct a comprehensive search of published and peer-reviewed randomised controlled clinical trials, with at least one intervention arm of a Food & Drug Administration-licensed or European Medicines Agency-licensed statin and a minimum treatment duration of 12 weeks. Our objective is to investigate the effect of statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) on lipid profile, particularly, cholesterol low-density lipoprotein and inflammation markers such as high-

sensitive C reactive protein (hsCRP), CRP, tumour necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, soluble cluster of differentiation 14 (sCD14) or sCD16 in adults, published in the last 20 years (between January 1999 and December 2019). We aim to identify the most potent statin to reduce systemic inflammation and optimal dosing. The following databases will be searched: Medline, Scopus, Web of Science and Cochrane Library of Systematic Reviews. The risk of bias of included studies will be assessed by Cochrane Risk of Bias Tool and Quality Assessment Tool for Quantitative Studies. The quality of studies will be assessed, to show uncertainty, by the Jadad Score. If sufficient evidence is identified, a meta-analysis will be conducted with risk ratios or ORs with 95% CIs in addition to mean differences. ETHICS AND DISSEMINATION: Ethics approval is not required as no primary data will be collected. Results will be presented at conferences and published in a peer-reviewed journal. PROSPERO REGISTRATION NUMBER: CRD42020169919.

[17] *Amor AJ, Castelblanco E, Hernández M et al.* **Advanced lipoprotein profile disturbances in type 1 diabetes mellitus: a focus on LDL particles**. Cardiovascular diabetology 2020; 19:126.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32772924
ABSTRACT
BACKGROUND: Lipoprotein disturbances have been associated with increased cardiovascular disease (CVD) risk in type 1 diabetes mellitus (T1DM). We assessed the advanced lipoprotein profile in T1DM individuals, and analysed differences with non-diabetic counterparts. METHODS: This cross-sectional study involved 508 adults with T1DM and 347 controls, recruited from institutions in a Mediterranean region of Spain. Conventional and advanced (assessed by nuclear magnetic resonance [NMR] spectroscopy) lipoprotein profiles were analysed. Crude and adjusted (by age, sex, statin use, body mass index and leukocyte count) comparisons were performed. RESULTS: The median (interquartile range) age of the study participants was 45 (38-53) years, 48.2% were men. In the T1DM group, the median diabetes duration was 23 (16-31) years, and 8.1% and 40.2% of individuals had nephropathy and retinopathy, respectively. The proportion of participants with hypertension (29.5 vs. 9.2%), and statin use (45.7% vs. 8.1%) was higher in the T1DM vs. controls ($p < 0.001$). The T1DM group had a better conventional (all parameters, $p < 0.001$) and NMR-lipid profile than the control group. Thus, T1DM individuals showed lower concentrations of atherogenic lipoproteins (VLDL-particles and LDL-particles) and higher concentrations of anti-atherogenic lipoproteins (HDL-particles) vs. controls, even after adjusting for several confounders ($p < 0.001$ for all). While non-diabetic women had a more favourable lipid profile than non-diabetic men, women with T1DM had a similar concentration of LDL-particles compared to men with T1DM (1231 [1125-1383] vs. 1257 [1128-1383] nmol/L, $p = 0.849$), and a similar concentration of small-LDL-particles to non-diabetic women (672.8 [614.2-733.9] vs. 671.2 [593.5-761.4] nmol/L, respectively; $p = 0.790$). Finally, T1DM individuals showed higher discrepancies between NMR-LDL-particles and conventional LDL-cholesterol than non-diabetic subjects (prevalence of LDL-cholesterol < 100 mg/dL & LDL-particles > 1000 nmol/L: 38 vs. 21.2%; $p < 0.001$). All these differences were largely unchanged in participants without lipid-lowering drugs (T1DM, $n = 275$; controls, $n = 317$). CONCLUSIONS: Overall, T1DM participants showed a more favourable conventional and NMR-lipid profile than controls. However, the NMR-assessment identified several lipoprotein derangements in LDL-particles among the T1DM population (higher discrepancies in NMR-LDL-particles vs. conventional

LDL-cholesterol; a worse profile in T1DM women) that were overlooked in the conventional analysis. Further studies are needed to elucidate their role in the development of CVD in this population.

[18] *Larsen AH, Wiggers H, Dollerup OL et al.* **Metformin Lowers Body Weight But Fails to Increase Insulin Sensitivity in Chronic Heart Failure Patients without Diabetes: a Randomized, Double-Blind, Placebo-Controlled Study**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32770520

ABSTRACT

PURPOSE: The glucose-lowering drug metformin has recently been shown to reduce myocardial oxygen consumption and increase myocardial efficiency in chronic heart failure (HF) patients without diabetes. However, it remains to be established whether these beneficial myocardial effects are associated with metformin-induced alterations in whole-body insulin sensitivity and substrate metabolism. METHODS: Eighteen HF patients with reduced ejection fraction and without diabetes (median age, 65 (interquartile range 55-68); ejection fraction 39 ± 6%; HbA1c 5.5 to 6.4%) were randomized to receive metformin (n = 10) or placebo (n = 8) for 3 months. We studied the effects of metformin on whole-body insulin sensitivity using a two-step hyperinsulinemic euglycemic clamp incorporating isotope-labeled tracers of glucose, palmitate, and urea. Substrate metabolism and skeletal muscle mitochondrial respiratory capacity were determined by indirect calorimetry and high-resolution respirometry, and body composition was assessed by bioelectrical impedance analysis. The primary outcome measure was change in insulin sensitivity. RESULTS: Compared with placebo, metformin treatment lowered mean glycated hemoglobin levels (absolute mean difference, - 0.2%; 95% CI - 0.3 to 0.0; p = 0.03), reduced body weight (- 2.8 kg; 95% CI - 5.0 to - 0.6; p = 0.02), and increased fasting glucagon levels (3.2 pmol L(-1); 95% CI 0.4 to 6.0; p = 0.03). No changes were observed in whole-body insulin sensitivity, endogenous glucose production, and peripheral glucose disposal or oxidation with metformin. Equally, resting energy expenditure, lipid and urea turnover, and skeletal muscle mitochondrial respiratory capacity remained unaltered. CONCLUSION: Increased myocardial efficiency during metformin treatment is not mediated through improvements in insulin action in HF patients without diabetes. CLINICAL TRIAL REGISTRATION: URL: https://clinicaltrials.gov . Unique identifier: NCT02810132. Date of registration: June 22, 2016.

[19] *Ying H, Wang J, Shen Z et al.* **Impact of Lowering Low-Density Lipoprotein Cholesterol with Contemporary Lipid-Lowering Medicines on Cognitive Function: A Systematic Review and Meta-Analysis**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32770521

ABSTRACT

PURPOSE: To evaluate the potential association between the lowering of low-density lipoprotein cholesterol (LDL-C) with contemporary lipid-lowering medicines and cognitive function. METHODS: Randomized controlled trials (RCTs) in databases including PubMed, Embase, and the Web of Science and all databases in the Cochrane Library and ClinicalTrials.gov were collected from inception to January 1, 2020. The cognitive function of patients receiving proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, statins and

ezetimibe was evaluated using meta-analysis. RESULTS: A total of 2910 studies were obtained from databases and other sources. Thirty-three studies were selected by screening, including 11 studies on alirocumab, 9 studies on evolocumab, 11 studies on statins and 2 studies on ezetimibe. In our study, a total of 128,691 patients with no cognitive impairment were divided into an intervention group (66,330 patients) and a control group (62,361 patients). The data were subjected to a random-effects model or a fixed-effects model for meta-analysis. The contemporary lipid-lowering medicines significantly reduced LDL-C in terms of both percentage (WMD: -45.06%, 95% CI -50.12% to -40.00%, P < 0.001) and absolute value (WMD: -64.01 mg/dL, 95% CI -72.25 to -55.78, P < 0.001). Compared with the control group, patients receiving treatment with contemporary lipid-lowering medicines did not show a significant difference in the rate of neurocognitive disorder (RR: 1.02, 95% CI 0.90 to 1.16, I(2) = 0.0%, p = 0.696). Subgroup analysis was performed according to the intervention and LDL-C stratification. The result of this subgroup analysis was consistent with the main findings. Regarding global cognitive performance, no difference in major cognition was found among the pooled data (SMD: 0.02, 95% CI -0.01 to 0.04, P = 0.002), except for psychomotor speed (SMD: 0.09, 95% CI 0.02 to 0.16, P = 0.0024). CONCLUSIONS: Contemporary lipid-lowering medicines were not associated with cognitive impairment in RCTs. A low LDL-C level did not influence the incidence of cognitive disorder or global cognitive performance.

[20] *Redinbo MR*. **The Microbiome Revolution Turns to Cholesterol**. Cell Host Microbe 2020; 28:154-156.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32791107
ABSTRACT
The story of twentieth century biomedical breakthroughs could be told through cholesterol. Revolutions in genetics, molecular biology, genomics, and antibody-based therapies defined cholesterol's impact on human health and cholesterol-lowering strategies. In this issue, Kenny et al. (2020) bring a key twenty-first century biomedical development-the microbiome revolution-to cholesterol.

[21] *Puchałowicz K, Rać ME*. **The Multifunctionality of CD36 in Diabetes Mellitus and Its Complications-Update in Pathogenesis, Treatment and Monitoring**. Cells 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32796572
ABSTRACT
CD36 is a multiligand receptor contributing to glucose and lipid metabolism, immune response, inflammation, thrombosis, and fibrosis. A wide range of tissue expression includes cells sensitive to metabolic abnormalities associated with metabolic syndrome and diabetes mellitus (DM), such as monocytes and macrophages, epithelial cells, adipocytes, hepatocytes, skeletal and cardiac myocytes, pancreatic β-cells, kidney glomeruli and tubules cells, pericytes and pigment epithelium cells of the retina, and Schwann cells. These features make CD36 an important component of the pathogenesis of DM and its complications, but also a promising target in the treatment of these disorders. The detrimental effects of CD36 signaling are mediated by the uptake of fatty acids and modified lipoproteins, deposition of lipids and their lipotoxicity, alterations in insulin response and the utilization of energy substrates, oxidative stress, inflammation, apoptosis, and fibrosis leading to the progressive, often irreversible organ dysfunction. This review summarizes the extensive knowledge of the contribution of CD36 to

DM and its complications, including nephropathy, retinopathy, peripheral neuropathy, and cardiomyopathy.

[22] *Banerjee S, Luo P, Reda DJ et al.* **Plaque Regression and Endothelial Progenitor Cell Mobilization With Intensive Lipid Elimination Regimen (PREMIER)**. Circulation. Cardiovascular interventions 2020; 13:e008933.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32791950
ABSTRACT
BACKGROUND: Low-density lipoproteins (LDLs) are removed by extracorporeal filtration during LDL apheresis. It is mainly used in familial hyperlipidemia. The PREMIER trial (Plaque Regression and Progenitor Cell Mobilization With Intensive Lipid Elimination Regimen) evaluated LDL apheresis in nonfamilial hyperlipidemia acute coronary syndrome patients treated with percutaneous coronary intervention. METHODS: We randomized 160 acute coronary syndrome patients at 4 Veterans Affairs centers within 72 hours of percutaneous coronary intervention to intensive lipid-lowering therapy (ILLT) comprising single LDL apheresis and statins versus standard medical therapy (SMT) with no LDL apheresis and statin therapy alone. Trial objectives constituted primary safety and primary efficacy end points and endothelial progenitor cell colony-forming unit mobilization in peripheral blood. RESULTS: Mean LDL reduction at discharge was 53% in ILLT and 17% in SMT groups (P<0.0001) from baseline levels of 116.3±34.3 and 110.7±32 mg/dL (P=0.2979), respectively. The incidence of the primary safety end point of major peri-percutaneous coronary intervention adverse events was similar in both groups (ILLT, 3; SMT, 0). The primary efficacy end point, percentage change in total plaque volume at 90 days by intravascular ultrasound, on average decreased by 4.81% in the ILLT group and increased by 2.31% in the SMT group (difference of means, -7.13 [95% CI, -14.59 to 0.34]; P=0.0611). The raw change in total plaque volume on average decreased more in the ILLT group than in the SMT group (-6.01 versus -0.95 mm(3); difference of means, -5.06 [95% CI, -11.61 to 1.48]; P=0.1286). Similar results were obtained after adjusting for participating sites, age, preexisting coronary artery disease, diabetes mellitus, baseline LDL levels, and baseline plaque burden. There was robust endothelial progenitor cell colony-forming unit mobilization from baseline to 90 days in the ILLT group (P=0.0015) but not in SMT (P=0.0844). CONCLUSIONS: PREMIER is the first randomized clinical trial to demonstrate safety and a trend for early coronary plaque regression with LDL apheresis in nonfamilial hyperlipidemia acute coronary syndrome patients treated with percutaneous coronary intervention. Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01004406 and NCT02347098.

[23] *Nanna MG, Navar AM*. **Teaching Old Treatments New Tricks**. Circulation. Cardiovascular interventions 2020; 13:e009725.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32791951
ABSTRACT

[24] *Rieck L, Bardey F, Grenkowitz T et al.* **Mutation spectrum and polygenic score in German patients with familial hypercholesterolemia**. Clinical genetics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32770674
ABSTRACT

Autosomal-dominant familial hypercholesterolemia (FH) is characterized by increased plasma concentrations of low-density lipoprotein cholesterol (LDL-C) and a substantial risk to develop cardiovascular disease. Causative mutations in three major genes are known: the LDL receptor gene (LDLR), the apolipoprotein B gene (APOB) and the proprotein convertase subtilisin/kexin 9 gene (PCSK9). We clinically characterized 336 patients suspected to have FH and screened them for disease causing mutations in LDLR, APOB, and PCSK9. We genotyped six single nucleotide polymorphisms (SNPs) to calculate a polygenic risk score for the patients and 1985 controls. The 117 patients had a causative variant in one of the analyzed genes. Most variants were found in the LDLR gene (84.9%) with 11 novel mutations. The mean polygenic risk score was significantly higher in FH mutation negative subjects than in FH mutation positive patients ($P < .05$) and healthy controls ($P < .001$), whereas the score of the two latter groups did not differ significantly. However, the score explained only about 3% of the baseline LDL-C variance. We verified the previously described clinical and genetic variability of FH for German hypercholesterolemic patients. Evaluation of a six-SNP polygenic score recently proposed for clinical use suggests that it is not a reliable tool to classify hypercholesterolemic patients.

[25] *Feuchtner G, Langer C, Barbieri F et al.* **The effect of omega-3 fatty acids on coronary atherosclerosis quantified by coronary computed tomography angiography**. Clinical nutrition (Edinburgh, Scotland) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32778459

ABSTRACT

BACKGROUND & AIMS: Data on the effects omega-3 fatty acids on coronary artery disease (CAD) are contradictory. While a recent metanalysis could not show improved cardiovascular outcomes, anti-atherogenic mechanisms are well known. OBJECTIVE: Aim was to assess the influence of Omega-3 polyunsaturated long-chain fatty acids (PUFA) supplementation on coronary atherosclerosis quantified by coronary computed tomography angiography (CTA). METHODS: 106 patients (59.4y± 10.7; 50% females) with low-to-intermediate risk referred to CTA were included. 53 patients under omega 3-PUFA (docosahexaenoic acid, DHA and eicosapentaenoic acid, EPA) supplementation were retrospectively matched with 53 controls (CR) for age, gender and coronary risk profile (smoking, arterial hypertension, family history, dyslipidemia, c-LDL, Cholesterol, TG, diabetes) (1:1, propensity score) and lifestyle habits (exercise, alcohol consumption and nutrition). CTA analysis included 1) stenosis severity score >70%severe, 50-70% moderate, 25-50%mild, <25% minimal), 2) total plaque burden (segment involvement score (SIS) and mixed non-calcified plaque burden (G-score) and 3) high-risk-plaque features (Napkin-Ring-Sign, low attenuation plaque (LAP), spotty calcification<3 mm, RI>1.1). CT-Density (Hounsfield Units, HU) of plaque was quantified by CTA. RESULTS: Prevalence of coronary atherosclerosis (any plaque: 83% vs. 90.6%, $p = 0.252$), >50% stenosis and stenosis severity score ($p = 0.134$) were not different between groups. Total and non-calcified plaque burden scores were lower in the omega-3 group (2.7 vs. 3.5, $p = 0.08$ and 4.5 vs. 7.4, $p = 0.027$ for SIS and G-score, resp.). Coronary artery calcium score (CACS) was similar (84.7 vs. 87.1AU). High-risk-plaque prevalence was lower in the Omega-3 group (3.8% vs. 32%, $p < 0.001$); the number of high-risk-plaques ($p < 0.001$) and Napkin-Ring-Sign prevalence was lower (3.8% vs. 20.9%) ($p < 0.001$), resp. CT-density (HU) of plaque was higher in the Omega-3 group (131.6 ± 2 vs. 62.1 ± 27, $p = 0.02$) indicating more fibrous-dense plaque component rather than lipid-rich atheroma. Mean duration of Omega-3 intake was

38.6 ± 52 months (range, 2-240). CONCLUSIONS: Omega-3-PUFA supplementation is associated with less coronary atherosclerotic "high-risk" plaque (lipid-rich) and lower total non-calcified plaque burden independent on cardiovascular risk factors. Our study supports direct anti-atherogenic effects of Omega-3-PUFA.

[26] *Atreya MR, Whitacre BE, Cvijanovich NZ et al.* **Proprotein Convertase Subtilisin/Kexin Type 9 Loss-of-Function Is Detrimental to the Juvenile Host With Septic Shock**. Critical care medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32769621
ABSTRACT
OBJECTIVES: Proprotein convertase subtilisin/kexin type 9 is a central regulator of lipid metabolism and has been implicated in regulating the host response to sepsis. Proprotein convertase subtilisin/kexin type 9 loss-of-function is associated with improved sepsis outcomes in the adult host through increased hepatic bacterial clearance. Thus, there is interest in leveraging proprotein convertase subtilisin/kexin type 9 inhibitors as a therapeutic strategy in adults with sepsis. We sought to validate this association in children with septic shock and in a juvenile murine model of sepsis. DESIGN: Prospectively enrolled cohort of children with septic shock; experimental mice. SETTING: Seventeen participating institutions; research laboratory. PATIENTS AND SUBJECTS: Five-hundred twenty-two children with septic shock; juvenile (14 d old) and adult (10-14 wk) mice with constitutive proprotein convertase subtilisin/kexin type 9 null and wildtype control mice (C57BL/6). INTERVENTIONS: Proprotein convertase subtilisin/kexin type 9 single-nucleotide polymorphisms, serum proprotein convertase subtilisin/kexin type 9, and lipid profiles in patients. Cecal slurry murine model of sepsis; survival studies in juvenile and adult mice, assessment of lipoprotein fractions, bacterial burden, and inflammation in juvenile mice. MEASUREMENTS AND MAIN RESULTS: PCSK9 loss-of-function genetic variants were independently associated with increased odds of complicated course and mortality in children with septic shock. PCSK9, low-density lipoprotein, and high-density lipoprotein concentrations were lower among patients with complicated course relative to those without. PCSK9concentrations negatively correlated with proinflammatory cytokine interleukin-8. Proprotein convertase subtilisin/kexin type 9 loss-of-function decreased survival in juvenile mice, but increased survival in adult mice with sepsis. PCSK9 loss-of-function resulted in low lipoproteins and decreased hepatic bacterial burden in juvenile mice. CONCLUSIONS: In contrast to the adult host, proprotein convertase subtilisin/kexin type 9 loss-of-function is detrimental to the juvenile host with septic shock. PCSK9 loss-of-function, in the context of low lipoproteins, may result in reduced hepatic bacterial clearance in the juvenile host with septic shock. Our data indicate that children should be excluded in sepsis clinical trials involving proprotein convertase subtilisin/kexin type 9 inhibitors.

[27] *Dodge M, Movahed MR*. **Screening of the Abdominal Aorta During Routine Echocardiographic Examination is Cost effective and leads to Increase Statin Utilization by Detecting Subclinical Atherosclerosis**. Crit Pathw Cardiol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32769485
ABSTRACT
BACKGROUND: Performing abdominal aorta screenings during routine echocardiographic examination can be useful for quick detection of asymptomatic abdominal aortic aneurysms

(AAA) without additional cost. Furthermore, detection of any atherosclerosis of the aorta during this screening would qualify the patient for statin therapy with potential to improve outcome. The goal of our study was to evaluate the effect of routine screening of abdominal aorta during echocardiographic examination. METHODS: Recently, we started performing routine AAA screening during routine echocardiographic examinations. We retrospectively studied a total of 727 patients with successful screening between the ages of 33 and 96 with a median age of 72.4. We evaluate the presence of atherosclerosis of aorta and its effect on lipid therapy and detection of asymptomatic AAA. RESULTS: We found 18 (2.4%) asymptomatic AAA's and 468 (64.3%) cases of atherosclerosis of abdominal aorta. Retrospectively, data was collected on preventative lipid therapy. Of the 468 patients that had detected atherosclerosis of aorta, 414 patients had clinical follow up. 240 (57.9%) of patients were already treated with a statin due to another indications. However, 38 (9.1%) of these patients had been started on statin drugs for the first time, 85 (20.5%) were set a new lower LDL goal, and 41 (9.9%) had an intensified statin treatment. CONCLUSIONS: Using a routine screening of the abdominal aorta during standard echocardiograms can markedly improve preventive statin therapy in patients with asymptomatic atherosclerosis detected during screening without additional cost and detect some AAA.

[28] *Rached F, Santos RD*. **The Role of Statins in Current Guidelines**. Current atherosclerosis reports 2020; 22:50.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32770357
ABSTRACT
PURPOSE OF REVIEW: The causal association of LDL-cholesterol (LDL-C) with atherosclerotic cardiovascular disease (ASCVD) has been demonstrated in robust experimental, epidemiological, genetic, and interventional randomized controlled trials (RCTs). The goal of this review is to show how the knowledge acquired from statin RCTs influenced and was recommended on guidelines for prevention of ASCVD during the last three decades. RECENT FINDINGS: Guideline recommendations have evolved with accruing information derived mostly from statin RCTs, and as decades passed, more intensive LDL-C lowering was recommended according to a given ASCVD risk. Recent guidelines are unanimous in recommending intensive LDL-C lowering for the highest-risk individuals; however, they differ regarding risk stratification tools, use of specific LDL-C targets, management of primary prevention individuals, and thresholds to start non-statin lipid-lowering therapies. Even considering the advent of non-statin therapies like ezetimibe and PCSK9 inhibitors, due to their efficacy, safety, and low cost, guidelines state that statins persist as the main component of ASCVD preventive strategies and should be prescribed in adequate doses to attain evidence-based LDL-C lowering.

[29] *Tian K, Xu Y, Sahebkar A, Xu S*. **CD36 in Atherosclerosis: Pathophysiological Mechanisms and Therapeutic Implications**. Current atherosclerosis reports 2020; 22:59.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32772254
ABSTRACT
PURPOSE OF REVIEW: Atherosclerosis is a chronic disease characterized by lipid retention and inflammation in the artery wall. The retention and oxidation of low-density lipoprotein (LDL) in sub-endothelial space play a critical role in atherosclerotic plaque formation and destabilization. Oxidized LDL (ox-LDL) and other modified LDL particles are avidly taken up by

endothelial cells, smooth muscle cells, and macrophages mainly through several scavenger receptors, including CD36 which is a class B scavenger receptor and membrane glycoprotein. RECENT FINDINGS: Animal studies performed on CD36-deficient mice suggest that deficiency of CD36 prevents the development of atherosclerosis, though with some debate. CD36 serves as a signaling hub protein at the crossroad of inflammation, lipid metabolism, and fatty acid metabolism. In addition, the level of soluble CD36 (unattached to cells) in the circulating blood was elevated in patients with atherosclerosis and other metabolic disorders. We performed a state-of-the-art review on the structure, ligands, functions, and regulation of CD36 in the context of atherosclerosis by focusing on the pathological role of CD36 in the dysfunction of endothelial cells, smooth muscle cells, monocytes/macrophages, and platelets. Finally, we highlight therapeutic possibilities to target CD36 expression/activity in atherosclerosis.

[30] *Bazarbashi N, Miller M*. **Icosapent Ethyl: Niche Drug or for the Masses?** Current cardiology reports 2020; 22:104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32770402
ABSTRACT
PURPOSE OF REVIEW: Despite achieving optimal levels of low-density lipoprotein cholesterol (LDL-C) with statins, the risk of atherosclerotic cardiovascular disease (ASCVD) persists. The purpose of this review is to outline the effects of icosapent ethyl (IPE), an ultra-purified eicosapentaenoic acid (EPA) on ASCVD risk assessment. RECENT FINDINGS: Many studies have shown that elevated triglycerides (TG) contribute to increased risk of ASCVD. However, the only outcomes trial to date to demonstrate a benefit in patients with elevated TG beyond its lipid-lowering properties is REDUCE-IT. Yet, despite IPE demonstrating a relatively modest reduction in TG (~ 20%), there was a 25% relative risk reduction in the primary endpoint and a 30% reduction in total events. Sub-analysis of REDUCE-IT also showed a statically significant decrease in cardiac arrest (HR 0.52 (0.31-0.86), p = 0.01) and sudden cardiac death (HR 0.69 (0.50-0.96), p = 0.03). The CVD benefits observed in REDUCE-IT coincide with on-treatment EPA levels. Icosapent ethyl's multiple bioactive properties contribute to CVD risk reduction beyond TG lowering effects. Because patients with a REDUCE-IT-like profile are highly prevalent in the USA and abroad, IPE should not be viewed as a niche drug, but rather part of a proven armamentarium that deserves widespread use in appropriate patients at elevated ASCVD risk.

[31] *Diamond DM, O'Neill BJ, Volek JS*. **Low carbohydrate diet: are concerns with saturated fat, lipids, and cardiovascular disease risk justified?** Current opinion in endocrinology, diabetes, and obesity 2020; 27:291-300.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32773573
ABSTRACT
PURPOSE OF REVIEW: There is an extensive literature on the efficacy of the low carbohydrate diet (LCD) for weight loss, and in the improvement of markers of the insulin-resistant phenotype, including a reduction in inflammation, atherogenic dyslipidemia, hypertension, and hyperglycemia. However, critics have expressed concerns that the LCD promotes unrestricted consumption of saturated fat, which may increase low-density lipoprotein (LDL-C) levels. In theory, the diet-induced increase in LDL-C increases the risk of cardiovascular disease (CVD). The present review provides an assessment of concerns with

the LCD, which have focused almost entirely on LDL-C, a poor marker of CVD risk. We discuss how critics of the LCD have ignored the literature demonstrating that the LCD improves the most reliable CVD risk factors. RECENT FINDINGS: Multiple longitudinal clinical trials in recent years have extended the duration of observations on the safety and effectiveness of the LCD to 2-3 years, and in one study on epileptics, for 10 years. SUMMARY: The present review integrates a historical perspective on the LCD with a critical assessment of the persistent concerns that consumption of saturated fat, in the context of an LCD, will increase risk for CVD.

[32] *Benhuri B, Ueyama H, Takagi H et al.* **PCSK9 Inhibitors and Ezetimibe Monotherapy in Patients Not Receiving Statins: A Meta-Analysis of Randomized Trials**. Current vascular pharmacology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32767943
ABSTRACT
BACKGROUND: Statins are the mainstay of treatment for low-density lipoprotein cholesterol (LDL-C) lowering, however, some patients cannot tolerate statins because of adverse effects. Ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are alternative treatment options. The purpose of this meta-analysis is to compare LDL-C reduction with ezetimibe vs PCSK9i in patients not on statins. METHODS: PubMed and EMBASE were searched until 14 March 2020 for randomized clinical trials (RCTs) assessing the efficacy of ezetimibe vs PCSK9i in patients not on statins. The primary outcome was reduction in LDL-C levels. A subgroup analysis of statin intolerant patients was also performed. RESULTS: We identified 8 RCTs that enrolled a total of 1602 patients comparing the two pharmacotherapies. PCSK9i lowered LDL-C levels significantly more than ezetimibe (mean difference (MD): -36.5; 95% confidence interval (CI) [-38.3, -34.7, p<0.00001, I2=4%]. In the statin intolerant subgroup, PCSK9i showed significantly greater reduction in LDL-C levels compared with ezetimibe (MD: -36.1; 95% CI [-39.2, -33.1, p<0.00001, I2=21%]. There were no significant differences in LDL-C reduction between different PCSK9i dosages (140 mg once every 2 weeks vs 420 mg once every 4 weeks) (MD: - 1.87; 95% CI [-4.45, 0.71, p<0.16, I2=0]. CONCLUSIONS: Among patients who are statin intolerant or not receiving statins, PCSK9i use is associated with significantly lower LDL-C levels than after treatment with ezetimibe. PCSK9i might be useful in the prevention and treatment of atherosclerotic cardiovascular disease (ASCVD) in this subset of patients.

[33] *Retnakaran R, Shah BR*. **Divergent Trajectories of Cardiovascular Risk Factors in the Years Before Pregnancy in Women With and Without Gestational Diabetes Mellitus: A Population-Based Study**. Diabetes Care 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32796027
ABSTRACT
OBJECTIVE: Women who develop gestational diabetes mellitus (GDM) have an elevated lifetime risk of cardiovascular disease, which has been attributed to an adverse cardiovascular risk factor profile that is apparent even within the first year postpartum. Given its presence in the early postpartum, we hypothesized that this adverse cardiovascular risk factor profile may develop over time in the years before pregnancy. RESEARCH DESIGN AND METHODS: With population-based administrative databases, we identified all nulliparous women in Ontario, Canada, who had singleton pregnancies between January 2011 and December 2016 and two

or more measurements of the following analytes between 2007 and the start of pregnancy: A1C, fasting glucose, random glucose, lipids, and transaminases. This population consisted of 8,047 women who developed GDM and 93,114 women who did not. RESULTS: The two most recent pregravid tests were performed at a median of 0.61 years and 1.86 years before pregnancy, respectively. Women who went on to develop GDM had higher pregravid A1C, fasting glucose, random glucose, LDL cholesterol, triglycerides, and ALT and lower HDL-cholesterol than their peers (all P < 0.0001). Notably, in the years before pregnancy, women who went on to develop GDM had higher annual increases than their peers in A1C (1.9-fold higher) (difference 0.0089%/year [95% CI 0.0043-0.0135]) and random glucose (4.3-fold), greater annual decrease in HDL cholesterol (5.5-fold), and lesser annual decline in LDL cholesterol (0.4-fold) (all P ≤ 0.0002). During this time, fasting glucose and triglycerides increased in women who developed GDM but decreased in their peers (both P < 0.0001). CONCLUSIONS: The adverse cardiovascular risk factor profile of women with GDM evolves over time in the years before pregnancy.

[34] Feingold KR. Dyslipidemia in Diabetes. In: Endotext. Edited by: Feingold KR, Anawalt B, Boyce A *et al.* South Dartmouth (MA): MDText.com, Inc.
Copyright © 2000-2020, MDText.com, Inc.; 2000.
[35] *Malev O, Lovrić M, Stipaničev D et al.* **Toxicity prediction and effect characterization of 90 pharmaceuticals and illicit drugs measured in plasma of fish from a major European river (Sava, Croatia)**. Environmental pollution (Barking, Essex : 1987) 2020; 266:115162.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32771868

ABSTRACT

Chemical analysis of plasma samples of wild fish from the Sava River (Croatia) revealed the presence of 90 different pharmaceuticals/illicit drugs and their metabolites (PhACs/IDrgs). The concentrations of these PhACs/IDrgs in plasma were 10 to 1000 times higher than their concentrations in river water. Antibiotics, allergy/cold medications and analgesics were categories with the highest plasma concentrations. Fifty PhACs/IDrgs were identified as chemicals of concern based on the fish plasma model (FPM) effect ratios (ER) and their potential to activate evolutionary conserved biological targets. Chemicals of concern were also prioritized by calculating exposure-activity ratios (EARs) where plasma concentrations of chemicals were compared to their bioactivities in comprehensive ToxCast suite of in vitro assays. Overall, the applied prioritization methods indicated stimulants (nicotine, cotinine) and allergy/cold medications (prednisolone, dexamethasone) as having the highest potential biological impact on fish. The FPM model pointed to psychoactive substances (hallucinogens/stimulants and opioids) and psychotropic substances in the cannabinoids category (i.e. CBD and THC). EAR confirmed above and singled out additional chemicals of concern - anticholesteremic simvastatin and antiepileptic haloperidol. Present study demonstrates how the use of a combination of chemical analyses, and bio-effects based risk predictions with multiple criteria can help identify priority contaminants in freshwaters. The results reveal a widespread exposure of fish to complex mixtures of PhACs/IDrgs, which may target common molecular targets. While many of the prioritized chemicals occurred at low concentrations, their adverse effect on aquatic communities, due to continuous chronic exposure and additive effects, should not be neglected.

[36] *Tomlinson B, Chan P, Zhang Y, Lam CWK*. **Efficacy and safety of add on therapies in patients with hypercholesterolemia undergoing statin therapy**. Expert opinion on pharmacotherapy 2020:1-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32772741
ABSTRACT
INTRODUCTION: Statins are the first-line treatment to reduce cardiovascular (CV) events, mainly by reducing low-density-lipoprotein cholesterol (LDL-C), but many patients need additional treatments to reach the current lipid goals. AREAS COVERED: Herein, the authors review the published literature on the efficacy and safety of the therapies that are most often added to statins to achieve lipid targets. EXPERT OPINION: Ezetimibe is usually the first additional treatment to achieve LDL-C targets. It reduces LDL-C by about a further 20% and has an excellent safety and tolerability profile. The monoclonal antibody proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab, and alirocumab, can reduce LDL-C by ≥50% when added to statins and they also have a well-established safety and tolerability record. The recently approved bempedoic acid is well tolerated and appears to be free of skeletal muscle-related problems, but the CV outcome study with this drug has not been completed. Inclisiran, a small-interfering RNA targeting PCSK9 is at an advanced stage of development and the available data indicate a satisfactory safety profile and LDL-C lowering efficacy similar to the PCSK9 monoclonal antibodies with the advantage of less frequent administration.

[37] *Głowinska-Olszewska B, Borysewicz-Sańczyk H, Sawicka B et al.* **Does Hashimoto's Thyroiditis Increase the Risk of Cardiovascular Disease in Young Type 1 Diabetic Patients?** Frontiers in endocrinology 2020; 11:431.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32793113
ABSTRACT
Background: Immunological and hormonal disorders have undoubted influence on the development of atherosclerotic process. Autoimmune diseases accompanying type 1 diabetes (T1D) may additionally accelerate atherosclerosis progression and increase the risk of cardiovascular events in the future. The influence of subclinical hypothyroidism on the cardiovascular system, in particular, has recently aroused great interest. The aim of our study was to assess intima-media thickness (cIMT) of common carotid arteries and the occurrence of classical atherosclerosis risk factors together with selected new biomarkers of cardiovascular diseases in young patients with type 1 diabetes mellitus coexisting with Hashimoto's disease (HD). Patients and Methods: The study included 50 adolescents and young adults with T1D with mean age 17.1 ± 3 years, with mean diabetes duration of 10.5 ± 3.3 years, including 20 patients with diagnosed HD: T1D and HD(+), and 30 patients with no additional diseases: T1D and HD(-). Twenty-two healthy, age-matched volunteers formed control group (C). We analyzed mean HbA(1)c value from all years of disease, BMI, blood pressure, lipids, new biomarkers of atherosclerosis (hsCRP, adiponectin, myeloperoxidase, NT-proBNP peptide, vitamin D), and cIMT of common carotid arteries. Results: In the group of patients with T1D and HD(+), significantly higher BMI was found: 23.3 ± 4.4 vs. 21.28 ± 2.9 in group HD(-) and 19.65 ± 2.4 kg/m(2) in group C ($p = 0.003$), and higher waist circumference: 79 ± 10.9 vs. 75.10 ± 7.6 in group HD(-) vs. 69.0 ± 7.4 cm in group C ($p < 0.001$). The mean value of HbA(1)c was higher in group T1D and HD(+): 8.8% than in group HD(-): 8.1% ($p = 0.04$). Significantly higher concentration of hsCRP and lower vitamin D were observed in T1D and

HD(+) in comparison to T1D and HD(-) and the control group. The IMT index in the HD(+) group was 0.46 ± 0.05 mm and was comparable to the HD(-) group but significantly higher than in healthy controls: 0.41 ± 0.03 mm (P < 0.05). Conclusions: Young patients with type 1 diabetes mellitus and with coexisting Hashimoto's thyroiditis have a higher BMI, a higher waist circumference, and a higher HbA(1)c value, which altogether may cause faster development of macroangiopathy in the near future. Additional risk for cardiovascular disease may result from low vitamin D and increased hsCRP concentration in this group of patients. Coexistence of Hashimoto's thyroiditis did not significantly affect the cIMT value in the studied population.

[38] *Huang CC, Charng MJ*. **Genetic Diagnosis of Familial Hypercholesterolemia in Asia**. Frontiers in genetics 2020; 11:833.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32793292
ABSTRACT
Familial hypercholesterolemia (FH) is a common genetic disease with an incidence of about 1 in 200-500 individuals. Genetic mutations markedly elevate low-density lipoprotein cholesterol and atherosclerotic cardiovascular disease (ASCVD) in FH patients. With advances in clinical diagnosis and genetic testing, more genetic mutations have been detected, including those in low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9), and so on. Globally, most FH patients remain undiagnosed, untreated, or inappropriately treated. Recently, there was a Global Call to Action by the Global Familial Hypercholesterolemia Community to reduce the health burden of FH. Asia, despite being the most populous continent with half of the global population, has low FH detection rates compared to Western countries. Therefore, we aimed to review the current status of FH genetic diagnosis in Asia to understand the gaps in FH diagnosis and management in this region.

[39] *Liu Y, Zhu Y, Jia W et al.* **Association of the Total White Blood Cell, Neutrophils, and Monocytes Count With the Presence, Severity, and Types of Carotid Atherosclerotic Plaque**. Frontiers in medicine 2020; 7:313.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32793608
ABSTRACT
Background: Previous studies have indicated that white blood cells (WBCs) might contribute to the development of atherosclerosis. However, the associations of WBCs and WBC subgroups with carotid atherosclerotic plaque (CAP) have not been compared. Methods: A cross-sectional study including 3,569 healthy Chinese adults was conducted between January 2016 and December 2018 in Zhengzhou, China, to explore the associations of WBC and WBC subtypes with the presence, severity, and types of CAPs. Fasting peripheral venous blood was collected for measurement of the total WBC and WBC subtype counts. The size, composition, and types of CAPs in the common carotid artery, the internal carotid artery, and the external carotid artery were measured bilaterally using B-mode ultrasound. Results: The total WBC, neutrophil, and monocyte counts showed significant associations with the presence of CAPs in men, but not in women, with the adjusted odds ratios (95% CI) in the highest (compared to the lowest) quartile 1.99 (1.33-2.97), 1.65 (1.10-2.47), and 2.17 (1.41-3.18) (P (trend) = 0.004, P (trend) = 0.004, and P (trend) < 0.001), respectively. The three leukocyte counts were also significantly associated with the severity of CAPs, as judged by the count of CAPs, maximal internal carotid plaque thickness, and the plaque score (all P < 0.01, P (trend) < 0.05).

Compared with individuals without CAPs, those with echolucent plaques had significantly increased total WBC and neutrophil counts, whereas those with polytype plaques had a significantly increased monocyte count. Conclusion: WBC, neutrophil, and monocyte counts were significantly associated with the presence, severity, and types of CAPs in a healthy Chinese population.

[40] *Syarifah-Noratiqah SB, Fairus S, Zulfarina MS et al.* **The Effects of Palm Oil on Plasma and Serum Lipid Parameters: A Systematic Review on Animal Intervention Studies**. Front Vet Sci 2020; 7:303.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32775343
ABSTRACT
Background: Accumulative evidences on the beneficial effects of palm oil are progressively reported; however, there are still several controversies related to their effects on the risks of cardiovascular disease (CVD). This review explores the effects of palm oil and its liquid fraction namely palm olein, which is commonly used as cooking oil on four lipid parameters; total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C), which play an important role as CVD-related biomarkers. A systematic review of the literature was conducted to identify the relevant studies on palm oil and the lipid parameters specifically focusing on the in-vivo animal model. Methods: A comprehensive search was conducted in Medline via EBSCOhost, Medline via OVID and Scopus. Studies were limited to the English language published between the years of 2000 and 2019. The main inclusion criteria were as follows: (1) Study with in-vivo animal experiments [the animal should be limited to mammals] (2) Study should have evaluated the effects of palm oil or palm olein on plasma or serum lipid parameter (3) Study should have used palm oil or palm olein in the form of pure or refined oil (4) The treatment of palm oil or palm olein was assessed using the following outcomes: plasma or serum TC, TG, HDL-C, and LDL-C concentration (5) Study should have control group and (6) studies on specific fatty acid, fraction enriched tocotrienol and tocopherol, crude palm oil, kernel oil, red palm oil, thermally oxidized palm oil, hydrogenated palm oil, and palm oil or palm olein based products namely margarine, palm milk, butter and cream were excluded. The quality and the risk of bias on the selected studies were assessed using the ARRIVE Guideline and SYRCLE's Risk of Bias tools, respectively. Results: The literature search successfully identified 17 potentially relevant articles, whereby nine of them met the inclusion criteria. All research articles included in this review were in vivo studies comprising seven rats, one hamster and one mice model. Conclusion: Significant positive outcomes were observed in several lipid parameters such as TC and LDL-C. The evidence from this review supported that palm oil and palm olein possess high potential as lipid-lowering agents.

[41] *Farhangi MA, Vajdi M, Fathollahi P*. **Dietary total antioxidant capacity (TAC), general and central obesity indices and serum lipids among adults: An updated systematic review and meta-analysis**. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition 2020:1-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32777987
ABSTRACT

Background: In the present meta-analysis, we aimed to summarize the relationship between dietary total antioxidant capacity (TAC), general and central obesity indices and lipid profile in adult population. Methods: The electronic databases of Web of Sciences, PubMed, Scopus and Cochrane library were searched for relevant studies from inception to October 2019. The effect size was indicated as weighted mean difference (WMD) and 95% confidence intervals (CI) by using random effects model. The I(2) index and Cochran's Q-test were used for evaluating heterogeneity. Results: From 2,469 studies identified, thirty-four studies (nineteen cross-sectional studies, thirteen cohort studies, two case-control studies) were included in the meta-analysis. According to our results, higher categories of TAC were associated with significantly lower serum triglyceride concentartions (TG; WMD: -7.58; CI: -11.42, -3.75; P < 0.001) and waist circumference (WC; WMD: -1.17; 95% CI: -1.47, -0.87; P < 0.001); while no significant change in body mass index (BMI; WMD: -0.17; 95% CI: -0.35, 0.01; P = 0.12), high density lipoprotein cholesterol (HDL-C; WMD: 0.61; 95% CI: -0.16, 1.40; P = 0.12), low density lipoprotein cholesterol (LDL-C; WMD: 1.34; 95% CI: -0.61, 3.30; P = 0.17) and total cholesterol (TC; WMD: 1.19; 95% CI: -1.46, 3.855; P = 0.37) was reported. Conclusion: Higher dietary TAC was related to reduced prevalence of central obesity, reduced WC and TG concentrations in the current meta-analysis. Moreover, subgroup analysis showed that TAC measurement index, geographical area, dietary assessment tool, health status and gender were potential sources of heterogeneity.

[42] *Cho DH, Lim IR, Kim JH et al.* **Protective Effects of Statin and Angiotensin Receptor Blocker in a Rat Model of Doxorubicin- and Trastuzumab-Induced Cardiomyopathy**. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32778498
ABSTRACT
BACKGROUND: Chemotherapy has led to improved survival in patients with breast cancer; however, it is associated with an increased risk of cardiac dysfunction and heart failure. We investigated the protective effects of rosuvastatin and candesartan, alone and in combination, in a doxorubicin- and trastuzumab-induced rat model of cardiomyopathy. METHODS: Forty-two rats were allocated into six groups (G1-G6): G1, control; G2, doxorubicin only; G3, doxorubicin + trastuzumab; G4, doxorubicin + trastuzumab + rosuvastatin; G5, doxorubicin + trastuzumab + candesartan; and G6, doxorubicin + trastuzumab + rosuvastatin + candesartan. Doxorubicin and trastuzumab were sequentially administered for 28 days. Left ventricular end-systolic dimension and longitudinal strain (LS) were assessed via echocardiography. Left ventricular (LV) performance was evaluated using a microcatheter in the LV apex on day 28. Blood for biomarker analysis was collected from the inferior vena cava before sacrifice. RESULTS: Doxorubicin in combination with trastuzumab increased the LV end-systolic dimension but worsened LS compared with the control group (all P < .05). The level of C-reactive protein was lower in the rosuvastatin treatment group (P = .007) than in the controls but not in the candesartan treatment group. Both rosuvastatin and candesartan attenuated the increase in glutathione. Candesartan treatment improved +dP/dt (P = .011), whereas rosuvastatin did not. In the combination treatment group, the worsening of LS was significantly attenuated compared with that in either the rosuvastatin or candesartan group (all P < .05). CONCLUSIONS: In a rat model of doxorubicin- and trastuzumab-induced cardiomyopathy, rosuvastatin alleviated systemic

inflammation, while candesartan improved LV performance. Combination therapy with rosuvastatin and candesartan demonstrated additional preventive effects on myocardial strain. The protective mechanisms of rosuvastatin and candesartan appear to be different but complementary in chemotherapy-induced cardiomyopathy.

[43] *Nidorf SM, Fiolet A, Abela GS*. **Viewing atherosclerosis through a crystal lens: How the evolving structure of cholesterol crystals in atherosclerotic plaque alters its stability**. Journal of clinical lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32792218
ABSTRACT
Reducing the residual risk of cardiovascular (CV) events in patients with atherosclerosis continues to be a challenge. Thus, understanding how cholesterol spontaneously self assembles into metastable structures that evolve into flat plate cholesterol crystals (CCs) in atherosclerotic plaque, and why they fundamentally change the nature of the disease provides a paradigm for the development of additional therapies. Specifically, flat plate CCs that form within lysosomes of macrophages may become large enough to disrupt lysosomal membranes leading to the release of cathepsin B and CCs fragments directly into the cytosol. In the cytosol, the surface of flat plate CCs can be recognized by complosome that together with cathepsin B may trigger pyrin domain-containing inflammasome. In addition, flat plate CCs in the cytosol may trigger caspase 8 initiating apoptosis. In the interstitial space, the surface of flat plate CCs can be recognized by complement and receptors on proinflammatory cells, and larger fragments can induce "frustrated phagocytosis" that together perpetuate inflammatory injury. In addition, rapid transition of metastable CCs into large flat plate CCs within lipid rich plaques can lead to traumatic injury by expansion of the plaque's necrotic core causing plaque disruption or rupture that may precipitate further inflammation. Other crystalloids in plaque including monosodium urate and calcium phosphate crystals can augment these processes. Thus, therapies that further limit the deposition of cholesterol in the vascular bed, slow the formation of flat plate CCs and inhibit crystal-induced inflammation may lead to further reduce CV risk in patients with established CV disease.

[44] *Merrelaar A, Buchtele N, Schriefl C et al.* **Low PCSK-9 levels Are Associated with Favorable Neurologic Function after Resuscitation from out of Hospital Cardiac Arrest**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32796672
ABSTRACT
Endotoxemia after cardiopulmonary resuscitation (CPR) is associated with unfavorable outcome. Proprotein convertase subtilisin/kexin type-9 (PCSK-9) regulates low-density lipoprotein receptors, which mediate the hepatic uptake of endotoxins. We hypothesized that PCSK-9 concentrations are associated with neurological outcome in patients after CPR. Successfully resuscitated out-of-hospital cardiac arrest patients were included prospectively (n = 79). PCSK-9 levels were measured on admission, 12 h and 24 h thereafter, and after rewarming. The primary outcome was favorable neurologic function at day 30, defined by cerebral performance categories (CPC 1-2 = favorable vs. CPC 3-5 = unfavorable). Receiver operating characteristic curve analysis was used to identify the PCSK-9 level cut-off for optimal discrimination between favorable and unfavorable 30-day neurologic function. Logistic regression models were calculated to estimate the effect of PCSK-9 levels on the primary

outcome, given as odds ratio (OR) and 95% confidence interval (95%CI). PCSK-9 levels on admission were significantly lower in patients with favorable 30-day neurologic function (median 158 ng/mL, (quartiles: 124-225) vs. 207 ng/mL (174-259); p = 0.019). The optimally discriminating PCSK-9 level cut-off was 165ng/mL. In patients with PCSK-9 levels ≥ 165 ng/mL, the odds of unfavorable neurological outcome were 4.7-fold higher compared to those with PCSK-9 levels < 165 ng/mL. In conclusion, low PCSK-9 levels were associated with favorable neurologic function.

[45] *Maseroli E, Comeglio P, Corno C et al.* **Testosterone treatment is associated with reduced adipose tissue dysfunction and nonalcoholic fatty liver disease in obese hypogonadal men**. Journal of endocrinological investigation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32772323
ABSTRACT
PURPOSE: In both preclinical and clinical settings, testosterone treatment (TTh) of hypogonadism has shown beneficial effects on insulin sensitivity and visceral and liver fat accumulation. This prospective, observational study was aimed at assessing the change in markers of fat and liver functioning in obese men scheduled for bariatric surgery. METHODS: Hypogonadal patients with consistent symptoms (n = 15) undergoing 27.63 ± 3.64 weeks of TTh were compared to untreated eugonadal (n = 17) or asymptomatic hypogonadal (n = 46) men. A cross-sectional analysis among the different groups was also performed, especially for data derived from liver and fat biopsies. Preadipocytes isolated from adipose tissue biopsies were used to evaluate insulin sensitivity, adipogenic potential and mitochondrial function. NAFLD was evaluated by triglyceride assay and by calculating NAFLD activity score in liver biopsies. RESULTS: In TTh-hypogonadal men, histopathological NAFLD activity and steatosis scores, as well as liver triglyceride content were lower than in untreated-hypogonadal men and comparable to eugonadal ones. TTh was also associated with a favorable hepatic expression of lipid handling-related genes. In visceral adipose tissue and preadipocytes, TTh was associated with an increased expression of lipid catabolism and mitochondrial bio-functionality markers. Preadipocytes from TTh men also exhibited a healthier morpho-functional phenotype of mitochondria and higher insulin-sensitivity compared to untreated-hypogonadal ones. CONCLUSIONS: The present data suggest that TTh in severely obese, hypogonadal individuals induces metabolically healthier preadipocytes, improving insulin sensitivity, mitochondrial functioning and lipid handling. A potentially protective role for testosterone on the progression of NAFLD, improving hepatic steatosis and reducing intrahepatic triglyceride content, was also envisaged. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02248467, September 25th 2014.

[46] *Zhai T, Wu X, Zhang N et al.* **Inflammatory risk factors for hypertriglyceridemia in patients with severe influenza**. J Int Med Res 2020; 48:300060520918058.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32776792
ABSTRACT
OBJECTIVE: Inflammation and viral infections can induce significant changes in lipid metabolism. Hypertriglyceridemia (HTG) often occurs secondary to obesity, which is an independent risk factor for influenza virus infection. However, the inflammatory risk factors contributing to HTG in patients with severe influenza have yet to be elucidated. MATERIALS AND METHODS: Plasma and bronchoalveolar lavage fluid (BALF) samples were collected

from 33 patients with severe influenza (n = 26 control patients with normal serum triglyceride levels and n = 7 HTG patients with serum triglycerides >2.3 mM). Levels of 45 putative inflammatory risk factors were quantitated using a commercial enzyme-linked immunosorbent assay kit. RESULTS: Plasma levels of interferon (IFN)-γ, interleukin (IL)-18, IL-1 receptor antagonist (IL-1RA), monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, hepatocyte growth factor, stem cell factor, and vascular endothelial growth factor A were significantly higher in HTG patients compared with control patients. BALF samples from HTG patients contained significantly higher levels of IL-1RA and lower levels of IFN-γ-inducible protein-10. CONCLUSION: HTG in patients with severe influenza is associated with alterations in several inflammatory risk factors. Our results provide new insights that may enable more effective clinical management of severe influenza combined with HCT.

[47] *Wiecek E, Torres-Robles A, Cutler RL et al.* **Impact of a Multicomponent Digital Therapeutic Mobile App on Medication Adherence in Patients with Chronic Conditions: Retrospective Analysis**. Journal of medical Internet research 2020; 22:e17834.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32784183

ABSTRACT

BACKGROUND: Strategies to improve medication adherence are widespread in the literature; however, their impact is limited in real practice. Few patients persistently engage long-term to improve health outcomes, even when they are aware of the consequences of poor adherence. Despite the potential of mobile phone apps as a tool to manage medication adherence, there is still limited evidence of the impact of these innovative interventions. Real-world evidence can assist in minimizing this evidence gap. OBJECTIVE: The objective of this study was to analyze the impact over time of a previously implemented digital therapeutic mobile app on medication adherence rates in adults with any chronic condition. METHODS: A retrospective observational study was performed to assess the adherence rates of patients with any chronic condition using Perx Health, a digital therapeutic that uses multiple components within a mobile health app to improve medication adherence. These components include gamification, dosage reminders, incentives, educational components, and social community components. Adherence was measured through mobile direct observation of therapy (MDOT) over 3-month and 6-month time periods. Implementation adherence, defined as the percentage of doses in which the correct dose of a medication was taken, was assessed across the study periods, in addition to timing adherence or percentage of doses taken at the appropriate time (±1 hour). The Friedman test was used to compare differences in adherence rates over time. RESULTS: We analyzed 243 and 130 patients who used the app for 3 months and 6 months, respectively. The average age of the 243 patients was 43.8 years (SD 15.5), and 156 (64.2%) were female. The most common medications prescribed were varenicline, rosuvastatin, and cholecalciferol. The median implementation adherence was 96.6% (IQR 82.1%-100%) over 3 months and 96.8% (IQR 87.1%-100%) over 6 months. Nonsignificant differences in adherence rates over time were observed in the 6-month analysis (Fr(2)=4.314, P=.505) and 3-month analysis (Fr(2)=0.635, P=.728). Similarly, the timing adherence analysis revealed stable trends with no significant changes over time. CONCLUSIONS: Retrospective analysis of users of a medication adherence management mobile app revealed a positive trend in maintaining optimal medication adherence over time. Mobile technology utilizing gamification, dosage reminders, incentives, education, and social community interventions appears to be a promising strategy to manage medication adherence in real practice.

[48] *Zhang C, Yang Y, Zhu DM et al.* **Neural correlates of the association between depression and high density lipoprotein cholesterol change**. Journal of psychiatric research 2020; 130:9-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32768711
ABSTRACT
There is evidence that major depressive disorder (MDD) is related to serum lipid level alterations. However, the neural correlates underlying this association remain poorly understood. Forty-nine patients with MDD and fifty healthy controls (HCs) underwent structural, resting-state functional and diffusion magnetic resonance imaging scans. Voxel-based morphometry, functional connectivity (FC) and tract-based spatial statistics analyses were performed to assess brain structure and function, respectively. Blood samples were collected to measure serum levels of lipid variables including total cholesterol, triglyceride and high density lipoprotein cholesterol (HDL-C). Correlation and mediation analyses were conducted to investigate the associations of serum lipid levels with brain imaging measures in MDD patients and HCs, respectively. We found that the serum HDL-C level in MDD patients was lower than that in HCs. The lower serum HDL-C level was associated with lower gray matter volume (GMV) in ventromedial prefrontal cortex (VMPFC), higher within-network FC of the default mode network, and lower micro-structural integrity in multiple white matter regions in MDD patients. Moreover, the within-default mode network FC mediated the relationship between GMV in VMPFC and serum HDL-C level; white matter integrity in genu of corpus callosum mediated the relationship between serum HDL-C level and depressive symptom severity. However, we did not observe any correlations between serum lipids and brain imaging parameters in HCs. These findings help to identify neural correlates underlying the association between depression and serum HDL-C change, which may provide new insight into intervention, treatment and prevention of depression from the perspective of regulating serum lipids.

[49] *Deedwania P, Murphy SA, Scheen A et al.* **Efficacy and Safety of PCSK9 Inhibition With Evolocumab in Reducing Cardiovascular Events in Patients With Metabolic Syndrome Receiving Statin Therapy: Secondary Analysis From the FOURIER Randomized Clinical Trial**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32785614
ABSTRACT
IMPORTANCE: The PCSK9 inhibitor evolocumab reduced low-density lipoprotein cholesterol and cardiovascular events in the FOURIER randomized clinical trial. Patients with metabolic syndrome (MetS) are at increased cardiovascular risk. OBJECTIVE: To investigate outcomes with evolocumab in patients with and without MetS. DESIGN, SETTING, AND PARTICIPANTS: The FOURIER trial randomized patients worldwide with stable atherosclerotic cardiovascular disease receiving statin to evolocumab vs placebo with follow-up for a median of 2.2 years. Data were collected February 2013 to November 2016. For this prespecified analysis, patients with the requisite data were stratified based on the National Cholesterol Education Program Adult Treatment Panel III MetS criteria; in secondary analyses, patients were further substratified by diabetes at baseline. Analysis was intention to treat. Analysis began March 2018 and ended April 2020. INTERVENTIONS: Patients were randomized to evolocumab or placebo. MAIN OUTCOMES AND MEASURES: The primary

end point was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was cardiovascular death, myocardial infarction, or stroke. RESULTS: Of 27 342 patients (mean [SD] age, 63 [9] years; 20 623 men [75.4%]) included in this analysis, 16 361 (59.8%) with baseline MetS were, when compared with patients without MetS, at higher risk of cardiovascular events (adjusted hazard ratio [95% CI], 1.31 [1.18-1.46]; P < .001 for the primary and 1.38 [1.20-1.57]; P < .001 for the key secondary end point). Evolocumab reduced low-density lipoprotein cholesterol similarly in patients with MetS (median [interquartile range], 92 [79-109] mg/dL vs 30 [19-48] mg/dL; P < .001) and without MetS (median [interquartile range], 92 [81-108] mg/dL vs 29 [18-44] mg/dl; P < .001). For the primary end point, the hazard ratios (95% CI) with evolocumab vs placebo were 0.83 (0.76-0.91) and 0.89 (0.79-1.01) in patients with and without MetS (P for interaction = .39). For the key secondary end point, the corresponding hazard ratios (95% CIs) were 0.76 (0.68-0.86) and 0.86 (0.74-1.01) (P for interaction = .23), respectively. Evolocumab did not increase the risk of new-onset diabetes or other major safety outcomes including worsening glycemic control, compared with placebo in patients with MetS. CONCLUSIONS AND RELEVANCE: Patients with atherosclerotic cardiovascular disease and MetS have substantial residual risk of cardiovascular events despite statin therapy. Evolocumab significantly reduced low-density lipoprotein cholesterol and cardiovascular risk in patients with MetS without increasing new-onset diabetes, worsening glycemic control, or other major safety events. These data suggest the addition of evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease and MetS is safe and efficacious to reduce residual cardiovascular risk. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01764633.

[50] *Zhang J, Feng R, Ferdous M et al.* **Effect of 2 Different Dosages of Rosuvastatin on Prognosis of Acute Myocardial Infarction Patients with New-Onset Atrial Fibrillation in Jinan, China**. Medical science monitor : international medical journal of experimental and clinical research 2020; 26:e925666.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32785210

ABSTRACT

BACKGROUND Atrial fibrillation (AF) often occurs in patients with acute myocardial infarction (AMI). This study aimed to observe the influence of different dosages of rosuvastatin on the prognosis of AMI patients with AF. MATERIAL AND METHODS We performed an observational, retrospective cohort study in Jinan, China, in which 323 AMI patients were recruited. All patients were randomized to receive optimal medication treatment and 10 mg or 20 mg of rosuvastatin. Holter monitor results, serum lipid levels, and heart function were recorded. We used multivariate Cox and Kaplan-Meier analyses to assess the independent factors and differences in AF and ischemia events and safety of rosuvastatin administered at different dosages. RESULTS TC, LDL-C, and TG at 1 and 12 months were significantly lower compared with those observed prior to treatment in both groups. The heart function of both groups was significantly improved after 12 months of treatment, especially in the 20 mg group. Multivariate Cox analysis showed that different dosages of rosuvastatin, age, smoking, drinking alcohol, and diabetes are independent factors related to the occurrence of AF and ischemic events. In addition, according to Kaplan-Meier analysis, no significant difference in adverse clinical events existed at different dosages of rosuvastatin. CONCLUSIONS Treatment with rosuvastatin can reduce the serum lipid level and improve cardiac function. Different dosages of rosuvastatin, age, smoking, drinking alcohol, and diabetes are

independent risk factors for AF and ischemia events. The results suggested it is safe to use 20 mg rosuvastatin in the 12 months after hospital admission.

[51] *Zou Y, Qi Z*. **Understanding the Role of Exercise in Nonalcoholic Fatty Liver Disease: ERS-Linked Molecular Pathways**. Mediators of inflammation 2020; 2020:6412916.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32774148
ABSTRACT
Nonalcoholic fatty liver disease (NAFLD) is globally prevalent and characterized by abnormal lipid accumulation in the liver, frequently accompanied by insulin resistance (IR), enhanced hepatic inflammation, and apoptosis. Recent studies showed that endoplasmic reticulum stress (ERS) at the subcellular level underlies these featured pathologies in the development of NAFLD. As an effective treatment, exercise significantly reduces hepatic lipid accumulation and thus alleviates NAFLD. Confusingly, these benefits of exercise are associated with increased or decreased ERS in the liver. Further, the interaction between diet, medication, exercise types, and intensity in ERS regulation is more confusing, though most studies have confirmed the benefits of exercise. In this review, we focus on understanding the role of exercise-modulated ERS in NAFLD and ERS-linked molecular pathways. Moderate ERS is an essential signaling for hepatic lipid homeostasis. Higher ERS may lead to increased inflammation and apoptosis in the liver, while lower ERS may lead to the accumulation of misfolded proteins. Therefore, exercise acts like an igniter or extinguisher to keep ERS at an appropriate level by turning it up or down, which depends on diet, medications, exercise intensity, etc. Exercise not only enhances hepatic tolerance to ERS but also prevents the malignant development of steatosis due to excessive ERS.

[52] *Kim YH, Her AY, Jeong MH et al.* **Impacts of renin-angiotensin system inhibitors on two-year clinical outcomes in diabetic and dyslipidemic acute myocardial infarction patients after a successful percutaneous coronary intervention using newer-generation drug-eluting stents**. Medicine (Baltimore) 2020; 99:e21289.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32791710
ABSTRACT
This study investigated the impacts of renin-angiotensin system inhibitors (RASIs) on 2-year clinical outcomes in diabetes and dyslipidemic acute myocardial infarction (AMI) patients after a successful percutaneous coronary intervention (PCI) using newer-generation drug-eluting stents (DESs).A total of 16,997 AMI patients were enrolled, and divided into four groups based on the presence or absence of diabetes and dyslipidemia as follows: diabetes -/dyslipidemia - (group A, 11,132 patients), diabetes +/dyslipidemia - (group B, 3,860 patients), diabetes - /dyslipidemia + (groupC, 1,328 patients), and diabetes +/dyslipidemia + (group D, 677 patients). The clinical endpoint was the occurrence of major adverse cardiac events (MACEs), the composite of total death, recurrent myocardial infarction (re-MI), and any repeat revascularization, including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-target vessel revascularization (non-TVR).After RASIs therapy, the cumulative incidences of MACEs (adjusted hazard ratio [aHR], 1.330; 95% confidence interval [CI], 1.022-1.732; P=.034), any repeat revascularization (aHR, 1.584; 95% CI, 1.092-2.298; P=.015), TLR, and TVR were significantly higher in group B than group C. However, the cumulative incidences of all-cause death, cardiac death, re-MI, and non-TVR were similar in groups B and C.In this study, under the newer-generation DESs era, repeat

revascularization rate reduction benefit of RASIs therapy in diabetic AMI patients was lesser than that in dyslipidemic AMI patients. However, larger randomized controlled studies are needed to confirm these results in the future.

[53] *Dashti HT, Bates D, Fiskio JM et al.* **Clinical Characteristics and Severity of COVID-19 Disease in Patients from Boston Area Hospitals**. medRxiv 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32793930
ABSTRACT
We summarize key demographic, clinical, and medical characteristics of patients with respect to the severity of COVID-19 disease using Electronic Health Records Data of 4,140 SARS-CoV-2 positive subjects from several large Boston Area Hospitals. We found that prior use of antihypertensive medications as well as lipid lowering and other cardiovascular drugs (such as direct oral anticoagulants and antiplatelets) all track with increased severity of COVID-19 and should be further investigated with appropriate adjustment for confounders such as age and frailty. The three most common prior comorbidities are hyperlipidemia, hypertension, and prior pneumonia, all associated with increased severity.

[54] *Giral P*. **Bempedoic Acid to Lower LDL Cholesterol - Safety and Efficacy**. The New England journal of medicine 2020; 383:e49.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32786202
ABSTRACT

[55] *Ray KK*. **Bempedoic Acid to Lower LDL Cholesterol - Safety and Efficacy. Reply**. The New England journal of medicine 2020; 383:e49.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32786203
ABSTRACT

[56] *Rezaeizadeh H, Mohammadpour Z, Bitarafan S et al.* **Dietary fish intake and the risk of multiple sclerosis: a systematic review and meta-analysis of observational studies**. Nutritional neuroscience 2020:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32787642
ABSTRACT
Objectives: There is some inconclusive evidence for the role of fish consumption in susceptibility to multiple sclerosis (MS). The present study aimed to systematically review and determine the association between dietary fish intake and risk of MS. Methods: A systematic search with related keywords was carried out in PubMed-MEDLIN, Scopus-EMBASE, and OVID-MEDLINE from inception up to September 2019 to find observational studies that evaluated the association between dietary fish intake and the risk of MS. Random effect and subgroup analyses were performed to calculate pooled estimates at 95% CIs. Results: Six articles met the inclusion criteria for systematic review and meta-analysis. The results of this study indicated that the consumption of fish decreases the risk of MS [OR (95% CIs): 0.77 (0.64, 0.92); p-value = 0.004; I (2) = 54.7%] compared with controls. Discussion: Dietary intake of at least 0.5 servings of fish per week during adolescence and after might reduce the risk of MS; however, further studies are required to prove this preventive effect.

[57] *Gylling H, Strandberg TE, Kovanen PT, Simonen P*. **Lowering Low-Density Lipoprotein Cholesterol Concentration with Plant Stanol Esters to Reduce the Risk of Atherosclerotic Cardiovascular Disease Events at a Population Level: A Critical Discussion**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32781511
ABSTRACT
Atherosclerotic cardiovascular diseases (ASCVDs) cause every fifth death worldwide. However, it is possible to prevent the progression of ASCVDs by reducing circulating concentrations of low-density lipoprotein cholesterol (LDL-C). Recent large meta-analyses demonstrated that by reducing the dietary intake of saturated fat and cholesterol, it is possible to reduce the risk of ASCVD events. Plant stanols, as fatty-acid esters, were developed as a dietary adjunct to reduce LDL-C levels as part of a heart-healthy diet. They reduce cholesterol absorption so that less cholesterol is transported to the liver, and the expression of LDL receptors is upregulated. Ultimately, LDL-C concentrations are reduced on average by 9-12% by consuming 2-3 g of plant stanol esters per day. In this review, we discuss recent information regarding the prevention of ASCVDs with a focus on dietary means. We also present new estimates on the effect of plant stanol ester consumption on LDL-C levels and the risk of ASCVD events. Plant stanol esters as part of a heart-healthy diet plausibly offer a means to reduce the risk of ASCVD events at a population level. This approach is not only appropriate for subjects with a high risk of ASCVD, but also for subjects at an apparently lower risk to prevent subclinical atherosclerosis.

[58] *Sethna CB, Alanko D, Wirth MD et al.* **Dietary inflammation and cardiometabolic health in adolescents**. Pediatric obesity 2020:e12706.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32776714
ABSTRACT
BACKGROUND: The Children's Dietary Inflammatory Index (C-DII) has been validated to characterize the inflammatory potential of an individual child's diet. OBJECTIVE: To determine the association between C-DII and markers of cardiometabolic risk (adiposity, blood pressure [BP], lipids, albuminuria, glomerular hyperfiltration) in adolescents. METHODS: Participants aged 12-18 enrolled in NHANES from 2005 to 2014 who completed a 24-hour dietary recall were included in this cross-sectional study. Regression models adjusted for age, sex, race and height examined associations of C-DII quartiles stratified by weight status. RESULTS: Among adolescents (mean age 15 years), the average C-DII score was 0.86 (SE 0.04). When comparing C-DII quartile 4 (most pro-inflammatory) to quartile 1 (most anti-inflammatory), there was a positive association with albuminuria (OR 1.44, 95% CI 1.02, 2.03). After stratifying by weight status, C-DII quartile was found to be significantly associated with albuminuria (OR 4.27, 95% CI 1.83, 9.92) and dyslipidemia (OR 1.87, 95% CI 1.15, 3.03) in adolescents who were overweight. Among adolescents with obesity, C-DII quartile was associated with higher SBP (β = 5.07, 95% CI 2.55-7.59) and lower DBP (β = -4.14, 95% CI -6.74, -1.54). CONCLUSION: Consuming a pro-inflammatory diet in adolescence was associated with alterations in albuminuria, lipid and BP measures.

[59] *Kam N, Perera K, Zomer E et al.* **Inclisiran as Adjunct Lipid-Lowering Therapy for Patients with Cardiovascular Disease: A Cost-Effectiveness Analysis**. PharmacoEconomics 2020; 38:1007-1020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32789593

ABSTRACT

BACKGROUND: Inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin-kexin type 9 (PCSK9). The comparison of inclisiran with statin versus statin alone in the ORION-10 trial demonstrated significant reductions in low-density lipoprotein cholesterol (LDL-C). Our study explored whether the use of inclisiran with statin versus statin alone for secondary prevention of cardiovascular events is cost effective from the Australian healthcare perspective, based on the price of currently available PCSK9 inhibitors. METHODS: A Markov model was developed based on the ORION-10 trial to model outcomes and costs incurred by patients over a lifetime analysis. The three health states were 'alive with cardiovascular disease (CVD)', 'alive with recurrent CVD', and 'dead'. Cost and utilities were estimated from published sources. The cost of inclisiran was estimated from the annual cost of evolocumab, a PCSK9 inhibitor currently available in Australia (AU$6334, based on 2020 data). Outcomes of interest were incremental cost-effectiveness ratios (ICERs) in terms of cost per quality-adjusted life-year (QALY) and cost per year of life saved (YoLS). All costs, QALYs and YoLS were discounted at 5% per annum in line with Australian standards. RESULTS: Among 1000 subjects followed-up over a lifetime analysis, inclisiran with statin compared with statin alone prevented 235 non-fatal myocardial infarctions (NFMIs; 151 NFMI and 84 repeat NFMI cases) and 114 coronary revascularisation cases, and increased years of life by 0.549 (discounted) and QALYs by 0.468 (discounted). At an annual price of AU$6334, the net marginal cost was AU$58,965 per person. The above values equated to ICERs of AU$107,402 per YoLS and AU$125,732 per QALY gained. Assuming a willingness-to-pay threshold of AU$50,000, inclisiran would have to be priced 60% lower than other available PCSK9 inhibitors to be considered cost effective. CONCLUSIONS: As an adjunct therapy to statin treatment in those who have persistently elevated LDL-C despite optimal statin therapy, inclisiran is effective in reducing cardiovascular events in patients with atherosclerotic CVD. Inclisiran is not cost effective from the Australian healthcare perspective, assuming acquisition costs of current PCSK9 inhibitors. The cost of inclisiran would have to be 60% lower than that of evolocumab.

[60] *Demnati C, Loly JP, Paquot N*. **[The diagnostic trap of acute pancreatitis with normal pancreatic enzymes]**. Revue medicale de Liege 2020; 75:521-523.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32779903

ABSTRACT

We report the case of a patient admitted in Emergency Care for abdominal pain and whose biological assessment did not show any increase in pancreatic enzymes. The abdominal CT-scan revealed pancreatitis of grade E according to the Balthazar radiological score. A diagnosis of acute necrotic pancreatitis secondary to hypertriglyceridemia was thus made. In cases of acute pancreatitis, the rate of pancreatic enzymes may rarely be normal for unclear reasons. In the case of an evocative clinical presentation, the diagnosis of acute pancreatitis cannot be ruled out on the basis of this normal dosage. A CT-scan of the pancreas is then indicated to confirm the diagnosis.

[61] *Fatahian A, Haftcheshmeh SM, Azhdari S et al.* **Promising Anti-atherosclerotic Effect of Berberine: Evidence from In Vitro, In Vivo, and Clinical Studies**. Rev Physiol Biochem Pharmacol 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32789786

ABSTRACT
Elevated levels of plasma cholesterol, impaired vascular wall, and presence of inflammatory macrophages are important atherogenic risk factors contributing to atherosclerotic plaque formation and progression. The interventions modulating these risk factors have been found to protect against atherosclerosis development and to decrease atherosclerosis-related cardiovascular disorders. Nutritional approaches involving supplements followed by improving dietary habits and lifestyle have become growingly attractive and acceptable methods used to control atherosclerosis risk factors, mainly high levels of plasma cholesterol. There are a large number of studies that show berberine, a plant bioactive compound, could ameliorate atherosclerosis-related risk factors. In the present literature review, we put together this studies and provide integrated evidence that exhibits berberine has the potential atheroprotective effect through reducing increased levels of plasma cholesterol, particularly low-density lipoprotein (LDL) cholesterol (LDL-C) via LDL receptor (LDLR)-dependent and LDL receptor-independent mechanisms, inhibiting migration and inflammatory activity of macrophages, improving the functionality of endothelial cells via anti-oxidant activities, and suppressing proliferation of vascular smooth muscle cells. In conclusion, berberine can exert inhibitory effects on the atherosclerotic plaque development mainly through LDL-lowering activity and suppressing atherogenic functions of mentioned cells. As the second achievement of this review, among the signaling pathways through which berberine regulates intracellular processes, AMP-activated protein kinase (AMPK) has a central and critical role, showing that enhancing activity of AMPK pathway can be considered as a promising therapeutic approach for atherosclerosis treatment.

[62] *Close RM, Close LM, Galdun P et al.* **Potential implications of six American Indian patients with myopathy, statin exposure and anti-HMGCR antibodies**. Rheumatology (Oxford, England) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32789452
ABSTRACT
OBJECTIVES: Statin-associated autoimmune myopathy is a rare condition associated with the formation of autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Underlying environmental and genetic risk factors remain poorly understood. American Indians have high rates of cardiovascular disease and associated co-morbidities that require lipid-lowering therapies. We observed this autoimmune myopathy in a series of American Indian statin users in rural Arizona. METHODS: We reviewed the charts of six American Indian patients with statin-associated autoimmune myopathy. We provide an illustrative case in addition to summaries of clinical presentations and treatment courses. RESULTS: This is the first report of statin-associated autoimmune myopathy in American Indians. These cases were all identified at the same geographically isolated hospital that exclusively serves an American Indian population with only 1800 statin users. There is relatively low migration. Each case was consistent with the previously described classical presentations for the disease. All six of our cases had diabetes and developed myopathy on high-dose atorvastatin, often with a recent change in statin type or dose. CONCLUSION: Providers serving American Indians need to be aware of the possibility of statin-associated autoimmune myopathy and familiar with its presentation. Larger, inclusive, population-based investigations are needed to elucidate risk factors for this condition, in particular the potential interactions between predisposing HLA

alleles, diabetes and specific statin exposures. This is necessary to identify effective and safe lipid-lowering medications.

[63] *Lee JA, Hall B, Allsop J et al.* **Lipid metabolism in astrocytic structure and function**. Semin Cell Dev Biol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32773177
ABSTRACT
Astrocytes are the most abundant glial cell in the central nervous system and are involved in multiple processes including metabolic homeostasis, blood brain barrier regulation and neuronal crosstalk. Astrocytes are the main storage point of glycogen in the brain and it is well established that astrocyte uptake of glutamate and release of lactate prevents neuronal excitability and supports neuronal metabolic function. However, the role of lipid metabolism in astrocytes in relation to neuronal support has been until recently, unclear. Lipids play a fundamental role in astrocyte function, including energy generation, membrane fluidity and cell to cell signaling. There is now emerging evidence that astrocyte storage of lipids in droplets has a crucial physiological and protective role in the central nervous system. This pathway links β-oxidation in astrocytes to inflammation, signalling, oxidative stress and mitochondrial energy generation in neurons. Disruption in lipid metabolism, structure and signalling in astrocytes can lead to pathogenic mechanisms associated with a range of neurological disorders.

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[65] Hill MF, Bordoni B. Hyperlipidemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing
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[66] Ramsamooj H, Preuss CV. Fluvastatin. In: StatPearls. Treasure Island (FL): StatPearls Publishing
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[67] Rudrappa M, Paul M. Chylothorax. In: StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2020, StatPearls Publishing LLC.; 2020.
[68] *Yu M, Liu W, Li J et al.* **Exosomes derived from atorvastatin-pretreated MSC accelerate diabetic wound repair by enhancing angiogenesis via AKT/eNOS pathway**. Stem cell research & therapy 2020; 11:350.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32787917
ABSTRACT
BACKGROUND: Mesenchymal stem cell (MSC)-derived exosomes emerge as promising candidates for treating delayed wound healing in diabetes due to the promotion of angiogenesis. Preconditioned MSC with chemical or biological factors could possibly enhance the biological activities of MSC-derived exosomes. The purpose of this research focused on whether exosomes derived from the bone marrow MSC (BMSC) pretreated with atorvastatin (ATV), could exhibit better pro-angiogenic ability in diabetic wound healing or not and its underlying molecular mechanism. METHODS: We isolated exosomes from non-pretreated BMSC (Exos) and ATV pretreated BMSC (ATV-Exos) and evaluated their characterization by

transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA) and Western blotting. In vivo, we made full-thickness skin defects in streptozotocin (STZ)-induced diabetic rats and the defects received multiple-point injection with PBS, Exos, or ATV-Exos. Two weeks later, histological analysis was conducted to evaluate the impact of different treatments on wound healing and the neovascularization was measured by micro-CT. In vitro, cell proliferation, migration, tube formation, and vascular endothelial growth factor (VEGF) secretion were measured in human umbilical vein endothelial cells (HUVEC). The role of miRNAs and AKT/eNOS signaling pathway in the promoted angiogenesis of ATV-Exos were assessed with their inhibitors. RESULTS: No significant difference in morphology, structure, and concentration was observed between ATV-Exos and Exos. In STZ-induced diabetic rats, ATV-Exos exhibited excellent abilities in facilitating the wound regeneration by promoting the formation of blood vessels compared with Exos without influencing liver and kidney function. Meanwhile, ATV-Exos promoted the proliferation, migration, tube formation, and VEGF level of endothelial cells in vitro. And AKT/eNOS pathway was activated by ATV-Exos and the pro-angiogenic effects of ATV-Exo were attenuated after the pathway being blocked. MiR-221-3p was upregulated by ATV-Exos stimulation, and miR-221-3p inhibitor suppressed the pro-angiogenesis effect of ATV-Exos. CONCLUSIONS: Exosomes originated from ATV-pretreated MSCs might serve as a potential strategy for the treatment of diabetic skin defects through enhancing the biological function of endothelial cells via AKT/eNOS pathway by upregulating the miR-221-3p.

[69] *Watase H, Shen M, Sui B et al.* **Differences in atheroma between Caucasian and Asian subjects with anterior stroke: A vessel wall MRI study**. Stroke and vascular neurology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32792458
ABSTRACT
BACKGROUND AND PURPOSE: While extracranial carotid artery stenosis is more common among Caucasians and intracranial artery stenosis is more common among Asians, the differences in atherosclerotic plaque characteristics have not yet been extensively examined. We sought to investigate plaque location and characteristics within extracranial carotid and intracranial arteries in symptomatic Caucasians and Chinese using vessel wall MRI. METHODS: Subjects with recent anterior circulation ischaemic stroke were recruited and imaged at two sites in the USA and China using similar protocols. Both extracranial carotid and intracranial arteries were reviewed to determine plaque location and characteristics. RESULTS: The prevalence of extracranial carotid plaque in Caucasians and Chinese was 73.1% and 49.1%, respectively (p=0.055). Prevalence of intracranial plaque was 38.5% and 69.1% in Caucasians and Chinese, respectively (p=0.02). Furthermore, 42% of Caucasians and 16% of Chinese had high-risk plaque (HRP) features (intraplaque haemorrhage, luminal surface disruption) in the extracranial carotid artery (p=0.03). The prevalence of HRP features in intracranial arteries was not significantly different between the two cohorts (4% vs 11%; p=0.42). CONCLUSIONS: Differences in the location and characteristics of cerebrovascular atherosclerosis were identified by vessel wall MRI in US Caucasian and Chinese subjects with recent anterior circulation ischaemic stroke. Extracranial carotid plaques with HRP features were more common in Caucasians. Intracranial plaques were more common in Chinese subjects, but no significant difference between the two cohorts in intracranial HRP prevalence was found. Larger studies using vessel wall imaging to investigate racial differences in

cerebrovascular disease may inform underlying mechanisms of HRP development and may ultimately help guide appropriate therapy.

[70] *Duran Karaduman B, Ayhan H, Keleş T, Bozkurt E*. **Association between monocyte to high-density lipoprotein cholesterol ratio and bicuspid aortic valve degeneration**. Turk J Med Sci 2020; 50:1307-1313.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32777897

ABSTRACT
BACKGROUND/AIM: From a pathophysiological point of view, inflammation is thought to be more dominant in bicuspid aortic valve (BAV) stenosis than tricuspid aortic valve (TAV) stenosis. Our study aimed to determine the association between monocyte to high- density lipoprotein cholesterol (HDL-C) ratio (MHR), a new inflammatory marker, and the speed of progression of stenosis and pathophysiology of BAV stenosis. MATERIALS AND METHODS: A total of 210 severe aortic stenosis patients (70 consecutive BAV patients, 140 matched TAV patients) were retrospectively enrolled in the study. Clinical and echocardiographic data and laboratory results related to our research were collected retrospectively from the patients' records. MHR was measured as the ratio of the absolute monocyte count to the HDL-C value. RESULTS: Seventy BAV (mean age: 72.0 ± 9.1 years, 42.9% female) and 140 TAV patients (mean age: 77.9 ± 8.3 years, 51.4% female) with severe aortic stenosis were enrolled in this study. There was no difference between the two groups in terms of another baseline demographic or clinic findings except age ($P < 0.001$). Monocyte count, hemoglobin level, mean platelet volume was significantly higher, and HDL-C level was significantly lower in the BAV group, while other lipid and CBC parameters were found to be similar. In the multivariate analysis, MHR ($P = 0.005$, 95% CI: 0.90–0.98) and, as expected, age ($P = 0.001$, 95% CI: 1.02–1.11) were found to be significant as the independent predictor of BAV, after adjusting for other risk factors. CONCLUSION: Our study showed a significant correlation between increased MHR and BAV. MHR was determined as a significant independent predictor for the speed of progression and diagnosis of severe BAV stenosis in multivariate analysis.