Literature update week 46 (2019)

[1] *Cannon CP, de Lemos JA, Rosenson RS et al.* **Getting to an ImprOved Understanding of Low-Density Lipoprotein-Cholesterol and Dyslipidemia Management (GOULD): Methods and baseline data of a registry of high cardiovascular risk patients in the United States**. American heart journal 2019; 219:70-77.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31726422

ABSTRACT

BACKGROUND: Guidelines for managing patients with atherosclerotic cardiovascular disease (ASCVD) recommend statin therapy initially. Target levels/goals for low-density lipoprotein-cholesterol (LDL-C) were initially included, subsequently de-emphasized in 2013, and then re-introduced as thresholds, leading to confusion in clinical practice. We designed a multicenter, observational registry of patients with ASCVD, to describe and track LDL-C treatment patterns in the United States over time. METHODS: Patients with ASCVD receiving any pharmacologic lipid-lowering therapy were eligible for enrollment in one of three cohorts: 1) currently receiving a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i), or not receiving PCSK9i with 2) LDL-C 70-99 mg/dL, or 3) LDL-C >/=100 mg/dL. Patients undergo a 1-year retrospective chart review, followed by chart reviews and phone interviews every 6 months for 2 years. RESULTS: A total of 5006 patients were enrolled at 119 centers. Mean age was 68 years, 40% of patients were female, 86% were white, 80% had coronary artery disease, and 33% had type 2 diabetes mellitus. Among those not on a PCSK9i, high-intensity statins and ezetimibe were utilized in only 44% and 9%, respectively. Among women vs men, only 36.6% vs 48.2% received high-intensity statins (P<.001). Among patients on a PCSK9i, only one-third were receiving a statin, suggesting statin intolerance is a driver of PCSK9i use at present. CONCLUSION: Our data on current practice in the US continue to illustrate that high-intensity statins and ezetimibe are underutilized in at-risk patients outside of clinical trials, particularly women. This study will track temporal changes in treatment patterns and identify opportunities for improvement in lipid management in patients with ASCVD.

[2] *Shaya FT, Sing K, Milam R et al.* **Lipid-Lowering Efficacy of Ezetimibe in Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analyses**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31724105

ABSTRACT

INTRODUCTION: Patients with atherosclerotic cardiovascular disease (ASCVD), especially those with recent (< 1 year) acute coronary syndrome (ACS), are at high risk for recurrent cardiovascular events. This risk can be reduced by lowering low-density lipoprotein cholesterol (LDL-C) levels. A comprehensive meta-analysis on the LDL-C-lowering efficacy of ezetimibe is lacking. This study attempts to address this gap. METHODS: A systematic literature review of randomized controlled trials evaluating the LDL-C-lowering efficacy of ezetimibe in the ASCVD population was conducted. MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for publications from database inception to August 2018 and for conference abstracts from 2015 to August 2018. Meta-analyses were conducted to evaluate the LDL-C-lowering efficacy of ezetimibe in the ASCVD population and the recent ACS subgroup. RESULTS: In total, 12 studies were eligible for the meta-analyses. Treatment with combination ezetimibe plus statin therapy showed greater absolute LDL-C reduction than statin monotherapy (mean difference - 21.86 mg/dL; 95% confidence interval [CI] - 26.56 to - 17.17; p < 0.0001) after 6 months of treatment (or at a timepoint closest to 6 months). Similarly, in

patients with recent ACS, combination ezetimibe plus statin therapy was favorable compared with statin monotherapy (mean treatment difference - 19.19 mg/dL; 95% CI - 25.22 to - 13.16; p < 0.0001). CONCLUSIONS: Ezetimibe, when added to statin therapy, provided a modest additional reduction in LDL-C compared with statin monotherapy. However, this may not be sufficient for some patients with ASCVD who have especially high LDL-C levels despite optimal statin therapy.

[3] *Williams DM, Finan C, Schmidt AF et al.* **Lipid lowering and Alzheimer's disease risk: a Mendelian randomization study**. Annals of neurology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31714636
ABSTRACT
OBJECTIVE: To examine whether genetic variation affecting the expression or function of lipid-lowering drug targets is associated with Alzheimer's disease (AD) risk, to evaluate the potential impact of long-term exposure to corresponding therapeutics. METHODS: We conducted Mendelian randomization analyses using variants in genes that encode the protein targets of several approved lipid-lowering drug classes: HMGCR (encoding the target for statins); PCSK9 (encoding the target for PCSK9 inhibitors e.g. evolocumab and alirocumab), NPC1L1 (encoding the target for ezetimibe); APOB (encoding the target of mipomersen). Variants were weighted by associations with low-density lipoprotein cholesterol (LDL-C) using data from lipid genetics consortia (N up to 295 826). We meta-analysed MR estimates for regional variants weighted by LDL-C on AD risk from two large samples (total N = 24718 cases, 56685 controls). RESULTS: Models for HMGCR, APOB and NPC1L1 did not suggest that the use of related lipid-lowering drug classes would affect AD risk. In contrast, exposure to PCSK9 inhibitors was predicted to increase AD risk in both of the AD samples (combined odds ratio per standard deviation lower LDL-C inducible by the drug target = 1.45; 95% confidence interval: 1.23, 1.69). This risk increase was opposite to, though more modest than, the degree of protection from coronary artery disease predicted by these same methods for PCSK9 inhibition. INTERPRETATION: We did not identify genetic support for the repurposing of statins, ezetimibe or mipomersen for AD prevention. Notwithstanding caveats to this genetic evidence, pharmacovigilance for AD risk among users of PCSK9 inhibitors may be warranted.

[4] *Stein B, Ward T, Hale G, Lyver E*. **Safety of High-Intensity Statins in the Veteran Population: Atorvastatin 40 to 80 mg Compared With Rosuvastatin 20 to 40 mg**. The Annals of pharmacotherapy 2019:1060028019888487.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31718234
ABSTRACT
Background: High-intensity statin therapy is recommended in patients with clinical atherosclerotic cardiovascular disease (ASCVD) or at high risk of ASCVD. Current evidence demonstrates efficacy of high-intensity statin therapy in reducing major adverse cardiovascular events; yet the comparative safety profile between high-intensity statin agents remains unknown. In 2011, when atorvastatin became generic, the Veteran's Health Administration made the formulary switch from rosuvastatin to atorvastatin. Currently, rosuvastatin is generic; however, at the time of this study, it was still under patent. Objective: The primary objective was to determine if high-intensity atorvastatin compared with rosuvastatin is associated with an increased incidence of adverse drug reactions (ADRs) in the veteran population. Methods: A retrospective cohort study at James A. Haley Veterans' Hospital compared patients receiving rosuvastatin 20 to 40mg from January 2009 to November 2011 (n = 4,165) and

atorvastatin 40 to 80mg from May 2012 to June 2016 (n = 5,852). Patients were excluded if they were nonadherent to statin therapy or had a documented ADR to atorvastatin prior to formulary switch. Results: A difference in overall ADR rates was found between atorvastatin and rosuvastatin groups (4.59% vs 2.91%; odds ratio [OR], 1.61; 95% CI, 1.29 to 2.00; P < 0.05). Statistically significant differences in abnormal liver transaminases (3.99% vs 1.39%; OR, 2.95; 95% CI, 2.21 to 3.94; P < 0.05) and statin-associated muscle symptoms (1.14% vs 0.5%; OR, 2.29; 95% CI, 1.39 to 3.74; P < 0.05) were identified between groups. Patients receiving rosuvastatin were on therapy 2.5 times longer before developing an ADR. Conclusion and Relevance: High-intensity atorvastatin compared with rosuvastatin is associated with an increased incidence of ADRs.

[5] *Guedeney P, Aboyans V, Dalon F et al.* **Epidemiology, treatment patterns and outcomes in patients with coronary or lower extremity artery disease in France**. Archives of cardiovascular diseases 2019; 112:670-679.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31708441
ABSTRACT
BACKGROUND: There is a dearth of updated epidemiological data on the prevalence and annual incidence of coronary artery disease (CAD) and lower extremity artery disease (LEAD) in Western countries. AIMS: To describe the incidence and prevalence of CAD and LEAD, associated medication patterns and long-term outcomes in France. METHODS: This was a retrospective cohort study using French claims data from a representative sample of the French general population. Any hospitalization or long-term disease status for CAD or LEAD between January 2010 and December 2016 was collected to identify incident cases. RESULTS: Of the 763,338patients screened in the study period, 8559 incident cases of CAD and 4399 of LEAD were identified, with an overall mean follow-up of 2.9+/-2.0years. The incidence of CAD, LEAD and CAD or LEAD remained stable over the years, and in 2016 were at 33.5 per 10,000person-years, 15.1per 10,000person-years and 42.5 per 10,000person-years, respectively. The prevalence of CAD increased from 3.1% in 2010 to 4.2% in 2016, and LEAD from 1.6% to 2.4%. Most patients received guideline-recommended medication with antithrombotic drugs and lipid-lowering drugs following the index event. However, most of the medications initiated were subsequently discontinued during follow-up. Incident CAD or LEAD was associated with considerable morbidity-particularly an incidence of all-cause hospitalization of 7976.9 per 10,000person-years-and all-cause mortality, with an incidence of 542.8 per 10,000person-years. CONCLUSION: In recent years, the prevalence of CAD or LEAD has increased progressively, resulting in considerable morbidity and mortality.

[6] *Koza Y, Aydin MD, Bayram E et al.* **Role of Cardiac Ganglia in the Prevention of Coronary Atherosclerosis: An Analytical Examination of cholesterol-fed Rabbits**. Balkan medical journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31712246
ABSTRACT
Background: The heart is innervated by the autonomic nervous system, which contributes to the control of the heart's rhythm and coronary circulation. It has been suggested that the cardiac fibers of the vagus nerve play important roles in controlling circulatory functions and in protecting against atherosclerotic pathologies in coronary arteries. Aims: We aimed to investigate the presence of atherosclerotic differences in the coronary arteries of cholesterol-fed rabbits by measuring the density of cardiac ganglia neurons. Study Design: Animal experimentation. Methods: This study was conducted

on 45 male rabbits. Over a period of 16 weeks, they were kept on an atherogenic diet of water ad libitum and high fat (8.6%) and saturated fatty acids with 205 mg/kg of cholesterol (1%) per day. Then, their hearts were extracted and examined by histopathological methods. Atherosclerotic plaques of the main coronary arteries were examined using the Cavalieri method. Atherosclerosis index values (AIVs) were estimated as wall surface area/plaque surface area, and the results were analyzed the Kruskal-Wallis and Mann Whitney-U tests. Results: While the average AIV was estimated to be </= 8% in 21 animals , the AIV was 9-20% in animals with minor plaque detection (n=11) and >/= 20% in animals with major plaque detection (n=10). Increased AIVs were more common in animals with low neuron densities than in animals with high neuron densities (P < 0.017). Conclusions: The low neuron density of the cardiac ganglia in cholesterol-fed rabbits is associated with an increased atherosclerotic plaque incidence and volume.

[7] *Ahmed A, Williams DJ, Cheed V et al.* **Pravastatin for early-onset preeclampsia: a randomized, blinded, placebo-controlled trial**. BJOG : an international journal of obstetrics and gynaecology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31715077

ABSTRACT

OBJECTIVE: Women with preeclampsia have elevated circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1). Statins can reduce sFlt-1 from cultured cells and improve pregnancy outcome in animals with a preeclampsia-like syndrome. We investigated the effect of pravastatin on plasma sFlt-1 levels during preeclampsia. DESIGN: Blinded (clinician and participant), proof of principle, placebo-controlled trial SETTING: 15 UK maternity units. POPULATION: We used a minimization algorithm to assign 62 women with early-onset preeclampsia (24(+0) - 31(+6) weeks' gestation) to receive pravastatin 40mg daily (n=30) or matched placebo (n=32), from randomization to childbirth. PRIMARY OUTCOME: Difference in mean plasma sFlt-1 levels over the first three days following randomization. RESULTS: The difference in the mean maternal plasma sFlt-1 levels over the first three days after randomisation between the pravastatin (n=27) and placebo (n=29) groups was 292pg/mL (95%CI: -1175- 592; p=0.5), and over days 1-14 was 48pg/ml (95% CI -1009 to 913; p=0.9). Women who received pravastatin had a similar length of pregnancy following randomization compared with those who received placebo (Hazard ratio 0.84; 95%CI: 0.50-1.40; p=0.6). The median time from randomization to childbirth was 9 days (IQR 5-14 days) for the pravastatin group and 7 days (IQR 4-11 days) for the placebo group. There were 3 perinatal deaths in the placebo-treated group and no deaths or serious adverse events attributable to pravastatin. CONCLUSIONS: We found no evidence that pravastatin lowered maternal plasma sFlt-1 levels once early onset preeclampsia had developed. Pravastatin appears to have no adverse perinatal effects.

[8] *Ray KK, Del Prato S, Muller-Wieland D et al.* **Alirocumab therapy in individuals with type 2 diabetes mellitus and atherosclerotic cardiovascular disease: analysis of the ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN studies**. Cardiovascular diabetology 2019; 18:149.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31706300

ABSTRACT

BACKGROUND: Individuals with diabetes often have high levels of atherogenic lipoproteins and cholesterol reflected by elevated low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), and LDL particle number (LDL-PN). The presence of atherosclerotic cardiovascular disease (ASCVD) increases the risk of future cardiovascular

events. We evaluated the efficacy and safety of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, alirocumab, among individuals with type 2 diabetes (T2DM), high LDL-C or non-HDL-C, and established ASCVD receiving maximally tolerated statin in ODYSSEY DM-DYSLIPIDEMIA (NCT02642159) and DM-INSULIN (NCT02585778). METHODS: In DM-DYSLIPIDEMIA, individuals with T2DM and mixed dyslipidemia (non-HDL-C >/= 100 mg/dL; n = 413) were randomized to open-label alirocumab 75 mg every 2 weeks (Q2W) or usual care (UC) for 24 weeks, with UC options selected before stratified randomization. In DM-INSULIN, insulin-treated individuals with T2DM (LDL-C >/= 70 mg/dL; n = 441) were randomized in a double-blind fashion to alirocumab 75 mg Q2W or placebo for 24 weeks. Study participants also had a glycated hemoglobin < 9% (DM-DYSLIPIDEMIA) or < 10% (DM-INSULIN). Alirocumab dose was increased to 150 mg Q2W at week 12 if week 8 LDL-C was >/= 70 mg/dL (DM-INSULIN) or non-HDL-C was >/= 100 mg/dL (DM-DYSLIPIDEMIA). Lipid reductions and safety were assessed in patients with ASCVD from these studies. RESULTS: This analysis included 142 DM-DYSLIPIDEMIA and 177 DM-INSULIN participants with ASCVD, including 95.1% and 86.4% with coronary heart disease, and 32.4% and 49.7% with microvascular diabetes complications, respectively. At week 24, alirocumab significantly reduced LDL-C, non-HDL-C, ApoB, and LDL-PN from baseline versus control. This translated into a greater proportion of individuals achieving non-HDL-C < 100 mg/dL (64.6% alirocumab/23.8% UC [DM-DYSLIPIDEMIA]; 65.4% alirocumab/14.9% placebo [DM-INSULIN]) and ApoB < 80 mg/dL (75.1% alirocumab/35.4% UC and 76.8% alirocumab/24.8% placebo, respectively) versus control at week 24 (all P < 0.0001). In pooling these studies, 66.4% (alirocumab) and 67.0% (control) of individuals reported treatment-emergent adverse events. The adverse event pattern was similar with alirocumab versus controls. CONCLUSIONS: Among individuals with T2DM and ASCVD who had high non-HDL-C/LDL-C levels despite maximally tolerated statin, alirocumab significantly reduced atherogenic cholesterol and LDL-PN versus control. Alirocumab was generally well tolerated. Trial registration Clinicaltrials.gov. NCT02642159. Registered 30 December 2015 and Clinicaltrials.gov. NCT02585778. Registered 23 October 2015.

[9] *Horimatsu T, Blomkalns AL, Ogbi M et al.* **Niacin protects against abdominal aortic aneurysm formation via GPR109A independent mechanisms: role of NAD+/nicotinamide**. Cardiovascular research 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31710686

ABSTRACT

AIMS: Chronic adventitial and medial infiltration of immune cells plays an important role in the pathogenesis of abdominal aortic aneurysms (AAA). Nicotinic acid (niacin) was shown to inhibit atherosclerosis by activating the anti-inflammatory G protein-coupled receptor GPR109A [also known as hydroxycarboxylic acid receptor 2 (HCA2)] expressed on immune cells, blunting immune activation and adventitial inflammatory cell infiltration. Here, we investigated the role of niacin and GPR109A in regulating AAA formation. METHODS AND RESULTS: Mice were supplemented with niacin or nicotinamide, and AAA was induced by angiotensin II (AngII) infusion or calcium chloride (CaCl2) application. Niacin markedly reduced AAA formation in both AngII and CaCl2 models, diminishing adventitial immune cell infiltration, concomitant inflammatory responses, and matrix degradation. Unexpectedly, GPR109A gene deletion did not abrogate the protective effects of niacin against AAA formation, suggesting GPR109A-independent mechanisms. Interestingly, nicotinamide, which does not activate GPR109A, also inhibited AAA formation and phenocopied the effects of niacin. Mechanistically, both niacin and nicotinamide supplementation increased nicotinamide adenine

dinucleotide (NAD+) levels and NAD+-dependent Sirt1 activity, which were reduced in AAA tissues. Furthermore, pharmacological inhibition of Sirt1 abrogated the protective effect of nicotinamide against AAA formation. CONCLUSIONS: Niacin protects against AAA formation independent of GPR109A, most likely by serving as an NAD+ precursor. Supplementation of NAD+ using nicotinamide-related biomolecules may represent an effective and well-tolerated approach to preventing or treating AAA. TRANSLATIONAL PERSPECTIVE: AAA are associated with pronounced adventitial and medial inflammation leading to matrix degradation and progressive aortic expansion. We report that niacin blunts aortic inflammation and matrix degradation, thereby suppressing AAA formation. These effects are independent of the niacin receptor GPR109A and mimicked by nicotinamide, which does not induce flushing. These results suggest that nicotinamide and related biomolecules that replete cellular NAD+ may be an effective medical therapy for AAA.

[10] *Jinnouchi H, Guo L, Sakamoto A et al.* **Diversity of macrophage phenotypes and responses in atherosclerosis**. Cell Mol Life Sci 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31720740
ABSTRACT
The presence of macrophages within the plaque is a defining hallmark of atherosclerosis. Macrophages are exposed to various microenvironments such as oxidized lipids and cytokines which effect their phenotypic differentiation and activation. Classically, macrophages have been divided into two groups: M1 and M2 macrophages induced by T-helper 1 and T-helper 2 cytokines, respectively. However, for a decade, greater phenotypic heterogeneity and plasticity of these cells have since been reported in various models. In addition to M1 and M2 macrophage phenotypes, the concept of additional macrophage phenotypes such as M (Hb), Mox, and M4 has emerged. Understanding the mechanisms and functions of distinct phenotype of macrophages can lead to determination of their potential role in atherosclerotic plaque pathogenesis. However, there are still many unresolved controversies regarding their phenotype and function with respect to atherosclerosis. Here, we summarize and focus on the differential subtypes of macrophages in atherosclerotic plaques and their differing functional roles based upon microenvironments such as lipid, intraplaque hemorrhage, and plaque regression.

[11] *Wang X, Chen J, Huang X*. **Rosuvastatin Attenuates Myocardial Ischemia-Reperfusion Injury via Upregulating miR-17-3p-Mediated Autophagy**. Cellular reprogramming 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31730378
ABSTRACT
Myocardial diseases usually appear ischemic. Reperfusion therapy is one of the effective methods that can improve clinical therapeutic efficacy. However, reperfusion results in myocardial injury named I/R injury. Rosuvastatin (RS) is HMG-CoA reductase inhibitor. We investigated the role of RS in the myocardial I/R injury in vitro and its active mechanism. Oxygen-glucose deprivation/reoxygenation (OGD/R) model was applied to investigate I/R in vitro. OGD/R decreased cell viability and increased levels of miR-17-3p and lactate dehydrogenase (LDH) leakage. Besides, RS decreased cleaved caspase-3 level and LDH leakage, promoted the levels of miR-17-3p and LC3II/LC3I, and increased cell viability when H9C2 cell was treated by OGD/R. miR-17-3p inhibitor reduced the H9C2 cell viability and LC3II/LC3I level, whereas miR-17-3p mimics increased H9C2 cell viability and LC3II/LC3I level. RS promoted cell viability and increased LC3II/LC3I level while it lowered LDH leakage, apoptosis rate, and the levels of cleaved caspase-3 and Cyto c. Our study suggested that RS reduced I/R injury in cardiocyte

via cleaved caspase-3/Cyto c apoptosis signaling pathway and autophagy. Moreover, the autophagy happens to cardiocyte by upregulating the expression of miR-17-3p.

[12] *Szarek M, Steg PG, DiCenso D et al.* **Alirocumab Reduces Total Hospitalizations and Increases Days Alive and Out of Hospital in the ODYSSEY OUTCOMES Trial**. Circulation. Cardiovascular quality and outcomes 2019; 12:e005858.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31707826
ABSTRACT
BACKGROUND: In ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), alirocumab was compared with placebo, added to high-intensity or maximum tolerated statin treatment after acute coronary syndrome in 18 924 patients. Alirocumab reduced first occurrence of the primary composite end point-coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or hospitalization for unstable angina-as well as total nonfatal cardiovascular events and all-cause deaths. The present analysis determined whether alirocumab reduced total (first and subsequent) hospitalizations and death and increased days alive and out of hospital (DAOH) and percent DAOH in ODYSSEY OUTCOMES. METHODS AND RESULTS: In prespecified analyses, hazard functions for total hospitalizations and death were jointly estimated by a semiparametric model, while in post hoc analyses, DAOH and percent DAOH were compared between treatment groups with Poisson regression and one-inflated beta regression, respectively. With 16 629 total hospitalizations and 726 deaths, 331 fewer hospitalizations, and 58 fewer deaths were observed with alirocumab compared with placebo, translating to 15.6 total hospitalizations or deaths avoided with alirocumab per 1000 patient-years of assigned treatment. Alirocumab reduced total hospitalizations (hazard ratio, 0.96 [95% CI, 0.92-1.00]; P=0.04) and increased DAOH relative to placebo (rate ratio, 1.003 [95% CI, 1.000-1.007]; P=0.05), primarily through a reduction in days dead (rate ratio, 0.847 [95% CI, 0.728-0.986]; P=0.03). Patients randomized to alirocumab were also more likely to survive to the end of the study without hospitalization (odds ratio, 1.06 [95% CI, 1.00-1.13]; P=0.03). CONCLUSIONS: Alirocumab reduced total hospitalizations with corresponding small increases in DAOH and percent DAOH. These outcomes provide alternative patient-centered metrics to capture the totality of alirocumab clinical efficacy after acute coronary syndrome. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01663402.

[13] *Damask A, Steg PG, Schwartz GG et al.* **Patients with High Genome-Wide Polygenic Risk Scores for Coronary Artery Disease May Receive Greater Clinical Benefit from Alirocumab Treatment in the Odyssey Outcomes Trial**. Circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31707832
ABSTRACT
Background: Alirocumab, an antibody that blocks proprotein convertase subtilisin/kexin type 9 (PCSK9), was associated with reduced major adverse cardiovascular events (MACE) and death in the ODYSSEY OUTCOMES trial. In this study, higher baseline LDL cholesterol (LDL-C) levels predicted greater benefit from alirocumab treatment. Recent studies indicate high polygenic risk scores (PRS) for coronary artery disease (CAD) identify individuals at higher risk who derive increased benefit from statins. Herein we perform post hoc analyses to determine whether high PRS for CAD identifies higher-risk individuals, independently from baseline LDLC and other known risk factors, who might derive

greater benefit from alirocumab treatment. Methods: ODYSSEY OUTCOMES was a randomized, double-blind, placebo-controlled trial comparing alirocumab or placebo in 18,924 patients with acute coronary syndrome and elevated atherogenic lipoproteins despite optimized statin treatment. The primary endpoint (MACE) comprised death from CAD, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization. A genome-wide PRS for CAD comprising 6,579,025 genetic variants was evaluated in 11,953 patients with available DNA samples. Analysis of MACE risk was performed in placebo treated patients while treatment benefit analysis was performed in all patients. Results: The incidence of MACE in the placebo group was related to PRS for CAD: 17.0% for high PRS patients (>90th percentile) and 11.4% for lower PRS patients (</=90th percentile) (p<0.001); this PRS relationship was not explained by baseline LDL-C or other established risk factors. Both the absolute and relative reduction of MACE by alirocumab compared to placebo was greater in high versus low PRS patients. There was an absolute reduction by alirocumab in high versus low PRS groups of 6.0% and 1.5%, respectively, and relative risk reduction by alirocumab of 37% in the high PRS group (hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.46-0.86; p = 0.004) versus 13% reduction in the low PRS group (HR 0.87; 95% CI 0.78-0.98; p=0.022; interaction p = 0.04). Conclusions: A high PRS for CAD is associated with elevated risk for recurrent MACE after ACS, and larger absolute and relative risk reduction with alirocumab treatment, providing an independent tool for risk stratification and precision medicine.

[14] *Hui N, Barter PJ, Ong KL, Rye KA*. **Altered HDL metabolism in metabolic disorders: insights into the therapeutic potential of HDL**. Clinical science (London, England : 1979) 2019; 133:2221-2235.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31722013

ABSTRACT

Metabolic disorders are associated with an increased risk of cardiovascular disease (CVD), and are commonly characterized by a low plasma level of high-density lipoprotein cholesterol (HDL-C). Although cholesterol lowering medications reduce CVD risk in these patients, they often remain at increased risk of CVD. Therapeutic strategies that raise HDL-C levels and improve HDL function are a potential treatment option for reducing residual CVD risk in these individuals. Over the past decade, understanding of the metabolism and cardioprotective functions of HDLs has improved, with preclinical and clinical studies both indicating that the ability of HDLs to mediate reverse cholesterol transport, inhibit inflammation and reduce oxidation is impaired in metabolic disorders. These cardioprotective effects of HDLs are supported by the outcomes of epidemiological, cell and animal studies, but have not been confirmed in several recent clinical outcome trials of HDL-raising agents. Recent studies suggest that HDL function may be clinically more important than plasma levels of HDL-C. However, at least some of the cardioprotective functions of HDLs are lost in acute coronary syndrome and stable coronary artery disease patients. HDL dysfunction is also associated with metabolic abnormalities. This review is concerned with the impact of metabolic abnormalities, including dyslipidemia, obesity and Type 2 diabetes, on the metabolism and cardioprotective functions of HDLs.

[15] *Rhee MY, Kim KJ, Kim SH et al.* **Ezetimibe and Rosuvastatin Combination Treatment Can Reduce the Dose of Rosuvastatin Without Compromising Its Lipid-Lowering Efficacy**. Clinical therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31727361

ABSTRACT
PURPOSE: The goal of this study was to compare the lipid-lowering efficacy of the combination of ezetimibe and low- or intermediate-intensity statin therapy versus that of high-intensity statin monotherapy. METHODS: This study is a post hoc analysis of an 8-week, randomized, double-blind, Phase III trial. Patients who had hypercholesterolemia and required lipid-lowering treatment were randomly assigned to 1 of 6 treatment groups: rosuvastatin 5 mg (R5, n = 68), rosuvastatin 10 mg (R10, n = 67), rosuvastatin 20 mg (R20, n = 69), and ezetimibe 10 mg combined with rosuvastatin 5 mg (R5 + E10, n = 67), rosuvastatin 10 mg (R10 + E10, n = 68), and rosuvastatin 20 mg (R20 + E10, n = 68) daily. The effects of coadministration of ezetimibe and a low dose of rosuvastatin on lipid parameters and the target achievement rate were compared between the R5 + E10 and R10 treatment groups, the R5 + E10 and R20 treatment groups, and the R10 + E10 and R20 treatment groups. FINDINGS: Reductions in total cholesterol, LDL-C, apolipoprotein B, the apolipoprotein B/A1 ratio, and non-HDL-C were not different between the R5 + E10 and R10 treatment groups (all, P > 0.017), the R5 + E10 and R20 treatment groups (all, P > 0.017), and the R10 + E10 and R20 treatment groups (all, P > 0.017). R5 + E10 treatment showed efficacy comparable to that of R10 or R20 in affording LDL levels <50% of the baseline level (R5 + E10 vs R10, 73.13% vs 62.69% [P = 0.1952]; R5 + E10 vs R20, 73.13% vs 73.91% [P = 0.9180]), LDL-C levels <70 mg/dL (R5 + E10 vs R10, 64.18% vs 55.22% [P = 0.2906]; R5 + E10 vs R20, 64.18% vs 62.32% [P = 0.8220]), and LDL-C levels <50% of the baseline level or <70 mg/dL (R5 + E10 vs R10, 77.61% vs 70.15% [P = 0.3255]; R5 + E10 vs R20, 77.61% vs 78.26% [P = 0.9273]). The R10 + E10 treatment group was better than the R20 treatment group in achieving the target LDL-C level <70 mg/dL (83.82% vs 62.32%; P = 0.0046), even among participants with a baseline LDL-C level >135 mg/dL (77.5% vs 48.8%, respectively; P = 0.0074). IMPLICATIONS: Ezetimibe combined with low- or intermediate-intensity statin therapy has lipid-lowering efficacy comparable to or better than that of high-intensity rosuvastatin monotherapy. The results of the present study indicate that the combination treatment with ezetimibe is advantageous in that it permits dose reduction of rosuvastatin without compromising the lipid-lowering efficacy of rosuvastatin. ClinicalTrials.gov identifier: NCT02205606.

[16] *Hamal S, Cherukuri L, Birudaraju D et al.* **Effect of semaglutide on coronary atherosclerosis progression in patients with type II diabetes: rationale and design of the semaglutide treatment on coronary progressiontrial**. Coronary artery disease 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31724966
ABSTRACT
BACKGROUND: Cardiovascular morbidity and mortality are a major burden in patients with type 2 diabetic mellitus. In a landmark study, semaglutide (an injectable glucagon like peptide-1 receptor agonist) has been shown to significantly reduce cardiovascular events, however, the mechanism of benefit is still unknown. The primary hypothesis of our current study is to assess the effect of semaglutide to reduce progression of noncalcified coronary atherosclerotic plaque volume as measured by serial coronary CTA as compared to placebo in persons with diabetes over 1 year. METHODS: One hundred forty patients will be enrolled after signing informed consent and followed up for 12 months and with a phone call 30 days after medical discontinuation. All the participants will undergo coronary artery calcium scoring and coronary computed tomography angiography at our center at baseline and 12 months. Eligible participants will be randomly assigned to semaglutide 2 mg/1.5 ml (1.34 mg/ml) prefilled pen for subcutaneous (SC) injection or placebo 1.5 ml, pen-injector

for SC injection in a 1:1 fashion as add-on to their standard of care. RESULTS: As of July 2019, the study was approximately 30% enrolled with an estimated enrollment completion by first quarter of 2020 and end of study by first quarter 2021. Thirty patients were enrolled as of 23 July 2019. Preliminary data of demographics and clinical characteristics were summarized. CONCLUSION: Our current study will provide important imaging-derived data that may add relevance to the clinically derived outcomes from liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results and semaglutide and cardiovascular outcomes in patients with type 2 diabetic mellitus 6 trials.

[17] *McGrail L, Garelnabi M*. **Polyphenolic compounds and gut microbiome in cardiovascular diseases**. Current pharmaceutical biotechnology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31713494
ABSTRACT
Onset of cardiovascular disease (CVD) is known to associate with multiple risk factors related to exogenous exposures on predisposed genetic makeup. Individual's diet and lifestyle have a cascade effect on microbiota biodiversity, thus impacting inflammation and heart health. Atherosclerosis is a type of CVD where chronic inflammation contributes to plaque buildup in the arteries resulting in narrowed blood vessels, which obstructs blood flow. Polyphenolic compounds, including flavonoids, are most commonly consumed in the form of plants, have been identified to have various mechanisms of action to reduce inflammatory responses in the body. Flavonoids provide a variety of nutraceutical activities including antioxidant, antimicrobial, anti-inflammatory, antiangiogenic, antitumor, and improved pharmacokinetic properties. Therefore, the medicinal use of polyphenolic compounds as an intervention for inflammatory responses in the body, especially relating to the gut microbiome, may significantly reduce the risk of atherosclerotic plaque development and disease onset. This review attempts to discuss the role of polyphenolic compounds and gut microbiome in cardiovascular diseases. We primarily reviewed studies conducted in cells and animals. These studies clearly illustrate that dietary polyphenolic compounds influences the microbiota makeup associated with atherosclerosis progression and prevention. Further studies in this field are key to potential therapeutic approaches.

[18] *Behera SS*. **Dietary Fish Oil Concentrates Associated Health Benefits: A Recent Development of Cardiovascular Risk Reduction**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31721698
ABSTRACT
Fish oil, an abundant source of omega-3 (n-3 or omega-3) polyunsaturated fatty acids (PUFAs) and contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). PUFAs are very effective in preventing/inhibiting cardiovascular incidents, particularly in individuals with high cardiovascular risk/accidents. In this review, composition, extraction of fish oil and its favorable/beneficial effects in cardiovascular diseases (CVDs) and molecular mechanism for its treatment/reduction are discussed. Moreover, application of fish oil for preventive/protective and remedial/curative properties in nutritive and health benefits have been summarized. All these aspects further search the opportunities/hope and scope with its expected opening and anticipations/possibilities to provide additional therapeutic substitutes for reduction of CVDs and registration of new drugs.

Literature update week 46 (2019)

[19] *Mozetic V, Pacheco RL, Latorraca COC, Riera R*. **Statins and/or fibrates for diabetic retinopathy: a systematic review and meta-analysis**. Diabetology & metabolic syndrome 2019; 11:92.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31719846

ABSTRACT
Evidence from observational studies have found a relationship between serum cholesterol and diabetic retinopathy (DR). Apart of the assumption that cholesterolemic control has benefits for patients with diabetes with or without retinopathy, the effects of lipid-lowering drugs have not been properly mapped and critically assessed so far. The objective of this study was to evaluate the effects of statins and/or fibrates on prevention and progression of DR. We conducted a Systematic review of randomized controlled trials (RCTs) following the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance to PRISMA Statement. GRADE approach was used to summarize the certainty of the evidence. Eight RCTs that fulfilled our eligibility criteria were included, assessing the effects of fibrates (n = 4), statins (n = 3) and fibrate plus statins (n = 1) for therapy (n = 8) or prevention (n = 4) of DR. Overall, the main concern regarding risk of bias assessment was due to incomplete outcome data because high rate of losses in five RCTs. Furthermore, the risk of reporting bias was rated unclear due the lack of previously published protocol in seven RCTs. Fibrates seemed to be associated with a 45% risk reduction of macular edema incidence (Relative Risk 0.55, 95% confidence interval of 0.38 to 0.81, 1309 participants, 2 RCTs, I(2) = 0%, low certainty of the evidence). The certainty of evidence for other outcomes was also very low or low, and we are uncertain regarding the effects of fibrates for DR. Overall, adverse events seemed to be similar between fibrate and placebo, but again based on the width of the confidence intervals, an important increase of adverse events cannot be rule out. The combination statin/fibrate did not seem to have benefit for visual acuity but is likely that further studies can modify this estimate since the current evidence is limited. Adverse events and quality of life were not measured or reported. Concluding, this study found eight RCTs, with limited methodological quality, that assessed the effects of fibrates and/or statins for DR. Based on these findings, we are uncertain about the effects of statins for DR. Fibrates seemed to reduce the incidence of macular edema (low certainty evidence) without increase adverse events (low to very low certainty evidence). Number of Protocol registration PROSPERO CRD42016029746.

[20] *Brouwers M, Simons N, Stehouwer CDA, Isaacs A*. **Non-alcoholic fatty liver disease and cardiovascular disease: assessing the evidence for causality**. Diabetologia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31713012

ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among individuals with type 2 diabetes. Although epidemiological studies have shown that NAFLD is associated with cardiovascular disease (CVD), it remains unknown whether NAFLD is an active contributor or an innocent bystander. Plasma lipids, low-grade inflammation, impaired fibrinolysis and hepatokines are potential mediators of the relationship between NAFLD and CVD. The Mendelian randomisation approach can help to make causal inferences. Studies that used common variants in PNPLA3, TM6SF2 and GCKR as instruments to investigate the relationship between NAFLD and coronary artery disease (CAD) have reported contrasting results. Variants in PNPLA3 and TM6SF2 were found to protect against CAD, whereas variants in GCKR were positively associated with CAD. Since all three genes have been associated with non-alcoholic steatohepatitis, the second stage of NAFLD, the question of whether low-grade inflammation is an important mediator of the relationship between NAFLD and CAD arises. In contrast,

the differential effects of these genes on plasma lipids (i.e. lipid-lowering for PNPLA3 and TM6SF2, and lipid-raising for GCKR) strongly suggest that plasma lipids account for their differential effects on CAD risk. This concept has recently been confirmed in an extended set of 12 NAFLD susceptibility genes. From these studies it appears that plasma lipids are an important mediator between NAFLD and CVD risk. These findings have important clinical implications, particularly for the design of anti-NAFLD drugs that also affect lipid metabolism.

[21] *Blaum C, Brunner FJ, Kroger F et al.* **Modifiable lifestyle risk factors and C-reactive protein in patients with coronary artery disease: Implications for an anti-inflammatory treatment target population**. European journal of preventive cardiology 2019:2047487319885458.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31707846
ABSTRACT
BACKGROUND: Modifiable lifestyle risk factors (modRF) of coronary artery disease (CAD) are associated with increased inflammation represented by elevated C-reactive protein (CRP) levels. Lifestyle changes may influence the inflammatory burden in patients with CAD, relevantly modifying the target population for emerging anti-inflammatory compounds. AIMS: The aims of this study were to analyse the association of modRF and CRP levels in CAD patients, and to define a potential target population for anti-inflammatory treatment with and without the optimisation of modRF. METHODS: We included all patients with angiographically documented CAD from the observational cohort study INTERCATH. Patients with recent myocardial infarction, malignancy, infectious disease, and pre-existing immunosuppressive medication including a history of solid organ transplantation were excluded. Overweight (body mass index (BMI) >/= 25 kg/m(2)), smoking, lack of physical activity (PA; <1.5 h/week), and poor diet (</=12 points of an established Mediterranean diet score (MDS), range 0-28 points) were considered as modRF. CRP was measured by a high-sensitivity assay (hsCRP) at baseline. We performed multivariable linear regressions with log-transformed hsCRP as the dependent variable. Based on these associations, we calculated potential hsCRP levels for each patient, assuming optimisation of the individual modRF. RESULTS: Of 1014 patients, 737 (73%) were male, the mean age was 69 years, and 483 (48%) had an hsCRP >/= 2 mg/l. ModRF were significantly overrepresented in patients with hsCRP >/= 2 mg/l compared to patients with an hsCRP < 2 mg/l (BMI >/= 25 kg/m(2): 76% vs 61%; PA < 1.5 h/week: 69% vs 57%; MDS </= 12: 46% vs 37%; smoking: 61% vs 54%; p < 0.05 for all). hsCRP increased with the incremental number of modRF present (median hsCRP values for N = 0, 1, 2, 3, and 4 modRF: 1.1, 1.0, 1.6, 2.4, 2.8 mg/l, p < 0.001). Multivariable linear regression adjusting for age, sex, intake of lipid-lowering medication, and diabetes mellitus revealed independent associations between log-transformed hsCRP and all modRF (BMI >/= 25 kg/m(2): exp(ss) = 1.55, p < 0.001; PA < 1.5 h/week: exp(ss) = 1.33, p < 0.001; MDS </= 12: exp(ss) = 1.18, p = 0.018; smoking: exp(ss) = 1.18, p = 0.019). Individual recalculation of hsCRP levels assuming optimisation of modRF identified 183 out of 483 (38%) patients with hsCRP >/= 2 mg/l who could achieve an hsCRP < 2 mg/l via lifestyle changes. CONCLUSION: modRF are strongly and independently associated with CRP levels in patients with CAD. A relevant portion of CAD patients with high inflammatory burden could achieve an hsCRP < 2 mg/l by lifestyle changes alone. This should be considered both in view of the cost and side-effects of pharmacological anti-inflammatory treatment and for the design of future clinical trials in this field.

[22] *Ismail FF, Sinclair R*. **Alopecia universalis treated with simvastatin/ezetimibe, minoxidil, and prednisolone in a 6-year-old girl**. International journal of dermatology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31732969
ABSTRACT

[23] *Desterke C, Chiappini F*. **Lipid Related Genes Altered in NASH Connect Inflammation in Liver Pathogenesis Progression to HCC: A Canonical Pathway**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31717414
ABSTRACT
Nonalcoholic steatohepatitis (NASH) is becoming a public health problem worldwide. While the number of research studies on NASH progression rises every year, sometime their findings are controversial. To identify the most important and commonly described findings related to NASH progression, we used an original bioinformatics, integrative, text-mining approach that combines PubMed database querying and available gene expression omnibus dataset. We have identified a signature of 25 genes that are commonly found to be dysregulated during steatosis progression to NASH and cancer. These genes are implicated in lipid metabolism, insulin resistance, inflammation, and cancer. They are functionally connected, forming the basis necessary for steatosis progression to NASH and further progression to hepatocellular carcinoma (HCC). We also show that five of the identified genes have genome alterations present in HCC patients. The patients with these genes associated to genome alteration are associated with a poor prognosis. In conclusion, using an integrative literature- and data-mining approach, we have identified and described a canonical pathway underlying progression of NASH. Other parameters (e.g. polymorphisms) can be added to this pathway that also contribute to the progression of the disease to cancer. This work improved our understanding of the molecular basis of NASH progression and will help to develop new therapeutic approaches.

[24] *Fotso Soh J, Almadani A, Beaulieu S et al.* **The effect of atorvastatin on cognition and mood in bipolar disorder and unipolar depression patients: A secondary analysis of a randomized controlled trial**. Journal of affective disorders 2019; 262:149-154.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31733459
ABSTRACT
OBJECTIVES: Statins have recently been linked to having effects on cognition and mood in mood disorders, though results are mixed. In this paper, we use data from a recent randomized controlled trial (RCT) to examine the effect of statins on cognition and mood in patients with Bipolar Disorder (BD) and Major Depressive Disorder (MDD). METHODS: This is a secondary analysis of a randomized, double-blind, placebo-controlled clinical trial (n=60) originally designed to examine the effect of atorvastatin (n=27) versus placebo (n=33) for lithium-induced diabetes insipidus in BD and MDD patients who were using lithium. For this analysis, the primary outcome was global cognition Z-score at 12-weeks adjusted for baseline. The secondary cognition outcomes were (1) Screen for Cognitive Impairment in Psychiatry (SCIP), and (2) executive function Z-score. The primary mood outcome (secondary outcome of this analysis) was depression relapse during 12-week follow-up (Mongomery Asberg Depression Rating Scale (MADRS) >/=10). The secondary mood outcomes were (1) relapse rate into a manic episode, and (2) relapse rate into any mood episode. RESULTS: After 12 weeks follow-up, atorvastatin and placebo groups did not differ in terms of global cognition Z-score (beta = -0.009287 (-0.1698,0.1512), p-value = 0.91). Similarly, composite Z-scores for SCIP and executive functions did not differ significantly. Depression relapse during 12-week follow-up was not significantly different

between the groups (chi(2) (1) = 0.148, p-value = 0.70). Similarly, there was no difference between groups regarding relapse into mania. CONCLUSION: In BD and MDD patients with lithium-induced nephrogenic diabetes insipidus randomized to atorvastatin or placebo, we found no significant differences in cognition and mood outcomes at 12-week follow-up.

[25] *Colantonio LD, Shannon ED, Orroth KK et al.* **Ischemic Event Rates in Very-High-Risk Adults**. Journal of the American College of Cardiology 2019; 74:2496-2507.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31727288
ABSTRACT
BACKGROUND: The 2018 American Heart Association/American College of Cardiology (AHA/ACC) cholesterol guideline includes recommendations for intensive lipid-lowering therapy in patients at very high risk for atherosclerotic cardiovascular disease (ASCVD) events. OBJECTIVES: This study sought to estimate event rates among adults with a history of ASCVD who met and did not meet the definition of very high risk in the 2018 AHA/ACC cholesterol guideline. METHODS: Data from U.S. adults with health insurance in the MarketScan database who had a history of ASCVD on January 1, 2016 (n = 27,775) were analyzed. Very high risk for ASCVD events was defined as a history of >/=2 major ASCVD events or 1 event and >/=2 high-risk conditions. Patients were followed through December 31, 2017, for ASCVD events, including myocardial infarction, ischemic stroke, and major adverse limb events. RESULTS: Overall, 15,366 patients (55.3%) with ASCVD met the definition of very high risk. Among patients with and without very high risk, the ASCVD event rate per 1,000 person-years was 53.1 (95% confidence interval [CI]: 50.1 to 56.1) and 17.0 (95% CI: 15.2 to 18.9), respectively. Among patients with >/=2 major ASCVD events and with 1 event and >/=2 high-risk conditions, the ASCVD event rate per 1,000 person-years was 89.8 (95% CI: 82.2 to 98.0) and 41.3 (95% CI: 38.3 to 44.4), respectively. The age- and sex-adjusted hazard ratios for ASCVD events among patients with very high risk, overall, with >/=2 major ASCVD events and with 1 event and >/=2 high-risk conditions versus those without very high risk were 2.98 (95% CI: 2.63 to 3.37), 4.89 (95% CI: 4.22 to 5.66), and 2.33 (95% CI: 2.04 to 2.66), respectively. CONCLUSIONS: The 2018 AHA/ACC cholesterol guideline directs intensive lipid-lowering therapy to adults with a very high ASCVD event rate.

[26] *Schwartz GG, Chaitman BR*. **Initiating PCSK9 Inhibition in Hospital for ACS: We Can, But Does That Mean We Should?** Journal of the American College of Cardiology 2019; 74:2463-2465.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31727283
ABSTRACT

[27] *Wang H, Deng J, Chen L et al.* **Acute glucose fluctuation induces inflammation and neurons apoptosis in hippocampal tissues of diabetic rats**. Journal of cellular biochemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31713299
ABSTRACT
It is well-recognized that glycemic disorders are leading causes of diabetic complications and acute fluctuation of blood glucose and reported more likely being related to oxidative stress, vasculopathy, and other diabetic complications than continuous hyperglycemia in patients with diabetic and animal models. To explore the hypothesis that acute glucose fluctuation (GF) aggravates inflammatory lesions and neuron apoptosis in the hippocampus of diabetic rats. Twenty female GK rats were randomly allocated into a glucose fluctuating group (GK-GF) and a continuous hyperglycemia group (GK-CHG)

and 10 age-matched female Wistar rats served as controls. GF was induced in the GK-GF group by injection with glucose and insulin at different periods of time per day for 6 weeks. Body weight was determined weekly. At the end of the study, blood hemoglobin A1c (HbA1c) and serum lipids were measured. Serum and hippocampus interleukin 1beta (IL-1beta), IL-6, IL-8, and tumor necrosis factor-alpha (TNF-alpha) were measured by enzyme-linked immunosorbent assay and real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Hippocampus Bcl-2, Bax, Pten, fas, and myc were quantified by qRT-PCR and Western blot analysis and Mirror Water Maze (MWM) test was performed. We successfully established an animal model with daily GF and a control model with CHG using GK diabetic rats. The GF and CHG rats showed lower weight gain during the 6-week experimental period with no significant difference in the levels of serum lipids such as total triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol compared with the control rats at the end of the study. Meanwhile, the GF and CHG rats showed higher blood HbA1c levels than that of control rats. MWM trainings tests detected that glucose disorders in GF and CHG rats tend to present longer latencies, more cross times and longer path length compared with those of the control rats, indicating impaired the hippocampus-regulated behavioral function such as spatial orientating and memory. Importantly, it was found that GF promoted the expression of TNF-alpha and IL-1beta in the hippocampus of the GF rats while continuous hyperglycemia in CHG rats had little effect on that. Furthermore, both GF and CHG diabetic rats had abnormal expression of apoptosis-associated genes in the hippocampus compared with control Wistar rats and neurons apoptosis in GF rats appears to be more severe than CHG rats. Overall, this study confirmed that GF is a more critical factor that would promote the neuron apoptosis and induce inflammation in the hippocampus than continuous hyperglycemia in diabetic animals, which shed new light on the importance of monitoring and administration of blood glucose in the prevention and therapy for diabetes.

[28] *Kashyap ML, Ganji S, Nakra NK, Kamanna VS*. **Niacin for treatment of nonalcoholic fatty liver disease (NAFLD): novel use for an old drug?** Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31706905

ABSTRACT

Niacin has been widely used clinically for over half a century for dyslipidemia. Recent new evidence indicates that niacin may be useful in the treatment of nonalcoholic fatty liver disease (NAFLD) and its sequential complications including nonalcoholic steatohepatitis and fibrosis. There is an urgent unmet need for a cost-effective solution for this public health problem affecting nearly one in three adults. Niacin inhibits and reverses hepatic steatosis and inflammation in animals and liver cell cultures. It prevents liver fibrosis in animals and decreases collagen in cultured human stellate cells. Its mechanism of action is by oxidative stress reduction and inhibition of diacylglycerol acyltransferase 2 and other possible targets. An uncontrolled clinical trial in 39 hypertriglyceridemic patients with steatosis showed reduction of liver fat by 47% and reductions in liver enzymes and C-reactive protein from the baseline when treated with niacin extended-release for 6 months These hypothesis-generating data indicate a novel repurposed use of niacin for NAFLD. Niacin beneficially affects NAFLD at 3 major stages directly and, by affecting steatosis, it indirectly decreases the cascade effect on inflammation and fibrosis. It offers the advantage potentially of combination with other drugs in development for evolving synergistically more intense and broader efficacy. In select patients, it may benefit frequently associated atherogenic dyslipidemia. A randomized placebo-controlled double-blind parallel trial (with

niacin alone or in combination with another drug in development) to assess the safety and efficacy of niacin on steatosis, inflammation, and fibrosis in patients with nonalcoholic steatohepatitis/NAFLD is warranted.

[29] *Perez de Isla L, Arroyo-Olivares R, Muniz-Grijalvo O et al.* **Long-term effect of 2 intensive statin regimens on treatment and incidence of cardiovascular events in familial hypercholesterolemia: The SAFEHEART study**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31706904
ABSTRACT
BACKGROUND: Maximal doses of potent statins are the basement of treatment of familial hypercholesterolemia (FH). Little is known about the use of different statin regimens in FH. OBJECTIVES: The objectives of the study were to describe the treatment changes and low-density lipoprotein cholesterol (LDL-C) goal achievement with atorvastatin (ATV) and rosuvastatin (RV) in the SAFEHEART cohort, as well as to analyze the incidence of atherosclerotic cardiovascular events (ACVEs) and changes in the cardiovascular risk. METHODS: SAFEHEART is a prospective follow-up nationwide cohort study in a molecularly defined FH population. The patients were contacted on a yearly basis to obtain relevant changes in life habits, medication, and ACVEs. RESULTS: A total of 1939 patients were analyzed. Median follow-up was 6.6 years (5-10). The estimated 10-year risk according the SAFEHEART risk equation was 1.61 (0.67-3.39) and 1.22 (0.54-2.93) at enrollment for ATV and RV, respectively (P < .001). There were no significant differences at the follow-up: 1.29 (0.54-2.82) and 1.22 (0.54-2.76) in the ATV and RV groups, respectively (P = .51). Sixteen percent of patients in primary prevention with ATV and 18% with RV achieved an LDL-C <100 mg/dL and 4% in secondary prevention with ATV and 5% with RV achieved an LDL-C <70 mg/dL. The use of ezetimibe was marginally greater in the RV group. One hundred sixty ACVEs occurred during follow-up, being its incidence rate 1.1 events/100 patient-years in the ATV group and 1.2 in the RV group (P = .58). CONCLUSION: ATV and RV are 2 high-potency statins widely used in FH. Although the reduction in LDL-C levels was greater with RV than with ATV, the superiority of RV for reducing ACVEs was not demonstrated.

[30] *Robinson JG, Farnier M, Kastelein JJP et al.* **Relationship between alirocumab, PCSK9, and LDL-C levels in four phase 3 ODYSSEY trials using 75 and 150 mg doses**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31708410
ABSTRACT
BACKGROUND: Alirocumab is a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9). OBJECTIVE: Changes in PCSK9, alirocumab, and low-density lipoprotein cholesterol (LDL-C) levels were assessed after treatment with alirocumab at doses of 75 or 150 mg every 2 weeks (Q2W). METHODS: Data were analyzed from 4 phase 3 trials (MONO; COMBO II; FH I; LONG TERM); all but MONO enrolled patients on statins. Three trials evaluated alirocumab 75 mg Q2W, with possible dose increase to 150 mg Q2W at week 12 based on week 8 LDL-C; LONG TERM studied alirocumab 150 mg Q2W. RESULTS: Patients on background statin therapy had higher mean baseline free PCSK9 concentrations vs patients not on statin. After alirocumab administration, increased alirocumab concentrations were associated with dramatic reductions in circulating free PCSK9, resulting in significant LDL-C reductions and a corresponding increase in inactive PCSK9:alirocumab complex. Alirocumab dose increase was associated with a further lowering of PCSK9 and LDL-C. Patients with higher baseline LDL-C levels (>160 mg/dL) were more likely to have their dose increased. LDL-C

reductions with alirocumab were consistent between patients with baseline PCSK9 levels above or below the median when the dose increase strategy was used. When started as alirocumab 150 mg Q2W, patients with PCSK9 levels above vs below the median had a greater LDL-C reduction. CONCLUSIONS: Alirocumab-induced changes in PCSK9 and LDL-C levels were consistent with the known physiologic relationship between PCSK9, LDL receptor, and LDL-C levels, as well as statin-induced increases in PCSK9 production.

[31] *Chistiakov DA, Kashirskikh DA, Khotina VA et al.* **Immune-Inflammatory Responses in Atherosclerosis: The Role of Myeloid Cells**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31717832
ABSTRACT
Inflammation plays a key role in the initiation and progression of atherosclerosis and can be caused by multiple agents, including increased concentration of circulating low-density lipoprotein (LDL) cholesterol. Areas of the arterial wall affected by atherosclerosis are enriched with lymphocytes and dendritic cells (DCs). Atherosclerotic plaques contain a variety of proinflammatory immune cells, such as macrophages, DCs, T cells, natural killer cells, neutrophils and others. Intracellular lipid accumulation in atherosclerotic plaque leads to formation of so-called foam cells, the cytoplasm of which is filled with lipid droplets. According to current understanding, these cells can also derive from the immune cells that engulf lipids by means of phagocytosis. Macrophages play a crucial role in the initial stages of atherogenesis by engulfing oxidized LDL (oxLDL) in the intima that leads to their transformation to foam cells. Dying macrophages inside the plaque form a necrotic core that further aggravates the lesion. Proinflammatory DCs prime differentiation of naive T cells to proinflammatory Th1 and Th17 subsets. In this review, we discuss the roles of cell types of myeloid origin in atherosclerosis-associated inflammation.

[32] *Girona J, Rodriguez-Borjabad C, Ibarretxe D et al.* **The Circulating GRP78/BiP Is a Marker of Metabolic Diseases and Atherosclerosis: Bringing Endoplasmic Reticulum Stress into the Clinical Scenario**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31717752
ABSTRACT
BACKGROUND: Glucose-regulated protein 78/Binding immunoglobulin protein (GRP78/BiP) is a protein associated with endoplasmic reticulum stress and is upregulated by metabolic alterations at the tissue-level, such as hypoxia or glucose deprivation, and it is hyper-expressed in fat tissue of obese individuals. OBJECTIVE: To investigate the role of the GRP78/BiP level as a metabolic and vascular disease biomarker in patients with type 2 diabetes (DM), obesity and metabolic syndrome (MS). METHODS: Four hundred and five patients were recruited, of whom 52.5% were obese, 72.8% had DM, and 78.6% had MS. The intimae media thickness (cIMT) was assessed by ultrasonography. The plasma GRP78/BiP concentration was determined, and its association with metabolic and vascular parameters was assessed. Circulating GRP78/BiP was also prospectively measured in 30 DM patients before and after fenofibrate/niacin treatment and 30 healthy controls. RESULTS: In the cross-sectional study, the GRP78/BiP level was significantly higher in the patients with obesity, DM, and MS. Age-, gender- and BMI-adjusted GRP78/BiP was directly associated with LDL-cholesterol, non-HDL-cholesterol, triglycerides, apoB, and cIMT. GRP78/BiP was positively associated to carotid plaque presence in the adjusted model, irrespective of obesity, DM and MS. In the prospective study, nicotinic acid treatment

produced a significant reduction in the GRP78/BiP levels that was not observed with fenofibrate. CONCLUSIONS: GRP78/BiP plasma concentrations are increased in patients with both metabolic derangements and subclinical atherosclerosis. GRP78/BiP could be a useful marker of metabolic and cardiovascular risk.

[33] *Guo W, Zhang H, Yang A et al.* **Homocysteine accelerates atherosclerosis by inhibiting scavenger receptor class B member1 via DNMT3b/SP1 pathway**. Journal of molecular and cellular cardiology 2019; 138:34-48.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31733201
ABSTRACT
Homocysteine (Hcy) is an independent risk factor for atherosclerosis, which is characterized by lipid accumulation in the atherosclerotic plaque. Increasing evidence supports that as the main receptor of high-density lipoprotein, scavenger receptor class B member 1 (SCARB1) is protective against atherosclerosis. However, the underlying mechanism regarding it in Hcy-mediated atherosclerosis remains unclear. Here, we found the remarkable inhibition of SCARB1 expression in atherosclerotic plaque and Hcy-treated foam cells, whereas overexpression of SCARB1 can suppress lipid accumulation in foam cells following Hcy treatment. Analysis of SCARB1 promoter showed that no significant change of methylation level was observed both in vivo and in vitro under Hcy treatment. Moreover, it was found that the negative regulation of DNMT3b on SCARB1 was due to the decreased recruitment of SP1 to SCARB1 promoter. Thus, we concluded that inhibition of SCARB1 expression induced by DNMT3b at least partly accelerated Hcy-mediated atherosclerosis through promoting lipid accumulation in foam cells, which was attributed to the decreased binding of SP1 to SCARB1 promoter. In our point, these findings will provide novel insight into an epigenetic mechanism for atherosclerosis.

[34] *Alakbarzade V, Pereira AC*. **What Proportion of Patients Admitted with Stroke or Transient Ischemic Attack May Be Suitable for Newer Cholesterol-Lowering Treatment?** Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2019:104457.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31732461
ABSTRACT
BACKGROUND: Protein convertase subtilisin-kexin type 9 (PCSK9) inhibitors effectively clear low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C). We evaluated stroke admissions potentially eligible for more intensive cholesterol treatment. METHODS: Retrospective analysis of consecutive admissions to a hyperacute stroke unit over 5 months in 2017. Records were individually searched. Data were collected on diagnosis, risk factors, and stroke work-up. European Society of Cardiology and European Atherosclerosis Society guidelines for the management of dyslipidaemias were used for screening patients eligible for PCSK9 inhibitors. RESULTS: Of 650 patient admissions: 351 (54%) had acute ischemic stroke or transient ischemic attack (TIA), 80 (12%) hemorrhage, and 219 (34%) mimic syndromes. Patients with hemorrhage (n=80), mimic syndromes (n=219), and absent LDL-C, or non-HDL-C testing (n=27) were subsequently excluded. 324 patients with acute ischemic stroke and TIA were further screened for PCSK9-inhibitor treatment eligibility. Forty-one (13%) patients with LDL-C greater than or equal to 1.8mmol/L (>/=70 mg/dL) on maximal tolerated statin dose and with concomitant "very high vascular risk" were identified. "Very high vascular risk" was defined as a documented history of cardiovascular disease and/or peripheral arterial disease. Of 41 patients eligible for PCSK9 inhibitors, median age was 82 years (range 53-96); median vascular risk

factors were 2 (range 1-5); 7 (17%) had TIA; 13 (31%) had history of preceding cerebrovascular events, 13 (31%) diabetes mellitus, 17 (42%) cardioembolic events, 9 (22%) lacunar syndrome, 11 (22%) symptomatic internal carotid artery stenosis (n=9 were >70%), and 4 (10%) undetermined aetiology. Eighty-three percent patients eligible for PCSK9 inhibitors also had non-HDL-C values greater than or equal to 2.6 mmol/L. CONCLUSIONS: Up to 13% of unselected acute ischemic stroke or TIA patients admitted to a hyper-acute stroke unit were potentially suitable for more intensive cholesterol treatment. Our data may act as a useful guide for sample size selection in future stroke trials testing PCSK9 inhibitors.

[35] *Cao YX, Jin JL, Sun D et al.* **Circulating PCSK9 and cardiovascular events in FH patients with standard lipid-lowering therapy**. Journal of translational medicine 2019; 17:367.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31711505
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin 9 (PCSK9) has been proposed as a novel target for coronary artery disease (CAD). Familial hypercholesterolemia (FH) is characterized by high prevalence of CAD and major cardiovascular events (MACEs). However, no data is available on the association between PCSK9 levels and MACEs in FH patients with standard lipid lowering therapy. METHODS: A total of 338 consecutive heterozygous FH (Dutch Lipid Clinic Network score >/= 6) was enrolled and followed up for the occurrence of MACEs. Multidetector CT and coronary angiography were performed to determine coronary artery calcification score (CACS) and Gensini score (GS). Multivariable Cox regression analyses were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Plasma PCSK9 concentrations were determined by enzyme immunoassay. RESULTS: PCSK9 was independently and positively associated CACS and GS at baseline. During a mean follow-up of 3 years, 33 (9.8%) events occurred. Patients with MACEs had higher median PCSK9 compared with those without (332.47 vs. 311.89 ng/mL, p = 0.038). Kaplan-Meier analysis revealed that patients with higher PCSK9 presented lower event-free survival (p = 0.0017). PCSK9 was statistically correlated with MACEs after adjusting for confounding factors, with the HR per SD being 1.86 (1.31-2.65) and 3.70 (1.16-11.82) for the highest tertile compared with the lowest tertile. Adding PCSK9 to Cox prediction model led to a statistical improvement in net reclassification and integrated discrimination. CONCLUSION: Elevated levels of PCSK9 were positively associated with the development of CAD and future cardiovascular events, suggesting that measurement of PCSK9 concentration might be useful for cardiovascular risk stratification. Further studies are needed to confirm our results.

[36] *Wang X, Musunuru K*. **Angiopoietin-Like 3: From Discovery to Therapeutic Gene Editing**. JACC. Basic to translational science 2019; 4:755-762.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31709322
ABSTRACT
Hyperlipidemia is a major causal risk factor for atherosclerosis and coronary heart disease (CHD). Angiopoietin-like 3 (ANGPTL3) has emerged as a promising molecular target to reduce CHD risk due to its regulation of all 3 major lipid traits: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Here, the authors review the discovery of ANGPTL3, the role of ANGPTL3 in lipoprotein metabolism, and the genetic association between naturally occurring ANGPTL3 loss-of-function mutations and CHD. In light of the favorable consequences of ANGPTL3 deficiency, various

therapeutic strategies to target ANGPTL3 are currently in development, including a monoclonal antibody, an antisense oligonucleotide, and gene editing.

[37] *Goldberg AC, Leiter LA, Stroes ESG et al.* **Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial**. Jama 2019; 322:1780-1788.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31714986
ABSTRACT
Importance: Additional treatment options are needed for patients who do not achieve sufficient reduction in low-density lipoprotein cholesterol (LDL-C) level with available lipid-lowering therapies. Objective: To assess the efficacy of bempedoic acid vs placebo in patients at high cardiovascular risk receiving maximally tolerated lipid-lowering therapy. Design, Setting, and Participants: Phase 3, randomized, double-blind, placebo-controlled clinical trial conducted at 91 clinical sites in North America and Europe from November 2016 to September 2018, with a final date of follow-up of September 22, 2018. A total of 779 patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both met randomization criteria, which included LDL-C level 70 mg/dL (1.8 mmol/L) or greater while receiving maximally tolerated lipid-lowering therapy. Interventions: Patients were randomized 2:1 to treatment with bempedoic acid (180 mg) (n = 522) or placebo (n = 257) once daily for 52 weeks. Main Outcomes and Measures: The primary end point was percent change from baseline in LDL-C level at week 12. Secondary measures included changes in levels of lipids, lipoproteins, and biomarkers. Results: Among 779 randomized patients (mean age, 64.3 years; 283 women [36.3%]), 740 (95.0%) completed the trial. At baseline, mean LDL-C level was 120.4 (SD, 37.9) mg/dL. Bempedoic acid lowered LDL-C levels significantly more than placebo at week 12 (-15.1% vs 2.4%, respectively; difference, -17.4% [95% CI, -21.0% to -13.9%]; P < .001). Significant reductions with bempedoic acid vs placebo were observed at week 12 for non-high-density lipoprotein cholesterol (-10.8% vs 2.3%; difference, -13.0% [95% CI, -16.3% to -9.8%]; P < .001), total cholesterol (-9.9% vs 1.3%; difference, -11.2% [95% CI, -13.6% to -8.8%]; P < .001), apolipoprotein B (-9.3% vs 3.7%; difference, -13.0% [95% CI, -16.1% to -9.9%]; P < .001), and high-sensitivity C-reactive protein (median, -18.7% vs -9.4%; difference, -8.7% [asymptotic confidence limits, -17.2% to -0.4%]; P = .04). Common adverse events included nasopharyngitis (5.2% vs 5.1% with bempedoic acid and placebo, respectively), urinary tract infection (5.0% vs 1.9%), and hyperuricemia (4.2% vs 1.9%). Conclusions and Relevance: Among patients at high risk for cardiovascular disease receiving maximally tolerated statins, the addition of bempedoic acid compared with placebo resulted in a significant lowering of LDL-C level over 12 weeks. Further research is needed to assess the durability and clinical effect as well as long-term safety. Trial Registration: ClinicalTrials.gov Identifier: NCT02991118.

[38] *Honigberg MC, Natarajan P*. **Bempedoic Acid for Lowering LDL Cholesterol**. Jama 2019; 322:1769-1771.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31714973
ABSTRACT

[39] *Grobelna MK, Strauss E, Krasinski Z*. **The role of proprotein convertase subtilisin-kexin type 9 (PCSK9) in the vascular aging process - is there a link?** Kardiochirurgia i torakochirurgia polska = Polish journal of cardio-thoracic surgery 2019; 16:128-132.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31708986

ABSTRACT

Lately there are many new, promising low-density lipoprotein cholesterol reducing therapies with PCSK9 inhibitors. We performed selected sampling of the publications in PubMed and made a review according to selected keywords. It summarizes the effect of PCSK9 on vascular aging, directly associated with lipid and glucose metabolism, chronic inflammation, atherosclerosis and hypertension. Serum level of PCSK9 is different in patients affected by certain illnesses (whose risk increases with age) than in healthy individuals. The same could be observed in the case of chronic inflammation. In this review we summarize what is known about the role PCSK9 in human metabolism and how this could affect the vascular aging process. Based on the available sources, we prove that PCSK9 is involved in many biochemical pathways associated with vascular aging. In the future, treatments using PCSK9 inhibition may not only reduce the cardiovascular risk but also slow down this process.

[40] *Kobalava ZD, Villevalde SV, Vorobyeva SV*. **Effects of High-Dose Statin Therapy on Cognitive Functions and Quality of Life in Very High Cardiovascular Risk Patients**. Kardiologiia 2018; 57:34-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31713504

ABSTRACT

AIM: To investigate the effects of intensive lipid-lowering therapy on cognitive functions and quality of life in patients (pts) with very high cardiovascular risk. MATERIAL AND METHODS: In 93 pts (58 men, 63.2+/-9.5 years old with history of clinically evident cardiovascular disease and fasting low-density lipoprotein cholesterol (LDL-C) >1.8 mmol/l or non-high-density lipoprotein cholesterol (non-HDL-C) >2.6 mmol/l the mental status and quality of life were assessed before and after 6 months of therapy with atorvastatin 80 mg/day. The Montreal Cognitive Assessment (MoCA) scale and Questionnaire SF-36 (russian version) were used to evaluate cognitive functions and quality of life. RESULTS: 59 (63%) pts had cognitive dysfunction (less than 26 scores by MoCA scale). We observed significant difference in cognitive status between pts >65 and.

[41] *Kucher AN, Nazarenko MS*. **The Role of MicroRNA in Atherogenesis**. Kardiologiia 2018; 57:65-76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31713508

ABSTRACT

This review provides modern data on the spectrum and the functional significance of micro-RNAs involved in atherogenesis and on some regulatory mechanisms that ensure the functioning of this class of molecules. We also outline some examples of micro-RNAs use as diagnostic and therapeutic targets.

[42] *Lee MY, Nam GE, Han K et al.* **Association between height and hypercholesterolemia in adults: a nationwide population-based study in Korea**. Lipids in health and disease 2019; 18:198.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31729984

ABSTRACT

BACKGROUND: Previous studies reported that stature is inversely related to the risk of cardiovascular disease. However, there is limited evidence on the association between height and lipid profiles. We aimed to examine the association of height with total cholesterol and hypercholesterolemia based on the nationally representative dataset of Korean adults. METHODS: The data of 13,701 adults aged >/=19 years who participated in the Korea National Health and Nutrition Examination Survey (2013-2015) were used in this nationwide population-based cross-sectional study. Hypercholesterolemia was

defined as a serum total cholesterol level >/= 240 mg/dL or use of lipid-lowering medications. Multivariable linear regression and logistic regression analyses were used to examine the association of height with mean total cholesterol level and odds ratios (ORs) of hypercholesterolemia. RESULTS: Approximately 17% of participants had hypercholesterolemia. Mean total cholesterol levels decreased in the higher quartile (Q) groups of height after adjusting for confounding variables including age, sex, body mass index, smoking status, alcohol consumption, physical activity, income, educational level, hypertension, and diabetes mellitus (P for trend = 0.035). After adjusting for these potential confounding variables, the adjusted ORs of hypercholesterolemia were significantly lower in the Q3 and Q4 groups than in the Q1 group; ORs decreased in the higher quartile groups of height (OR: 0.83, 95% confidence interval: 0.71-0.99 in Q3; 0.81, 0.69-0.95 in Q4, P for trend = 0.007). The association between height (Q4 vs. Q1-Q3) and hypercholesterolemia was stronger in men or individuals without hypertension or diabetes than in women or individuals with such diseases. CONCLUSIONS: Height is inversely associated with total cholesterol level and odds of hypercholesterolemia among Korean adults. Childhood environment related to short stature may be associated with hypercholesterolemia and cardiovascular health in adulthood.

[43] *Zhan X, Yang M, Zhou R et al.* **Triglyceride to high-density lipoprotein cholesterol ratio is associated with increased mortality in older patients on peritoneal dialysis**. Lipids in health and disease 2019; 18:199.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31729985
ABSTRACT
BACKGROUND: The triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (TG/HDL-C) has been suggested as a simple method to identify unfavorable cardiovascular (CV) outcomes in the general population. The aim of this study was to investigate the association between the TG/HDL-C ratio and all-cause and CV mortality in peritoneal dialysis (PD) patients. METHODS: We retrospectively analyzed patients on PD from November 1, 2005, to February 28, 2017, with a follow-up period lasting until May 31, 2017. The main outcomes were all-cause and CV mortality. RESULTS: Among the 973 PD patients, the mean age was 49.67 +/- 14.58 (y). During a median follow-up period of 27.2 months (IQR = 13.4-41.5 months), 229 (23.5%) patients died, with 120 (12.3%) dying as a result of CV diseases. The median serum TG/HDL-C ratio was 1.11 (IQR = 0.71-1.80). In a multivariate Cox regression analysis, patients with higher TG/HDL-C ratio levels (tertile 3) had a higher incidence of CV mortality (adjusted HR = 2.12; 95% CI: 1.21-3.72; P = 0.009) and all-cause mortality (adjusted HR = 2.08; 95% CI: 1.37-3.14; P = 0.001) compared to patients in tertile 1. These associations persisted after excluding the patients who have already taken lipid-lowering medications. For older patients (> 60 years), each 1-unit higher baseline TG/HDL-C level was associated with a 48% (95% CI: 1.06-2.07; P = 0.021) increased risk of all-cause mortality and a 59% (95% CI: 1.03-2.45; P = 0.038) increased risk of CV mortality; however, this association was not observed in patients </=60 years of age. CONCLUSIONS: A higher serum TG/HDL-C ratio was an independent predictor of all-cause and CV mortality in PD patients. Furthermore, an elevated TG/HDL-C ratio was significantly associated with higher all-cause and CV mortality in older PD patients.

[44] *Fonseca MIH, de Almeida-Pititto B, Bensenor IM et al.* **Changes in lipoprotein subfractions following menopause in the Longitudinal Study of Adult Health (ELSA-Brasil)**. Maturitas 2019; 130:32-37.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31706433

ABSTRACT

INTRODUCTION: It is unclear how aging and menopause-induced lipid changes contribute to the elevated cardiovascular risk in menopausal women. We examined the association between lipid profiles and menopausal status and duration of menopause in the Longitudinal Study of Adult Health (ELSA-Brasil). METHODS: This is a cross-sectional analysis of baseline data from women in the ELSA-Brasil, stratified by duration of menopause into 5 groups: pre-menopause, <2 years, 2-5.9 years, 6-9.9 years and >/=10 years of menopause, excluding menopause <40 years or of non-natural cause; also excluded were women using lipid-lowering drugs or hormone replacement. Comparisons were performed using ANOVA with Bonferroni correction. Associations of menopause categories and time since menopause with lipid variables obtained by vertical auto-profile were tested using multiple linear regression. RESULTS: From 1916 women, postmenopausal groups had unadjusted higher total cholesterol, LDL-c, real LDL-c, IDL-c, VLDL-c, triglycerides, non-HDL-c, VLDL3-c, triglyceride-rich lipoprotein remnants (TRL-c) and buoyant LDL-c concentrations than pre-menopausal women, with no difference among postmenopausal groups. In multiple linear regression, duration of menopause <2 years was significantly associated with TRL-c [7.21mg/dL (95% CI 3.59-10.84)] and VLDL3-c [2.43mg/dL (95%CI 1.02-3.83)]. No associations of menopausal categories with HDL-c or LDL-c subfractions were found, and nor were associations of time since menopause with lipid subfractions. CONCLUSIONS: In a large sample of Brazilian women, deterioration of the lipid profile following menopause was confirmed, which could contribute to the increased cardiovascular risk. Our findings suggest a postmenopausal elevation in triglyceride-rich lipoprotein remnants. How lipoprotein subfractions change after the onset of menopause warrants investigation in studies with appropriate designs.

[45] *Gu L, Gong Y, Zhao C et al.* **Lunasin Improves the LDL-C Lowering Efficacy of Simvastatin via Inhibiting PCSK9 Expression in Hepatocytes and ApoE(-/-) Mice**. Molecules (Basel, Switzerland) 2019; 24.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31731717

ABSTRACT

Statins are the most popular therapeutic drugs to lower plasma low density lipoprotein cholesterol (LDL-C) synthesis by competitively inhibiting hydroxyl-3-methyl-glutaryl-CoA (HMG-CoA) reductase and up-regulating the hepatic low density lipoprotein receptor (LDLR). However, the concomitant up-regulation of proprotein convertase subtilisin/kexin type 9 (PCSK9) by statin attenuates its cholesterol lowering efficacy. Lunasin, a soybean derived 43-amino acid polypeptide, has been previously shown to functionally enhance LDL uptake via down-regulating PCSK9 and up-regulating LDLR in hepatocytes and mice. Herein, we investigated the LDL-C lowering efficacy of simvastatin combined with lunasin. In HepG2 cells, after co-treatment with 1 muM simvastatin and 5 muM lunasin for 24 h, the up-regulation of PCSK9 by simvastatin was effectively counteracted by lunasin via down-regulating hepatocyte nuclear factor 1alpha (HNF-1alpha), and the functional LDL uptake was additively enhanced. Additionally, after combined therapy with simvastatin and lunasin for four weeks, ApoE(-/-) mice had significantly lower PCSK9 and higher LDLR levels in hepatic tissues and remarkably reduced plasma concentrations of total cholesterol (TC) and LDL-C, as compared to each monotherapy. Conclusively, lunasin significantly improved the LDL-C lowering efficacy of simvastatin by counteracting simvastatin induced elevation of PCSK9 in hepatocytes and ApoE(-/-) mice. Simvastatin combined with lunasin could be a novel regimen for hypercholesterolemia treatment.

[46] *Carcel C, Wang X, Sandset EC et al.* **Sex differences in treatment and outcome after stroke: Pooled analysis including 19,000 participants**. Neurology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31719135
ABSTRACT
OBJECTIVE: To explore the sex differences in outcomes and management after stroke using a large sample with high-quality international trial data. METHODS: Individual participant data were obtained from 5 acute stroke randomized controlled trials. Data were obtained on demographics, medication use, in-hospital treatment, and functional outcome. Study-specific crude and adjusted models were used to estimate sex differences in outcomes and management, and then pooled using random-effects meta-analysis. RESULTS: There were 19,652 participants, of whom 7,721 (40%) were women. After multivariable adjustments, women with ischemic stroke had higher survival at 3-6 months (odds ratio [OR] 0.82, 95% confidence interval [CI] 0.70-0.97), higher likelihood of disability (OR 1.20, 95% CI 1.06-1.36), and worse quality of life (weighted mean difference -0.07, 95% CI -0.09 to 0.04). For management, women were more likely to be admitted to an acute stroke unit (OR 1.17, 95% CI 1.01-1.34), but less likely to be intubated (OR 0.58, 95% CI 0.36-0.93), treated for fever (OR 0.82, 95% CI 0.70-0.95), or admitted to an intensive care unit (OR 0.83, 95% CI 0.74-0.93). For preadmission medications, women had higher odds of being prescribed antihypertensive agents (OR 1.22, 95% CI 1.13-1.31) and lower odds of being prescribed antiplatelets (OR 0.86, 95% CI 0.79-0.93), glucose-lowering agents (OR 0.86, 95% CI 0.78-0.94), or lipid-lowering agents (OR 0.85, 95% CI 0.77-0.94). CONCLUSIONS: This analysis suggests that women who had ischemic stroke had better survival but were also more disabled and had poorer quality of life. Variations in hospital and out-of-hospital management may partly explain the disparities.

[47] *Abou-Saleh H, Ouhtit A, Halade GV, Rahman MM*. **Bone Benefits of Fish Oil Supplementation Depend on its EPA and DHA Content**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31717258
ABSTRACT
The preventive effect of high-dose (9%) regular-fish oil (FO) against bone loss during aging has been demonstrated, but the effects of a low-dose (1%-4%) of a highly purified concentrated FO (CFO) has not been elucidated. The aim of this study was to determine the dose-dependent effect of a CFO against bone loss in C57BL/6 female mice during aging. Twelve-month old mice were fed with 1% and 4% CFO and 4% safflower oil (SFO) diets, including a group with a 4% regular-FO diet and a group with a lab chow diet for 12 months. Bone mineral density (BMD) was analyzed by dual-energy x-ray absorptiometry (DXA) before and after the dietary intervention. At the end of dietary intervention, bone resorption markers in serum and inflammatory markers in bone marrow and splenocytes and inflammatory signaling pathways in the bone marrow were analyzed. As compared to the 4% SFO control, 4% CFO maintained higher BMD during aging, while 1% CFO offered only a mild benefit. However, the 1% CFO fed group exhibited slightly better BMD than the 4% regular-FO fed group. BMD loss protection by CFO was accompanied by reduced levels of the bone resorption marker, TRAP, and the osteoclast-stimulating-factor, RANKL, without affecting the decoy-receptor of RANKL, osteoprotegerin (OPG). Further, CFO supplementation was associated with an increase in the production of IL-10, IL-12, and IFN-gamma and a decrease in the production of TNF-alpha and IL-6, and the activation of NF-kappaB, p38 MAPK, and JNK signaling pathways. In conclusion, the

supplementation of 4% CFO is very efficient in maintaining BMD during aging, whereas 1% CFO is only mildly beneficial. CFO supplementation starting at middle age may maintain better bone health during aging.

[48] *Alfawaz H, Naeef AF, Wani K et al.* **Improvements in Glycemic, Micronutrient, and Mineral Indices in Arab Adults with Pre-Diabetes Post-Lifestyle Modification Program**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31731609
ABSTRACT
The present study aimed to investigate the changes in dietary patterns of adult Saudis with prediabetes who underwent a six-month lifestyle modification program. A total of 160 Saudis with prediabetes (baseline fasting glucose 5.6-6.9 mmol/L), aged 20-60 years, were enrolled in one of the two arms: A one-time general advice about lifestyle modification (GA group) at orientation or a well-structured and monitored nutrition and lifestyle counseling for six months (guidance group). Fasting blood samples and a dietary recall for daily intakes of macro/micronutrients using a validated computerized food database "ESHA-the Food Processor Nutrition Analysis program" were collected pre- and post-intervention. Compliance to reference daily intake (RDI) was also calculated at both time points. At baseline, overall, severe deficiencies in the majority of micronutrient intakes were observed. Post intervention, clinically significant improvements in the glycemic indices (fasting glucose and insulin resistance) were seen over time in the guidance group. Also, significant improvements in dietary habits and physical activity levels were more apparent in the guidance group than the GA group, particularly in the daily intakes of total carbohydrate (46.9% compliance post vs. 20.3% at baseline); dietary fiber (21.9% vs. 3.1%); and some micronutrients like vitamin B6 (21.3% vs. 6.7%), vitamin B12 (45.3% vs. 28%), vitamin C (21.9% vs. 7.8%), riboflavin (40% vs. 10.7%), niacin (41.3% vs. 14.7%), magnesium (18.8% vs. 4.7%), iron (54.7% vs. 34.4%), and copper (37.3% vs. 13.3%). The study highlights the effects of a six-month lifestyle modification program in improving dietary micronutrient intakes of Saudis with prediabetes. Since micronutrient intake was observed to be low, fortification of these micronutrients in the Saudi diet is recommended.

[49] *Bittner V*. **Implications for REDUCE IT in clinical practice**. Prog Cardiovasc Dis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31715195
ABSTRACT
Statin therapy is effective in primary and secondary prevention, but substantial residual risk remains on statin treatment, especially among high risk and very high risk patients. Add-on therapy with ezetimibe and proprotein convertase subtilisin /kexin type 9 (PCSK9) inhibitors provides additional risk reduction through further reduction in low density lipoprotein cholesterol. Elevated triglycerides/triglyceride rich lipoproteins contribute to atherogenesis and to the residual risk on statin therapy. Addition of icosapent ethyl to statins has recently been shown to markedly lower risk of ASCVD events in patients with established atherosclerotic CVD (ASCVD) and high risk patients with type II diabetes mellitus. These data are discussed in the context of current guidelines and synthesized in a decision pathway to guide combination lipid-lowering therapy in patients at high ASCVD risk.

[50] *Stone NJ, Grundy SM*. **The 2018 AHA/ACC/Multi-Society Cholesterol guidelines: Looking at past, present and future**. Prog Cardiovasc Dis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31733217

ABSTRACT
The authors review more than three decades of progress in providing clinicians and patients with guidance on risk assessment, patient evaluation and cholesterol management. Beginning with the National Cholesterol Education Program's Initial Adult Treatment Panel report, the cholesterol guidelines increasingly reflect the progress made in understanding the benefits of improved lifestyle and nutrition to improve lipid profiles, major risk factors and reduce ASCVD risk. Moreover, they now provide qualitative and quantitative assessment tools to guide appropriate risk reduction LDL-C lowering therapy. Use of the Pooled Cohort Equations to determine Low, Borderline, Intermediate and High 10-year ASCVD risk is now joined by recognition of conditions and biomarkers that enhance ASCVD risk. This personalizes the risk discussion for the patient. An important addition is the selective use of coronary artery calcium (CAC) scoring to reclassify risk in patients at borderline or intermediate risk, but for whom a risk decision regarding statin therapy is uncertain. In secondary prevention, current guidelines provide criteria for determining a "very high" risk group in whom risk is especially high and in whom aggressive LDL-C lowering can be shown to provide increased absolute benefit. Current guidelines provide a comprehensive look at children and adolescents, young adults, elderly, women and issues specific to women through the life course. They provide guidance for those adults at risk due to severe hypercholesterolemia, persistent hypertriglyceridemia after secondary causes have been addressed, those with inflammatory disorders and HIV, those adults with chronic kidney disease, and those affected by issues of race/ethnicity. They conclude with a brief summary of recommendations emphasizing important concepts for providing safety with LDL-C lowering therapy. This combination of best external evidence and clinical expertise from the expert panel should provide a solid foundation for lipid management of patients at risk for or with clinical ASCVD.

[51] *Shivakoti R, Dalli J, Kadam D et al.* **Lipid mediators of inflammation and Resolution in individuals with tuberculosis and tuberculosis-Diabetes**. Prostaglandins Other Lipid Mediat 2019; 147:106398.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31726221

ABSTRACT
Individuals with concurrent tuberculosis (TB) and Type 2 diabetes (DM) have a higher risk of adverse outcomes. To better understand potential immunological differences, we utilized a comprehensive panel to characterize pro-inflammatory and pro-resolving (i.e., mediators involved in the resolution of inflammation) lipid mediators in individuals with TB and TB-DM. A nested cross-sectional study of 40 individuals (20 newly diagnosed DM and 20 without DM) was conducted within a cohort of individuals with active drug-susceptible treatment-naive pulmonary TB. Lipid mediators were quantified in serum samples through lipid mediator profiling. We conducted correlation-based analysis of these mediators. Overall, the arachidonic acid-derived leukotriene and prostaglandin families were the most abundant pro-inflammatory lipid mediators, while lipoxins and maresins families were the most abundant pro-resolving lipid mediators in individuals with TB and TB-DM. Individuals with TB-DM had increased correlations and connectivity with both pro-inflammatory and pro-resolving lipid mediators compared to those with TB alone. We identified the most abundant lipid mediator metabolomes in circulation among individuals with TB and TB-DM; in addition, our data shows a substantial number of significant correlations between both pro-inflammatory and pro-resolving lipid mediators in individuals with TB-DM, delineating a molecular balance that potentially defines this comorbidity.

Literature update week 46 (2019)

[52] *Schoeler M, Caesar R*. **Dietary lipids, gut microbiota and lipid metabolism**. Reviews in endocrine & metabolic disorders 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31707624
ABSTRACT
The gut microbiota is a central regulator of host metabolism. The composition and function of the gut microbiota is dynamic and affected by diet properties such as the amount and composition of lipids. Hence, dietary lipids may influence host physiology through interaction with the gut microbiota. Lipids affect the gut microbiota both as substrates for bacterial metabolic processes, and by inhibiting bacterial growth by toxic influence. The gut microbiota has been shown to affect lipid metabolism and lipid levels in blood and tissues, both in mice and humans. Furthermore, diseases linked to dyslipidemia, such as non-alcoholic liver disease and atherosclerosis, are associated with changes in gut microbiota profile. The influence of the gut microbiota on host lipid metabolism may be mediated through metabolites produced by the gut microbiota such as short-chain fatty acids, secondary bile acids and trimethylamine and by pro-inflammatory bacterially derived factors such as lipopolysaccharide. Here we will review the association between gut microbiota, dietary lipids and lipid metabolism.

[53] *da Silva PM, Aguiar C, Morais J*. **Suboptimal lipid levels in clinical practice among Portuguese adults with dyslipidemia under lipid-lowering therapy: Data from the DISGEN-LIPID study**. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2019; 38:559-569.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31706732
ABSTRACT
INTRODUCTION: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Portugal. Hypercholesterolemia has a causal role in atherosclerotic CVD. Guidelines recommend that cardiovascular (CV) risk reduction should be individualized and treatment goals identified. Low-density lipoprotein cholesterol (LDL-C) is the primary treatment target. METHODS: DISGEN-LIPID was a cross-sectional observational study conducted in 24 centers in Portugal in dyslipidemic patients aged >/=40 years, on lipid-lowering therapy (LLT) for at least three months and with an available lipid profile in the previous six months. RESULTS: A total of 368 patients were analyzed: 48.9% men and 51.1% women (93.9% postmenopausal), of whom 73% had a SCORE of high or very high CV risk. One quarter had a family history of premature CVD; 31% had diabetes; 26% coronary heart disease; 9.5% cerebrovascular disease; and 4.1% peripheral arterial disease. Mean baseline lipid values were total cholesterol (TC) 189 mg/dl, LDL-C 116 mg/dl, high-density lipoprotein cholesterol (HDL-C) 53.5 mg/dl, and triglycerides (TG) 135 mg/dl. Women had higher TC (p<0.001), LDL-C (non-significant) and HDL-C (p<0.001), and lower TG (p=0.002); 57% of men and 63% of women had LDL-C>100 mg/dl (p=0.28), and 58% of men and 47% of women had LDL-C>70 mg/dl (p=0.933). CONCLUSION: These observational data show that, despite their high-risk profile, more than half of patients under LLT, both men and women, did not achieve the recommended target levels for LDL-C, and a large proportion also had abnormal HDL-C and/or TG. This is a renewed opportunity to improve clinical practice in CV prevention.