[1] *Carvajal-Juarez I, Espinola-Zavaleta N, Antonio-Villa NE et al.* **Optimal Medical Treatment or Invasive Approach in Patients with Significantly Obstructive Coronary Artery Disease and Ischemia**. Arch Med Res 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32327292
ABSTRACT
INTRODUCTION: Stable ischemic heart disease (SIHD) is a condition that develops in subjects after myocardial infarction. Evidence suggests that optimal medical treatment (OMT) is not inferior to intervention (INT) using percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). AIM: To compare clinical outcomes in subjects with SIHD who only received OMT and those who received INT+OMT. METHODS: We retrospectively examined subjects with SIHD who underwent myocardial perfusion study-SPECT/CT in a reference center in Mexico. We assigned two branches: INT+OMT (subjects with previous PCI or CABG) and OMT (subjects with antiplatelet drugs, beta-blockers, renin-angiotensin-system blockade, nitrates, calcium-channel blockers, and aggressive lipid-lowering therapy). Clinical outcomes at follow-up were angina relief, functional class improvement, hospitalization, myocardial reinfarction and death from any cause. RESULTS: We included 100 subjects; 51 with OMT and 49 with INT+OMT. 54 subjects had 1 affected vessel and 46 more than 2. INT+OMT group had up to 14 fold likelihood (95% CI: 3.38-63.35) of achieving angina relief and 2.2 fold likelihood (95% CI: 0.92-5.57, p = 0.077) for functional class improvement. No differences were found in hospitalization, myocardial infarction and death from any cause compared to OMT. CONCLUSIONS: Subjects with OMT have no higher risk of adverse clinical outcomes compared to INT+OMT. However, the INT+OMT provides angina relief and functional class improvement compared to OMT.

[2] *Wu G, Wei W, Zhang J et al.* **A self-driven bioinspired nanovehicle by leukocyte membrane-hitchhiking for early detection and treatment of atherosclerosis**. Biomaterials 2020; 250:119963.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32334199
ABSTRACT
Atherosclerosis, as a silent killer, remains one of the most common causes of human morbidity and mortality worldwide due to the lack of efficient strategy for early detection and targeted therapy. In this work, a self-driven bioinspired nanovehicle is developed, which can accurately manage early atherosclerosis with simultaneously multiple-targeting, dual-modality therapy as well as noninvasive magnetic resonance imaging (MRI). The magnetic nanoclusters (MNCs) with satisfactory superparamagnetism are camouflaged with leukocyte membranes, thus acquiring inherently targeting and transmigrating capabilities to intimal foam cells in early atherosclerotic lesions, which is validated using tailor-made microfluidic devices and transwell assays. Upon sequentially embedding an anti-inflammatory drug simvastatin (ST) and decorating a targetable apolipoprotein A-I mimetic 4F peptide (AP), the as-fabricated MNC@M-ST/AP exhibits excellent anti-atherosclerotic effects by alleviating inflammation and oxidative stress as well as promoting cholesterol efflux via RCT pathways. This bioinspired leukocyte membrane-hitchhiking strategy will open new perspectives for the future clinical translations of biocompatible nanosystem in early detection and treatment of atherosclerosis.

[3] *Li W, Park H, Guo E et al.* **Aerobic Exercise Training Inhibits Neointimal Formation via Reduction of PCSK9 and LOX-1 in Atherosclerosis**. Biomedicines 2020; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32325897

ABSTRACT

The purpose of this study was to investigate whether aerobic exercise training inhibits atherosclerosis via the reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) expression in balloon-induced common carotid arteries of a high-fat-diet rats. Male SD (Sprague Dawley) rats fed an eight-weeks high-fat diet were randomly divided into three groups; these were the sham-operated control (SC), the balloon-induced control (BIC) and the balloon-induced exercise (BIE). The aerobic exercise training groups were performed on a treadmill. The major findings were as follows: first, body weight gain was significantly decreased by aerobic exercise training compared to the BIC without change of energy intake. Second, neointimal formation was significantly inhibited by aerobic exercise training in the balloon-induced common carotid arteries of high-fat-diet rats compared to the BIC. Third, low-density lipoprotein (LDL) receptor (LDLr) expression was significantly increased by aerobic exercise training in the livers of the high-fat diet group compared to the BIC, but not the proprotein convertase subtilisin/kexin type 9 (PCSK9) expression. Fourth, aerobic exercise training significantly decreased the expression of PCSK9, the lectin-like oxidized LDL receptor-1 (LOX-1), and vascular cell adhesion molecule-1 (VCAM-1) in balloon-induced common carotid arteries of high-fat-diet rats compared to the BIC. In conclusion, our results suggest that aerobic exercise training increases LDLr in the liver and inhibits neointimal formation via the reduction of PCSK9 and LOX-1 in balloon-induced common carotid arteries of high-fat-diet-induced rats.

[4] *Hadi YB, Naqvi SF, Abdelqader A et al.* **Reduced risk of post ERCP pancreatitis in statin users**. BMC gastroenterology 2020; 20:125.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32326889

ABSTRACT

BACKGROUND: One of the most feared complications of endoscopic retrograde cholangiopancreatography (ERCP), with an incidence of 3.5 to 15%, is post ERCP pancreatitis (PEP). Given the role of statins in the reduction of systemic and pancreatic intraluminal inflammation, we hypothesized that the use of statins may lower the risk of PEP. METHODS: A retrospective cohort study of all patients undergoing ERCP at West Virginia University during the years 2016 and 2017 was performed. Possible association of collected variables with PEP was assessed with Univariate tests and multivariable logistic regression analyses. RESULTS: A total of 1162 ERCPs were included. Mean age was 60.12 years (SD: 17.5). 51.3% of the participants were female. Two hundred and sixty-three participants underwent more than one ERCP during the study period. Seven hundred and ninety-nine ERCPs (78.8%) were conducted in participants who were not taking a statin medication at the time of ERCP, while 363 participants were on statin medications at the time of ERCP; 118 and 245 participants were taking high dose statins (atorvastatin 40-80 mg or rosuvastatin 20 mg), and low/medium dose statins (all other statin regimens) at the time of the procedure, respectively. The overall incidence of PEP in the cohort was 7.3%. In the non-statin and statin groups, 9.5 and 3.4% of participants developed PEP, respectively. On univariate analysis, young age, no statin use,

history of PEP, and endoscopic sphincterotomy were found to be significantly associated with the development of PEP. In a binary logistic regression model, young age (P = 0.033), history of PEP (P = 0.0001, OR 2.41, 95% CI: 1.05-5.51) and endoscopic sphincterotomy (P = 0.038, OR 2.85, 95% CI: 1.7-4.78) were found to be associated with increased risk of PEP. Statin usage was found to be protective against PEP, (OR 0.35, 95% CI: 0.18-0.69). CONCLUSION: Chronic statin usage is protective against post ERCP pancreatitis, and our findings suggest a potential role of these drugs as prophylactic agents. Randomized controlled trials are needed to establish any potential clinical application.

[5] *Heleniak ZT, Illersperger S, Brakemeier S et al.* **Influence of lipid profile and statin administration on arterial stiffness in renal transplant recipients**. Cardiology journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32329037
ABSTRACT
BACKGROUND: Hyperlipidemia is one of the major risk factors for developing a cardiovascular disease (CVD) and it is a frequent post-transplant complication, occurring in up to 60% of the renal transplant recipients (RTRs). Lipid lowering therapy with HMG-CoA reductase inhibitors (statins) is generally recommended and may reduce the overall cardiovascular risk. The aim of this study was to evaluate the lipid profile, statin administration and their relationship with arterial stiffness parameters in renal transplant recipients. METHODS: Three hundred and forty-four stable RTRs (62.5% male) transplanted between 1994 and 2018 were randomly enrolled to the study. The following parameters of arterial stiffness was measured in each patient: carotid femoral pulse wave velocity (baPWV left and right, cfPWV) and pulse pressure (PP right and left). The study group was divided based on the use statins: 143 (41.6%) and 201 (58.4%). RTRs were qualified to the statin (+) and the statin (-) group, respectively. RESULTS: In the statin (+) as compared to statin (-) group there were more patients with a CVD (32.9% vs. 14.9%) and diabetes (25.2% vs. 14.4%). In the whole study group, CVD was associated with a significant increase of both baPWV and cfPWV as well as PP (8.5 mmHg). There were significant differences in arterial stiffness parameters (baPWV, cfPWV, PP) between the statin (+) and the statin (-) group. CONCLUSIONS: Arterial stiffness was increased in RTRs with CVD and hyperlipidemia. The control of hyperlipidemia was poor in RTRs.

[6] *Tabas I, Bornfeldt KE*. **Intracellular and Intercellular Aspects of Macrophage Immunometabolism in Atherosclerosis**. Circulation research 2020; 126:1209-1227.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32324504
ABSTRACT
Macrophage immunometabolism, the changes in intracellular metabolic pathways that alter the function of these highly plastic cells, has been the subject of intense interest in the past few years, in part because macrophage immunometabolism plays important roles in atherosclerosis and other inflammatory diseases. In this review article, part of the Compendium on Atherosclerosis, we introduce the concepts of (1) intracellular immunometabolism-the canonical pathways of intrinsic cell activation leading to changes in intracellular metabolism, which in turn alter cellular function; and (2) intercellular immunometabolism-conditions in which intermediates of cellular metabolism are transferred

from one cell to another, thereby altering the function of the recipient cell. The recent discovery that the metabolite cargo of dead and dying cells ingested through efferocytosis by macrophages can alter metabolic pathways and downstream function of the efferocyte is markedly changing the way we think about macrophage immunometabolism. Metabolic transitions of macrophages contribute to their functions in all stages of atherosclerosis, from lesion initiation to formation of advanced lesions characterized by necrotic cores, to lesion regression following aggressive lipid lowering. This review article discusses recent advances in our understanding of these different aspects of macrophage immunometabolism in atherosclerosis. With the increasing understanding of the roles of macrophage immunometabolism in atherosclerosis, new exciting concepts and potential targets for intervention are emerging.

[7] *Ferraz-Amaro I, Delgado-Frias E, Hernandez-Hernandez V et al.* **Proprotein convertase subtilisin/kexin type 9 in patients with systemic sclerosis**. Clinical and experimental rheumatology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32324120
ABSTRACT
OBJECTIVES: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that regulates cholesterol metabolism through low-density lipoprotein receptor degradation, and which has been linked to cardiovascular risk. The purpose of the present study was to examine whether PCSK9 serum levels are disrupted in patients with systemic sclerosis (SS) compared to controls, and if PCSK9 is related to disease-related data and the subclinical atherosclerosis that occurs in these patients. METHODS: Cross-sectional study that encompassed 146 individuals; 73 patients with SS and 73 age- and sex-matched controls. PCSK9, lipoproteins serum concentrations, and standard lipid profiles were assessed in patients and controls. Carotid intima-media thickness (cIMT) and the presence of carotid plaques were evaluated in SS patients. A multivariable analysis, adjusted for traditional cardiovascular risk factors, was performed to evaluate the differences in PCSK9 between patients and controls, the association of SS-related manifestations with PCSK9 levels, and if PCSK9 was associated with subclinical carotid atherosclerosis in SS patients. RESULTS: After multivariable analysis, PCSK9 was downregulated in SS patients compared to controls (beta coefficient -78 (95%CI -106 - -50) ng/ml, p=0.000) and skin thickness was associated with higher serum levels of PCSK9 (beta coef. 22 (7-37) units, p=0.005). PCSK9 was significantly and positively associated with cIMT (beta coef. 0.65 (0.06-1.24) ng/ml, p=0.031) in SS patients after multivariable adjustment. CONCLUSIONS: PCSK9 serum concentration is downregulated in SS patients compared to controls and is directly associated with disease severity subrogated parameters. PCSK9 was independently related to cIMT in SS patients.

[8] *Masana L, Lopez Miranda J, Civeira F et al.* **Clinical profile of patients treated with evolocumab in lipid/internal medicine units of Spain. Observational study (RETOSS-IMU)**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32317124
ABSTRACT

OBJECTIVE: To describe the clinical characteristics, the reasons for initiating therapy, and the effects of treatment in the initial phase of evolocumab availability in lipid/internal medicine units in Spain. METHODS: Retrospective, observational study, based on the medical records of consecutive patients initiating treatment with evolocumab (from February 2016 to July 2017) in 20 internal medicine units in Spain. A review was made of the demographic and clinical characteristics of the patients, the lipid lowering treatment, and the evolution of the lipid profiles between 12weeks pre-initiation and 12+/-4weeks post-initiation of evolocumab. RESULTS: A total of 136 patients were analysed, of whom 64.0% were men, and the mean age (standard deviation, SD) was 56.6 (11.5) years. The large majority (75%) had familial hypercholesterolaemia (4 homozygous), and 51.0% of them had suffered at least one cardiovascular event. Atherosclerotic cardiovascular disease (ASCVD) was present in 61% of all patients. At initiation of evolocumab, 61.0% of the patients were taking high-intensity statins, and 60.3% were receiving ezetimibe. The mean (and SD) of LDL-C levels at initiation of evolocumab was 169.1 (56.6) mg/dL. The LDL-C was greater than 160mg/dL in 46.4% of patients, and >/=190mg/dL in 26.5%. During the observation period, evolocumab produced significant reductions in LDL-C of 55.7% (P<.0001), achieving mean values of 74.3mg/dL. At week12, more than half (53.8%) of patients achieved LDL-C levels <70mg/dL, and 26.9% <50mg/dL. CONCLUSIONS: In the lipid/internal medicine units, evolocumab was mainly prescribed in patients with familial hypercholesterolaemia, with or without ASCVD. The initial use of evolocumab was in accordance with the guidelines of the Spanish Society of Arteriosclerosis (SEA) of 2016, with LDL-C levels being well above the recommended thresholds for treatment initiation. Evolocumab treatment in clinical practice reduced LDL-C levels by about 55%, a similar reduction to that reported in clinical trials. Most patients achieved LDL-C goals.

[9] *Lin YC, Lai TS, Wu HY et al.* **Effects and Safety of Statin and Ezetimibe Combination Therapy in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis**. Clinical pharmacology and therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32320058

ABSTRACT

The efficacy and safety of statin and ezetimibe combination therapy in patients with chronic kidney disease (CKD) remains unclear. To assess the effect of statin and ezetimibe combination therapy on controlling lipid profiles and reducing cardiovascular events in patients with CKD, we conducted a systematic review and meta-analysis. We selected randomized controlled trials comparing this combination therapy with statin monotherapy or placebo in patients with CKD from the PubMed, Embase, and Cochrane Central Register of Controlled Trials databases published before September 1, 2018 on the Internet. Eight articles on seven studies, with a total of 14,016 patients with CKD, were selected from 412 full-text articles. Statin and ezetimibe combination therapy had beneficial effects on serum total cholesterol (weighted mean difference (WMD) -20.31 mg/dL, 95% confidence interval (CI), -26.87 to -13.75 mg/dL, P < 0.001), low-density lipoprotein cholesterol (WMD -17.22 mg/dL, 95% CI, -18.93 to -15.51 mg/dL, P < 0.001), and triglycerides (WMD -15.08 mg/dL, 95% CI, -23.41 to -6.75 mg/dL, P < 0.001) compared with statin monotherapy. Statin and ezetimibe combination therapy significantly reduced all-cause mortality and major adverse cardiovascular events (risk

ratio 0.86, 95% CI, 0.77 to 0.97, P = 0.01). The incidence of adverse events was low, with no significant difference between statin and ezetimibe combination therapy and statin monotherapy. In conclusion, the statin and ezetimibe combination therapy significantly improved serum lipid profiles and reduced risks of all-cause deaths and major adverse cardiovascular events compared with the control group in patients with CKD.

[10] *Clebak KT, Dambro AB*. **Hyperlipidemia: An Evidence-based Review of Current Guidelines**. Cureus 2020; 12:e7326.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32313767
ABSTRACT
Cholesterol treatment guidelines have evolved in the United States from the 1988 Adult Treatment Panel (ATP) I, the ATP II guidelines, ATP III guidelines, the 2013 American College of Cardiology/American Heart Association guidelines, to the most recent 2016 recommendations from the United States Protective Services Task Force. The use of statins to treat hyperlipidemia has been widely accepted and recommended in adults aged 40-75 years old with at least one risk factor and a calculated 10-year cardiovascular disease risk of 10%. However, statin use is associated with myalgias, myopathy, musculoskeletal injury, liver injury, and increased diabetes risk. The evidence for non-statin treatments is mixed. Bile acid sequestrants and ezetimibe reduce cardiovascular events. There is no evidence that the addition of any fibric acid derivative to a statin improves cardiovascular outcomes. Available evidence suggests that the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme inhibitors likely leads to little or no difference in mortality despite lowering lipid levels.

[11] *Khan AA, Ahmed S, Mohammed A, Elzouki AY*. **Autoimmune-like Drug-induced Liver Injury Caused by Atorvastatin and Demonstration of the Safety Profile of Pravastatin: A Case Report and Literature Review**. Cureus 2020; 12:e7299.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32313740
ABSTRACT
Statin-induced liver injury is a well-recognized but rare phenomenon with hepatocellular, cholestatic, and mixed phenotypes. Most studies do not recommend regular monitoring of liver function tests (LFTs) after starting statins unless clinically indicated. We report a case of autoimmune-like atorvastatin-induced liver injury (aminotransferases > 5 times the upper limit of normal) that was detected on routine follow-up after three months in an asymptomatic patient. In addition to elevation in transaminases, the patient had weakly positive ANAs. Anti-smooth muscle antibody (ASMA) was positive in titers of 1:680. Screening for viral hepatitis A-E was negative. Other diagnostic investigations showed complete blood examination, including eosinophils, renal function tests, electrolytes, total protein, albumin, prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR), serum ferritin, and iron saturation to be in the normal range. Ultrasound and computed tomography (CT) abdomen showed normal liver, gall bladder, biliary tree, and pancreas. The patient was managed as a case of autoimmune-like drug-induced liver injury (DILI) caused by atorvastatin and the medication was discontinued. LFTs returned to completely normal 30 days after the discontinuation of atorvastatin. Furthermore, switching to pravastatin for dyslipidemia

management four months after stopping atorvastatin did not lead to hepatotoxicity, illustrating the safety profile of pravastatin in patients who are unable to tolerate atorvastatin.

[12] *Bajaj A, Cuchel M*. **Homozygous familial hypercholesterolemia: what treatments are on the horizon?** Current opinion in lipidology 2020; 31:119-124.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32332430
ABSTRACT
PURPOSE OF REVIEW: Homozygous familial hypercholesterolemia (HoFH) is a rare disorder associated with early atherosclerotic disease due to impairment of the LDL receptor (LDLR) pathway. Because of their molecular defect, current treatment options have limited success in bringing HoFH patient to LDL-C target and morbidity and mortality remain high. We review current and upcoming therapies directed at HoFH, including gene therapy. RECENT FINDINGS: Recent real-world studies have confirmed the strength in lomitapide as a treatment adjunct to statins and other lipid-lowering therapies in HoFH patients. The approval of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor monoclonal antibodies has also been a welcome addition to the treatment armamentarium offering an additional average reduction in LDL-C levels of 24% when added to background lipid-lowering therapies in this population. Although achieving adequate LDL-C levels in this population is difficult, there are several therapies on the horizon that may help more patients reach goal. Evinacumab, a monoclonal antibody against ANGPTL3, has been shown to substantially reduce LDL-C of an average of 49%, independently of residual LDLR activity. RNA interference targeting PCSK9 and ANGPTL3 shows promise in clinical trials. Adeno-associated virus-mediated gene transfer and gene editing techniques are in early clinical and preclinical development. SUMMARY: LDL-C lowering in HoFH patients remains very challenging. However, novel treatment options are emerging. Upcoming therapies directed at PCSK9 and ANPTL3 may offer additional LDL-C reduction, to help patients achieve adequate LDL-C levels. Gene therapy and gene editing techniques, if proven effective, may offer a unique opportunity to treat patients with a one-time treatment.

[13] *Basu D, Goldberg IJ*. **Regulation of lipoprotein lipase-mediated lipolysis of triglycerides**. Current opinion in lipidology 2020; 31:154-160.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32332431
ABSTRACT
PURPOSE OF REVIEW: To discuss the recent developments in structure, function and physiology of lipoprotein lipase (LpL) and the regulators of LpL, which are being targeted for therapy. RECENT FINDINGS: Recent studies have revealed the long elusive crystal structure of LpL and its interaction with glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 (GPIHBP1). New light has been shed on LpL being active as a monomer, which brings into questions previous thinking that LpL inhibitors like angiopoietin-like 4 (ANGPTL4) and stabilizers like LMF1 work on disrupting or maintaining LpL in dimer form. There is increasing pharmaceutical interest in developing targets to block LpL inhibitors like ANGPTL3. Other approaches to reducing circulating triglyceride levels have been using an apoC2 mimetic and reducing apoC3. SUMMARY: Lipolysis of triglyceride-rich lipoproteins by LpL is a central event in lipid metabolism, releasing fatty acids for uptake by tissues and

generating low-density lipoprotein and expanding high-density lipoprotein. Recent mechanistic insights into the structure and function of LpL have added to our understanding of triglyceride metabolism. This has also led to heightened interest in targeting its posttranslational regulators, which can be the next generation of lipid-lowering agents used to prevent hypertriglyceridemic pancreatitis and, hopefully, cardiovascular disease.

[14] *Salinas CAA, Chapman MJ*. **Remnant lipoproteins: are they equal to or more atherogenic than LDL?** Current opinion in lipidology 2020; 31:132-139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32332433
ABSTRACT
PURPOSE OF REVIEW: To critically appraise new insights into the biology of remnant lipoproteins and their putative role in the pathophysiology of atherosclerotic cardiovascular disease, and to compare the atherogenicity of remnant particles with that of low-density lipoproteins (LDL). RECENT FINDINGS: New in-vivo stable isotope tracer studies of the kinetics of apoB48 and apoB100-containing lipoproteins in postprandial conditions have revealed that apoB48-containing very low-density lipoproteins (VLDL) accumulated markedly in hypertriglyceridemic patients. These intestinally-derived particles were cleared slowly, and represented up to 25% of circulating VLDL; as part of the remnant particle population, they may increase cardiovascular risk. Importantly, the PCSK9 inhibitor, evolocumab, was shown to reduce remnant levels (-29%) during the postprandial period in diabetic patients on statin therapy - an effect which may be additive to that of LDL-cholesterol reduction in conferring cardiovascular benefit. In recent Mendelian randomization studies, the effect of lowering triglyceride-rich lipoproteins or LDL-cholesterol translated to similar clinical benefit per unit of apoB. Finally, in randomized trials involving statin-treated patients with atherosclerotic cardiovascular disease, remnant cholesterol levels were associated with coronary atheroma progression independently of LDL-cholesterol. SUMMARY: Overall, data from observational studies in large cohorts, Mendelian randomization studies, meta-regression analyses, and post-hoc analyses of randomized trials are consistent with the contention that remnants are highly atherogenic particles and contribute to the atherosclerotic burden in an equivalent manner to that of LDL.

[15] *Shah VN, Grimsmann JM, Foster NC et al.* **Undertreatment of cardiovascular risk factors in the type 1 diabetes exchange clinic network (United States) and the prospective diabetes follow-up (Germany/Austria) registries**. Diabetes Obes Metab 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32329127
ABSTRACT
AIM: To examine the control of cardiovascular risk factors in type 1 diabetes (T1D) registries from the United States and Germany/Austria. MATERIALS AND METHODS: Data on individuals aged >/=12 years with T1D for >/=1 year, from the T1D Exchange Clinic Network (T1DX, United States) and the Prospective Diabetes Follow-up Registry (DPV, Germany/Austria) from 1 January 2016 to 31 March 2018 were analysed. Linear and logistic regression models adjusted for age groups, sex, duration of diabetes and minority status were used to compare clinical characteristics and achievement of diabetes management targets between registries. RESULTS: The cohort consisted of 47 936 patients (T1DX, n = 19 442;

DPV, n = 28 494). Achievement of HbA1c goals (<7.0%, ages 18-65 years; all others, <7.5%) was better in the DPV for those aged <65 years (all P < .001). However, more older adults (aged >/=65 years) in the T1DX achieved an HbA1c goal of <7.5% compared with DPV (70% vs. 50%, P < .001). The frequency of patients with overweight (53% vs. 51%, P < .001) and obesity (19% vs. 9%, P < .001) was higher in T1DX. The frequency of meeting blood pressure goals (84% vs. 66%, P < .001) and lipid goals (73% vs. 62%, P < .001) was higher in T1DX; this was observed across all age groups (all P < .001). Few young adults aged <26 years received antihypertensive and lipid-lowering medications, respectively, despite indications in both registries (T1DX: 5% and 3%, DPV: 3% and 1%). CONCLUSION: A minority of patients with T1D achieve glycaemic targets and the majority are inadequately treated for hypertension and dyslipidaemia. This highlights the need for improved diabetes and cardiovascular risk management strategies in T1D.

[16] *Berkelmans GFN, Greving JP, van der Graaf Y et al.* **Would treatment decisions about secondary prevention of CVD based on estimated lifetime benefit rather than 10-year risk reduction be cost-effective?** Diagn Progn Res 2020; 4:4.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32318625
ABSTRACT
Objective: To test the hypothesis that treatment decisions (treatment with a PCSK9-mAb versus no treatment) are both more effective and more cost-effective when based on estimated lifetime benefit than when based on estimated risk reduction over 10 years. Methods: A microsimulation model was constructed for 10,000 patients with stable cardiovascular disease (CVD). Costs and quality-adjusted life years (QALYs) due to recurrent cardiovascular events and (non)vascular death were estimated for lifetime benefit-based compared to 10-year risk-based treatment, with PCSK9 inhibition as an illustration example. Lifetime benefit in months gained and 10-year absolute risk reduction were estimated using the SMART-REACH model, including an individualized treatment effect of PCSK9 inhibitors based on baseline low-density lipoprotein cholesterol. For the different numbers of patients treated (i.e. the 5%, 10%, and 20% of patients with the highest estimated benefit of both strategies), cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER), indicating additional costs per QALY gain. Results: Lifetime benefit-based treatment of 5%, 10%, and 20% of patients with the highest estimated benefit resulted in an ICER of euro36,440/QALY, euro39,650/QALY, or euro41,426/QALY. Ten-year risk-based treatment decisions of 5%, 10%, and 20% of patients with the highest estimated risk reduction resulted in an ICER of euro48,187/QALY, euro53,368/QALY, or euro52,390/QALY. Conclusion: Treatment decisions (treatment with a PCSK9-mAb versus no treatment) are both more effective and more cost-effective when based on estimated lifetime benefit than when based on estimated risk reduction over 10 years.

[17] *Markham A.* **Bempedoic Acid: First Approval**. Drugs 2020; 80:747-753.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32314225
ABSTRACT
Bempedoic acid is a non-statin antihyperlipidaemic drug being developed by Esperion Therapeutics for the treatment of hypercholesterolaemia. Based on positive findings in the

phase III CLEAR clinical trial programme, bempedoic acid has been approved in the USA and in the EU as monotherapy (NEXLETOL((R)) in the USA, Nilemdo((R)) in the EU) and as a fixed-dose combination with ezetimibe (NEXLIZET((R)) in the USA, Nustendi((R)) in the EU). This article summarizes the milestones in the development of bempedoic acid leading to these first approvals.

[18] *Blom DJ, Chen J, Yuan Z et al.* **Effects of evolocumab therapy and low LDL-C levels on vitamin E and steroid hormones in Chinese and global patients with type 2 diabetes**. Endocrinology, diabetes & metabolism 2020; 3:e00123.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32318641
ABSTRACT
Aims: We assessed the change from baseline in vitamin E, steroid hormones, adrenocorticotropic hormone (ACTH), and gonadotropins, overall and by lowest achieved low-density lipoprotein-cholesterol (LDL-C) level, in patients with type 2 diabetes and dyslipidaemia after 12 weeks of treatment with evolocumab. Materials and Methods: This was a prespecified analysis of vitamin E, cortisol, ACTH, gonadal hormones and gonadotropins in the 12-week, placebo-controlled BERSON trial of evolocumab in patients with type 2 diabetes and dyslipidaemia. In BERSON, 981 (451 in China) patients on daily atorvastatin 20 mg were randomized to placebo or one of two doses of evolocumab. We measured analyte levels at baseline and week 12 (vitamin E in all patients; steroid/gonadal hormones only in Chinese patients). Results: In both the global and Chinese populations, absolute vitamin E levels decreased from baseline to week 12 by approximately 6 mumol/L ($P < .0001$) among evolocumab-treated patients; however, when normalized for LDL-C, apoB or non-HDL-C, we observed no decrease in vitamin E levels. In Chinese patients, levels of cortisol and ACTH as well as the cortisol:ACTH ratio did not change significantly from baseline to week 12. No patient had a cortisol:ACTH ratio <3.0 (nmol/pmol), suggestive of adrenocortical deficiency. We did not observe clinically relevant changes for gonadal hormones and gonadotropins (oestradiol and testosterone in female and male patients, respectively, luteinizing and follicle-stimulating hormones for both). Conclusions: In the BERSON study, evolocumab did not adversely affect vitamin E, steroid hormone or gonadotropin levels in the Chinese or global type 2 diabetic populations.ClinicalTrials.gov NCT02662569.

[19] *Gerussi A, Luca M, Cristoferi L et al.* **New Therapeutic Targets in Autoimmune Cholangiopathies**. Frontiers in medicine 2020; 7:117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32318580
ABSTRACT
Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune cholangiopathies characterized by limited treatment options. A more accurate understanding of the several pathways involved in these diseases has fostered the development of novel and promising targeted drugs. For PBC, the characterization of the role of farnesoid X receptor (FXR) and perixosome-proliferator activated receptor (PPAR) has paved the way to several clinical trials including different molecules with choleretic and antinflammatory action. Conversely, different pathogenetic models have been proposed in PSC such as the "leaky gut" hypothesis, a dysbiotic microbiota or a defect in mechanisms protecting against bile acid

toxicity. Along these theories, new treatment approaches have been developed, ranging from drugs interfering with trafficking of lymphocytes from the gut to the liver, fecal microbiota transplantation or new biliary acids with possible immunomodulatory potential. Finally, for both diseases, antifibrotic agents are under investigation. In this review, we will illustrate current understanding of molecular mechanisms in PBC and PSC, focusing on actionable biological pathways for which novel treatments are being developed.

[20] *Kirichenko TV, Sukhorukov VN, Markin AM et al.* **Medicinal Plants as a Potential and Successful Treatment Option in the Context of Atherosclerosis**. Frontiers in pharmacology 2020; 11:403.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32322201
ABSTRACT
Atherosclerosis is a chronic multifactorial disease characterized by mainly changes of blood lipids profile and inflammation in vessel wall. The cardiovascular disease based on atherosclerosis is currently the leading cause of mortality in developed countries. Therefore, timely prevention and therapy of atherosclerosis are able to reduce the risk of the development of its clinical manifestations. Anti-atherosclerotic activity of medicinal plants mainly appears in their multiple effects such as anti-inflammatory, antioxidant, anti-atherogenic, hypotensive, lipid-lowering, anti-thrombotic. Moreover, most of medicinal plants are characterized by their pleiotropic anti-atherosclerotic action. In addition, the medicinal plants-derived pharmacological substances and/or compounds are characterized by relative safety and fewer side effects that allows considering them as one of potential anti-atherosclerotic effective agents. The direct anti-atherosclerotic effect of some medicinal plants was confirmed in clinical trials of carotid Intima-media thickness (IMT) progression during long-term medication with medicinal plants. This review attempted to determine the current status of the databases PubMed and Scopus (until November, 2019) to investigate the medicinal plants possessing anti-atherosclerotic activity in experimental and clinical studies.

[21] *Yang CL, Zeng YD, Hu ZX, Liang H.* **PCSK9 promotes the secretion of pro-inflammatory cytokines by macrophages to aggravate H/R-induced cardiomyocyte injury via activating NF-kappaB signalling**. General physiology and biophysics 2020; 39:123-134.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32329440
ABSTRACT
The upregulation of proprotein convertase subtilisin/kexin type 9 (PCSK9) was reported to be involved in regulating the levels of inflammatory markers and apoptosis in macrophages. This study aims to investigate the function and regulation of PCSK9 in myocardial ischaemia. The results of our study showed dramatically increased expression of PCSK9 induced by hypoxia/reoxygenation (H/R) stress rather than by apoptosis in primary murine cardiomyocytes and HL-1 cells. Moreover, PCSK9 promoted H/R-induced pro-inflammatory cytokine release from macrophages, while silencing of PCSK9 inhibited the expression of the pro-inflammatory cytokines TNF-alpha, IL-6 and IL-1beta. Additionally, PCSK9 facilitated the release of pro-inflammatory cytokines from macrophages under H/R conditions, which decreased cardiomyocyte viability and promoted apoptosis of cardiomyocytes. For the underlying

mechanisms, we identified PCSK9-induced NF-kappaB activation as being involved in the cardiomyocyte apoptosis, which was blocked by the NF-kappaB inhibitor BAY 11-7082. Collectively, this study provides new insights into the therapeutic possibility of regulating PCSK9 in cardiomyocytes for the treatment of ischaemic cardiomyopathy.

[22] *Montalvan Sanchez EE, Urrutia SA, Rodriguez AA et al.* **Cardiovascular risk assessment in the resource limited setting of Western Honduras: An epidemiological perspective**. International journal of cardiology. Heart & vasculature 2020; 27:100476.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32309530

ABSTRACT

Cardiovascular Disease (CVD) epidemiology varies significantly among Low and Middle-Income Countries. Honduras is the Central American country with the highest Ischemic Heart Disease and CVD mortality rates. The aim of this study was to assess the individual CVD risk factors and calculate Cardiovascular Risk Assessment Scores (CVRAS) from the population. Methods: A cross-sectional study in western Honduras. Estimation of CV risk was performed using Framingham, MESA, ACC/AHA-PCEs and ESC SCORE calculators. Results: 38% were male. For men and women respectively; 49% and 48% had self-reported hypertension (HTN), on measured blood pressure only 18% and 30% had normal readings. Diabetes Mellitus was reported in 19% and 22%. Tobacco use was 14% and 3%. Self-reported regular exercise was 39.9% and 25%. Obesity was diagnosed in 24% and 24%. Lipid profile; total cholesterol was >/=200 mg/dl in 63% of subjects. LDL-C was elevated (>100 mg/dl) in 74% of participants, 9% had LDL-C levels higher than 190 mg/dl. Triglycerides were high (>160 mg/dl) in 60%, of these subjects 22% were taking lipid-lowering medications. 52% reported family-history of CVD. The risk calculation for men and women respectively for each CVRAS were; AHA/ACC-PCEs high risk (score >/= 7.5%) in 62% and 30%, FRS high risk (score >/= 20%) 46% and 15%, MESA high risk (Score >/= 7.5%) in 70.6% and 17.7%, ESC SCORE high risk (score >/= 5% in 32.4% and 11.8%). Conclusions: CV risk calculations revealed higher than rates than expected with consequently reflected on higher than estimated CVRAS. This represents the first report of its kind in Honduras.

[23] *Lakshmanan S, Rezvanizadeh V, Budoff MJ*. **Comprehensive plaque assessment with serial coronary CT angiography: translation to bedside**. The international journal of cardiovascular imaging 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32307630

ABSTRACT

The purpose of this review is to highlight the utility of comprehensive plaque assessment by serial coronary computed tomography angiography (CCTA) to understand atherosclerosis and its effect on cardiovascular risk stratification and management. CCTA is a validated, noninvasive imaging modality for coronary atherosclerotic plaque characterization. Numerous clinical trials have used approach of serial CCTA to demonstrate the potential benefits of multiple treatment strategies to reduce coronary plaque progression and its translation to benefits with cardiovascular outcomes. Serial CCTA trials for cardiovascular therapies combined with clinical outcome studies are providing mechanistic correlations of coronary atherogenesis and cardiovascular risk reduction, thereby establishing a new standard of care

in addressing cardiac disease. Advancements in CCTA imaging and plaque analysis continue to expand the potential for CCTA in the evaluation of cardiovascular risk and targeted treatment of CAD.

[24] *Zhang S, Li H, Yuan L et al.* **Molecular characterization of gut microbiota in highlipid dietinduced hyperlipidemic rats treated with simvastatin**. International journal of molecular medicine 2020; 45:1601-1615.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32323749

ABSTRACT

Hyperlipidemia is a major risk factor for cardiovascular diseases. Simvastatin (SV), a cholesterollowering agent, has been widely used in the treatment of hyperlipidemia. Gut microbiota is known to influence drug response, including that to statins. However, the effect of SV on the gut microbiota of hyperlipidemic rats is not fully understood. To investigate the influence of SV on gut microbiota in hyperlipidemic rats, the molecular characterization of gut microbiota and the potential functions of genes involved in the downstream metabolic pathways were analyzed using highthroughput sequencing technology and the Phylogenetic Investigation of Communities by Reconstruction of Unobserved States approach. The results revealed that SV treatment could reduce the gut microbial diversity and drive marked remodeling of the fecal bacterial community composition. At the phylum level, the relative abundance of Firmicutes and Actinobacteria was decreased following SV therapy, whereas that of Bacteroidetes was elevated. At the genus level, the percentage of the genera Bacteroides, Sutterella and Phascolarctobacterium was significantly increased, but that of Bifidobacterium, Ruminococcaceae_NK4A214, Ruminococcaceae_UCG009, Intestinimonas and Tyzzerella was significantly decreased. Additionally, functional prediction analysis indicated that in the SVassociated microbiota, genes involved in energy, carbohydrate, amino acid and nucleotide metabolism likely exhibited enrichment. Briefly, to the best of our knowledge, the present study was the first to establish a profound and comprehensive association between the SVinduced alterations of the gut flora and the consequent influences of downstream metabolic pathways by gut microbiota. These findings suggested that the gut microbiota may contribute to the SV hypolipidemic efficacy in the progression of hyperlipidemia, which could provide insights for the prevention and treatment of hyperlipidemia.

[25] *Martinez-Lopez D, Roldan-Montero R, Garcia-Marques F et al.* **Complement C5 Protein as a Marker of Subclinical Atherosclerosis**. Journal of the American College of Cardiology 2020; 75:1926-1941.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32327104

ABSTRACT

BACKGROUND: The mechanisms underlying early atherosclerotic plaque formation are not completely understood. Moreover, plasma biomarkers of subclinical atherosclerosis are lacking. OBJECTIVES: The purpose of this study was to analyze the temporal and topologically resolved protein changes taking place in human aortas with early atherosclerosis to find new potential diagnostic and/or therapeutic targets. METHODS: The protein composition of healthy aortas (media layer) or with early atheroma (fatty streak and fibrolipidic,

media and intima layers) was analyzed by deep quantitative multiplexed proteomics. Further analysis was performed by Western blot, immunohistochemistry, real-time polymerase chain reaction, and enzyme-linked immunosorbent assay. Plasma levels of complement C5 were analyzed in relation to the presence of generalized (>2 plaques) or incipient (0 to 2 plaques) subclinical atherosclerosis in 2 independent clinical cohorts (PESA [Progression of Early Subclinical Atherosclerosis] [n = 360] and NEFRONA [National Observatory of Atherosclerosis in Nephrology] [n = 394]). RESULTS: Proteins involved in lipid transport, complement system, immunoglobulin superfamily, and hemostasis are increased in early plaques. Components from the complement activation pathway were predominantly increased in the intima of fibrolipidic plaques. Among them, increased C5 protein levels were further confirmed by Western blot, enzyme-linked immunosorbent assay and immunohistochemistry, and associated with in situ complement activation. Plasma C5 was significantly increased in individuals with generalized subclinical atherosclerosis in both PESA and NEFRONA cohorts, independently of risk factors. Moreover, in the PESA study, C5 plasma levels positively correlated with global plaque volume and coronary calcification. CONCLUSIONS: Activation of the complement system is a major alteration in early atherosclerotic plaques and is reflected by increased C5 plasma levels, which have promising value as a novel circulating biomarker of subclinical atherosclerosis.

[26] *Preiss D, Tobert JA, Hovingh GK, Reith C*. **Lipid-Modifying Agents, From Statins to PCSK9 Inhibitors: JACC Focus Seminar**. Journal of the American College of Cardiology 2020; 75:1945-1955.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32327106
ABSTRACT
Mendelian randomization studies and randomized trials have conclusively demonstrated that lower low-density lipoprotein (LDL) cholesterol results in fewer cardiovascular events. This review describes key stages in the evolution of LDL cholesterol-lowering treatment. Data from over 25 cardiovascular outcome trials confirm that, within a few years, statins lower the relative risk of major atherosclerotic events by about 22% per 38.7 mg/dl (1 mmol/l) reduction in LDL cholesterol, with similar benefit across patient subgroups. Meta-analyses of these trials have established the safety of statins with regard to nonvascular mortality and cancer. Other agents available for prescription include ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which both reduce major atherosclerotic events in proportion to their effects on LDL cholesterol and have good safety profiles, though PCSK9 inhibitors remain costly. Investigational LDL cholesterol-lowering agents currently being tested in cardiovascular outcome studies are bempedoic acid, an adenosine triphosphate-citrate lyase inhibitor that reduces cholesterol synthesis, and inclisiran, a double-stranded small interfering ribonucleic acid that inhibits PCSK9 synthesis.

[27] *Rymer JA, Mues KE, Monda KL et al.* **Use of Low-Density Lipoprotein-Lowering Therapies Before and After PCSK9 Inhibitor Initiation**. Journal of the American Heart Association 2020; 9:e014347.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32326795
ABSTRACT

Background Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are used to reduce low-density lipoprotein (LDL) cholesterol. PCSK9i use after initiation, as well as persistence with or alterations to other LDL-lowering therapy after PCSK9i initiation, is not well understood. Methods and Results We conducted a retrospective study of alirocumab or evolocumab (PCSK9i) new users from July 2015 to December 2017 in the MarketScan Early View database of US commercial insurance beneficiaries. We determined the prevalence of PCSK9i interruption (>/=30-day gap in supply) and LDL-lowering therapy use in the year after PCSK9i initiation. The average age of 6151 patients initiating PCSK9i therapy was 63 years, 44.4% were women, and 76.8% had atherosclerotic cardiovascular disease. Overall, 52.2% (95% CI, 50.8%-53.7%) of patients had an interruption in PCSK9i therapy in the first year after treatment initiation and 62.5% remained on PCSK9i therapy at 1-year postinitiation. Also, 27.7% of patients were taking a statin at the time of PCSK9i initiation, with only 22.4% on statin therapy at 1 year after PCSK9i initiation. Ezetimibe use decreased from 20.9% at the time of PCSK9i initiation to 12.0% a year later. By 1 year after PCSK9i initiation, 44.0% of patients had experienced an interruption in all LDL-lowering therapies, and 26.6% were no longer on any LDL-lowering therapies. Conclusions After PCSK9i initiation, statins were often discontinued, whereas more than half of patients experienced an interruption in PCSK9i therapy. These results suggest that many new PCSK9i users may remain at high risk for cardiovascular events because of interruptions in LDL-lowering therapy.

[28] *Shiffman D, Louie JZ, Devlin JJ et al.* **Gaps in Dyslipidemia Care Among Working-Aged Individuals With Employer-Sponsored Health Care**. Journal of the American Heart Association 2020; 9:e015807.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32319337

ABSTRACT

Background The American Heart Association and American College of Cardiology guidelines defined patient-management groups that would benefit from lowering of low-density lipoprotein cholesterol (LDL-C). We assessed gaps in dyslipidemia care among employees and spouses with health benefits. Methods and Results We studied 17 889 employees and spouses who were covered by an employer-sponsored health plan and participated in an annual health assessment. Using medical claims, laboratory tests, and risk assessment questionnaires, we found that 43% of participants were in one of 4 patient-management groups: secondary prevention, severe hypercholesterolemia (LDL-C >/=190 mg/dL at least once in the preceding 5 years), diabetes mellitus, or elevated 10-year risk of cardiovascular disease. To assess gaps in dyslipidemia care, we used LDL-C </=70 mg/dL as the goal for both the secondary prevention group and those in the elevated 10-year risk group with >20% risk; LDL-C </=100 mg/dL was used for the other groups. Among those in patient-management groups, 27.3% were in the secondary prevention group, 7.4% were in the severe hypercholesterolemia group, 29.9% were in the diabetes mellitus group, and 35.4% were in the elevated 10-year risk group. About 74% of those in patient-management groups had above-goal LDL-C levels, whereas only 31% had evidence of a lipid-lowering therapy in the past 6 months: 45% in the secondary prevention group, 31% in the severe hypercholesterolemia group, 36% in the diabetes mellitus group, and 17% in the elevated 10-year risk group. Conclusions The substantial gaps in LDL-C

treatment and goal attainment among members of an employer-sponsored medical plan who were mostly aware of their LDL-C levels indicate the need for gap-closure initiatives.

[29] *Yi H, Wu M, Zhang Q et al.* **Reversal of HER2 Negativity: An Unexpected Role for Lovastatin in Triple-Negative Breast Cancer Stem Cells**. Journal of Cancer 2020; 11:3713-3716.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32328175
ABSTRACT
Effective treatment modality for triple-negative breast cancer (TNBC) is currently lacking due to the absence of defined receptor targets. Recently, we have demonstrated that lovastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor and a lipid-lowering drug, can selectively inhibit TNBC by targeting cancer stem cells in vivo and in vitro. Interestingly, we found that lovastatin induced the reappearance of human epidermal growth factor receptor 2 (HER2), one of the triple receptors that are missing in TNBC. This prompted us to explore the possibility of regaining sensitivity of TNBC cancer stem cells to receptor tyrosine kinase-targeting drugs. We found that while the combination of lovastatin with a HER2 inhibitor was not sufficient to show synergism, addition of an epidermal growth factor receptor (EGFR/HER1) inhibitor to this combination resulted in significant synergistic inhibitory effect on cell viability. Our findings provide a potential novel strategy of designing a cocktail composed of a lipid-lowering drug and two receptor tyrosine kinase inhibitors for the treatment of TNBC.

[30] *Daniels S, Caprio S, Chaudhari U et al.* **PCSK9 inhibition with alirocumab in pediatric patients with heterozygous familial hypercholesterolemia: The ODYSSEY KIDS study**. Journal of clinical lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32331936
ABSTRACT
BACKGROUND: Heterozygous familial hypercholesterolemia (HeFH) is a genetic disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C). OBJECTIVE: This phase 2 dose-finding study (NCT02890992) evaluated the efficacy, safety, and dose selection of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab in pediatric HeFH patients. METHODS: HeFH patients (n = 42) who were aged 8-17 years, had body weight (BW) >/=25 kg, and had LDL-C >/=130 mg/dL despite optimal statin/other lipid-modifying therapies were enrolled in 4 cohorts according to BW: cohort #1: 30 mg (<50 kg) or 50 mg (>/=50 kg) every 2 weeks (Q2W), #2: 40 mg (<50 kg) or 75 mg (>/=50 kg) Q2W, #3: 75 mg (<50 kg) or 150 mg (>/=50 kg) every 4 weeks (Q4W), #4: 150 mg (<50 kg) or 300 mg (>/=50 kg) Q4W. Primary endpoint was LDL-C % change from baseline to week 8. RESULTS: Mean age was 12.4 years and 95% of patients were on a statin. Baseline LDL-C levels were 160.0-188.9 mg/dL and free PCSK9 was 186.4-201.7 ng/mL across the cohorts. At week 8, the higher dose cohorts (2 and 4) demonstrated the greatest reductions in LDL-C (-46% and -45%, respectively). Free PCSK9 levels were lowest at week 8 in cohorts 2 and 4 (42.2 ng/mL and 8.6 ng/mL, respectively). Adverse events were reported in 50-90% of patients across the cohorts, and 2 patients discontinued due to adverse events. CONCLUSIONS: In pediatric HeFH patients, LDL-C reductions were greatest in the higher dose cohorts. Alirocumab was generally well tolerated at all doses.

[31] *deFilippi C, Toribio M, Wong LP et al.* **Differential Plasma Protein Regulation and Statin Effects in HIV-infected and Non-HIV-infected Patients Utilizing a Proteomics Approach Protein Regulation and Statin Effects in HIV**. The Journal of infectious diseases 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32310273
ABSTRACT
BACKGROUND: PWH (people with HIV) demonstrate increased atherosclerotic cardiovascular disease (ASCVD). Statins are being studied to prevent ASCVD in HIV, but little is known regarding the effects of statins on a broad range of inflammatory and cardiovascular proteins in this population. METHODS: We used a highly specific discovery proteomic approach (Protein Extension Assay), to determine statin effects on over 350 plasma proteins in relevant ASCVD pathways among HIV and non-HIV groups. Responses to pitavastatin calcium were assessed in 89 PWH in the INTREPID trial and 46 non-HIV participants with features of central adiposity and insulin resistance. History of CVD was exclusionary for both studies. RESULTS: Among participants with HIV, PCOLCE (enzymatic cleavage of Type I procollagen) significantly increased after pitavastatin therapy and PLA2G7 (systemic marker of arterial inflammation) decreased. Among participants without HIV, integrin subunit alpha M (integrin adhesive function) and defensin alpha-1 (neutrophil function) increased after pitavastatin therapy and PLA2G7 decreased. At baseline, comparing participants with and without HIV, differentially expressed proteins included proteins involved in platelet and endothelial function and immune activation. CONCLUSIONS: Pitavastatin affected proteins important to platelet and endothelial function and immune activation, and effects differed to a degree within PWH and participants without HIV.

[32] **Bempedoic acid (Nexletol) for lowering LDL-cholesterol**. The Medical letter on drugs and therapeutics 2020; 62:53-55.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32324179
ABSTRACT

[33] *Bergens O, Veen J, Montiel-Rojas D et al.* **Impact of healthy diet and physical activity on metabolic health in men and women: Study Protocol Clinical Trial (SPIRIT Compliant)**. Medicine (Baltimore) 2020; 99:e19584.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32311926
ABSTRACT
INTRODUCTION: Healthy dietary patterns and physical activity (PA) represent important lifestyle behaviors with considerable potential to influence on age-related metabolic health. Yet, data on the combined effects of these lifestyle behaviors on metabolic health including low-grade systemic inflammation in aging populations remain scarce. Therefore, this protocol describes a randomized controlled trial aiming to examine the impacts of healthy dietary patterns alone or combined with PA on metabolic health in middle-aged and older men and women. MATERIAL AND METHODS: The ORUDIET study is a 3-arm randomized controlled 16-week trial: Healthy Diet (HD), Healthy diet plus PA (HD-PA), and control (CON). The trial is open label, randomized with allocation concealment, parallel groups with passive controls.

Participants without overt disease aged between 55 and 70 years, with BMI below 35, a current intake of a maximum of 1 serving of fruit and vegetable per day, and noncompliance to PA guidelines are eligible for inclusion. Participants in HD are instructed to increase fruit and vegetable intake to 5 servings per day (equivalent to 500 g). Participants in HD-PA receive the same dietary intervention as the HD and are additionally instructed to engage in moderate-to-vigorous physical activities for at least 150 minutes per week. The primary study outcomes are changes in metabolic and inflammatory health biomarkers. Secondary outcomes are changes in body composition and perceived health. ETHICS AND DISSEMINATION: The study protocol has been approved by the ethical review board in Uppsala, Sweden. The results will be published in peer-reviewed journals and disseminated in national and international conferences. TRIAL REGISTRATION NUMBER: NCT04062682 Pre-results.

[34] *Kim CH, Park Y, Chun MY, Kim YJ*. **Exercise-induced hypertension can increase the prevalence of coronary artery plaque among middle-aged male marathon runners**. Medicine (Baltimore) 2020; 99:e19911.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32332671
ABSTRACT
Marathon runners demonstrate a high incidence of coronary artery plaque; however, studies on runners with exercise-induced hypertension (EIH) are sparse. We aimed to investigate the prevalence of coronary artery plaque among marathon runners with EIH.Veteran male marathon runners (>/=40 and <60 years) underwent an exercise stress test. They were divided into 2 groups: normal blood pressure group (NBPG, n = 22), with resting systolic blood pressure (SBP)/diastolic blood pressure <140/90 mm Hg and maximal exercise SBP <210 mm Hg, and EIH group (EIHG, n = 28), with resting blood pressure <140/90 mm Hg and maximal exercise SBP >/=210 mm Hg. Coronary artery plaque and stenosis were compared using multi-detector computed tomography.The proportion of subjects with a coronary artery calcium (CAC) score >/=10 or >/=100 units, 1 or >/=2 plaques, or plaques in >/=2 blood vessels was higher in the EIHG than in the normal blood pressure group (NBPG) (P<.05). The absolute CAC score was higher in the EIHG (42.6 +/- 67.8) than in the NBPG (2.8 +/- 6.0; P < .05). The CAC score distribution was higher in the EIHG (5-300 units) than in the NBPG (P < .05). The prevalence of coronary plaques and maximal luminal artery stenosis was higher in the EIHG than in the NBPG (P < .05). The EIHG showed 12 cases of stenosis, whereas the NBPG showed only 1 case (P < .05).In marathon runners, EIH was associated with increased prevalence of coronary artery plaques and could be a new risk factor for coronary artery plaque formation. Therefore, preventive measures and EIH monitoring using an exercise stress test, alongside multi-detector computed tomography, are recommended.

[35] *Secchi F, Di Leo G, Delnevo A et al.* **Peripheral artery disease: how much inter-leg symmetry? A contrast-enhanced magnetic resonance angiography study**. Medicine (Baltimore) 2020; 99:e19637.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32311934
ABSTRACT
The aim of this observational retrospective study was to qualitatively and quantitatively evaluate the symmetry of atherosclerotic plaques in patients with peripheral artery disease

(PAD) undergoing contrast-enhanced magnetic resonance angiography of lower limbs. We retrospectively evaluated the peripheral magnetic resonance angiography of 82 patients considering the iliac, femoral and tibial arteries. Stenosis was scored 0 (none), 1 (<50%), 2 (50%-74%), 3 (75%-99%), and 4 (occluded). Symmetry was quantified as the percentage of bilaterally-diseased arteries and using the inter-leg absolute score difference (0-4). Signs test and Cohen kappa were also calculated. Seventy-one (87%) patients had >/=1 bilaterally-diseased artery, and 168 (20%) of 820 artery pairs were bilaterally affected. At least 1 bilateral stenosis was observed from 11% (right internal iliac) to 73% (right superficial femoral). All 10 arteries showed symmetry, none of the inter-leg comparisons being significantly different (P >/= .100). Cohen kappa ranged from 0.208 (common femoral) to 0.533 (internal iliac). This study showed that PAD was symmetrically distributed between the 2 legs, with the internal iliac artery being the most symmetric segment. Symmetry of PAD was quantified in 20%.

[36] *Correa-Rodriguez M, Pocovi-Gerardino G, Callejas-Rubio JL et al.* **Dietary Intake of Free Sugars is Associated with Disease Activity and Dyslipidemia in Systemic Lupus Erythematosus Patients**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32326626

ABSTRACT

Diet has been closely associated with inflammatory autoimmune diseases, including systemic lupus erythematosus (SLE). Importantly, the consumption of dietary sugars has been positively linked to elevated levels of some inflammation markers, but the potential role of their consumption on the prognosis of autoimmune diseases has not yet been examined. The aim of this study was to evaluate the association between the dietary intake of free sugars and clinical parameters and cardiovascular (CVD) risk markers in patients with SLE. A cross-sectional study including a total of 193 patients with SLE (aged 48.25 +/- 12.54 years) was conducted. The SLE Disease Activity Index (SLEDAI-2K) and the SDI Damage Index were used to asses disease activity and disease-related damage, respectively. Levels of C-reactive protein (CRP; mg/dL), homocysteine (Hcy; micromol/L), anti-double stranded DNA antibodies (anti-dsDNA) (IU/mL), complement C3 (mg/dL), and complement C4 (mg/dL), among other biochemical markers, were measured. The main factors we considered as risk factors for CVD were obesity, diabetes mellitus, hypertension, and blood lipids. The dietary-intrinsic sugar and added-sugar content participants consumed were obtained via a 24-h patient diary. Significant differences were observed in dietary sugar intake between patients with active and inactive SLE (in grams: 28.31 +/- 24.43 vs. 38.71 +/- 28.87; p = 0.035) and free sugar intake (as a percentage: 6.36 +/- 4.82 vs. 8.60 +/- 5.51; p = 0.020). Linear regression analysis revealed a significant association between free sugars intake (by gram or percentage) and the number of complications (beta (95% CI) = 0.009 (0.001, 0.0018), p = 0.033)); (beta (95% CI) = 0.046 (0.008, 0.084), p = 0.018)), and SLEDAI (beta (95% CI) = 0.017 (0.001, 0.034), p = 0.043)); (beta (95% CI) = 0.086 (0.011, 0.161), p = 0.024)) after adjusting for covariates. Free sugars (g and %) were also associated with the presence of dyslipidaemia (beta (95% CI) = -0.003 (-0.005, 0.000), p = 0.024)) and (beta (95% CI) = -0.015 (-0.028, -0.002), p = 0.021)). Our findings suggest that a higher consumption of free sugars might negatively impact the activity and complications of SLE. However, future longitudinal research on SLE patients, including dietary intervention trials, are necessary to corroborate these preliminary data.

[37] *Davis DW, Navalta JW, McGinnis GR et al.* **Effects of Acute Dietary Polyphenols and Post-Meal Physical Activity on Postprandial Metabolism in Adults with Features of the Metabolic Syndrome**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32316418

ABSTRACT

Approximately 22% of U.S. adults and 25% of adults globally have metabolic syndrome (MetS). Key features, such as dysglycemia and dyslipidemia, predict type 2 diabetes, cardiovascular disease, premature disability, and death. Acute supplementation of dietary polyphenols and post-meal physical activity hold promise in improving postprandial dysmetabolism. To our knowledge, no published review has described the effects of either intervention on postprandial glucose, insulin, lipids, and markers of oxidative damage and inflammation in adults with features of MetS. Thus, we conducted this review of controlled clinical trials that provided dietary polyphenols from oils, fruits, teas, and legumes during a dietary challenge, or implemented walking, cycling, and stair climbing and descending after a dietary challenge. Clinical trials were identified using ClinicalTrials.gov, PubMed, and Google Scholar and were published between 2000 and 2019. Dietary polyphenols from extra virgin olive oil, grapes, blackcurrants, strawberries, black tea, and black beans improved postprandial glucose, insulin, and markers of oxidative damage and inflammation, but results were not consistent among clinical trials. Freeze-dried strawberry powder distinctly improved postprandial insulin and markers of oxidative damage and inflammation. Post-meal physical activity attenuated postprandial glucose, but effects on postprandial lipids and markers of oxidative damage and inflammation were inconclusive. Consuming dietary polyphenols with a meal and completing physical activity after a meal may mitigate postprandial dysmetabolism in adults with features of MetS.

[38] *Kanikowska D, Korybalska K, Mickiewicz A et al.* **Flaxseed (Linum Usitatissimum L.) Supplementation in Patients Undergoing Lipoprotein Apheresis for Severe Hyperlipidemia-A Pilot Study**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32325781

ABSTRACT

Being rich in polyunsaturated fatty acids, flaxseed (Linum usitatissimum L.) is thought to be able to decrease lipid levels and dampen inflammation. In this pilot study, we aimed to determine whether flaxseed supplementation could improve the profiles of lipids and inflammatory mediators in patients with severe hyperlipidemia resistant to conventional lipid-lowering pharmacotherapy and requiring lipoprotein apheresis. To this end, six patients received, blindly-in addition to their normal lipoprotein apheresis regimen-a 10-week dietary supplementation with flaxseed (28 g/d) administered in biscuits. This was followed by a 10-week washed out-period and a 10-week supplementation phase with whole wheat placebo. Blood samples were collected at the end of each phase, before the lipoprotein apheresis session. The primary endpoint was the lipid profile and the secondary endpoints were the concentrations of inflammatory mediators and tolerability. Flaxseed supplementation was well-tolerated and resulted in a consistent and significant decrease in total cholesterol and low-density lipoprotein (LDL) levels. The median (and range) percentage decrease was 11.5% (0-

18.8) and 7.3% (4.4-26.6), for cholesterol (p = 0.015) and LDL-C (p = 0.003), respectively. On the other hand, there was no significant effect of flaxseed on lipoprotein(a) (Lp(a)), C-reactive protein (CRP), and interleukin 6 (IL-6) concentrations. These observations indicate that flaxseed can produce a cholesterol- and LDL-lowering effect in patients treated with lipoprotein apheresis. Thus, flaxseed supplementation may help to control cholesterol in this patient population. The flaxseed supplementation protocol applied may be of use for further adequately-powered studies to validate and extend our findings.

[39] *Sabbatinelli J, Orlando P, Galeazzi R et al.* **Ubiquinol Ameliorates Endothelial Dysfunction in Subjects with Mild-to-Moderate Dyslipidemia: A Randomized Clinical Trial**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32326664
ABSTRACT
In this randomized, double-blind, single-center trial (ANZCTR number ACTRN12619000436178) we aimed to investigate changes in endothelium-dependent vasodilation induced by ubiquinol, the reduced form of coenzyme Q10 (CoQ10), in healthy subjects with moderate dyslipidemia. Fifty-one subjects with low-density lipoprotein (LDL) cholesterol levels of 130-200 mg/dL, not taking statins or other lipid lowering treatments, moderate (2.5%-6.0%) endothelial dysfunction as measured by flow-mediated dilation (FMD) of the brachial artery, and no clinical signs of cardiovascular disease were randomized to receive either ubiquinol (200 or 100 mg/day) or placebo for 8 weeks. The primary outcome measure was the effect of ubiquinol supplementation on FMD at the end of the study. Secondary outcomes included changes in FMD on week 4, changes in total and oxidized plasma CoQ10 on week 4 and week 8, and changes in serum nitrate and nitrite levels (NOx), and plasma LDL susceptibility to oxidation in vitro on week 8. Analysis of the data of the 48 participants who completed the study demonstrated a significantly increased FMD in both treated groups compared with the placebo group (200 mg/day, +1.28% +/- 0.90%; 100 mg/day, +1.34% +/- 1.44%; p < 0.001) and a marked increase in plasma CoQ10, either total (p < 0.001) and reduced (p < 0.001). Serum NOx increased significantly and dose-dependently in all treated subjects (p = 0.016), while LDL oxidation lag time improved significantly in those receiving 200 mg/day (p = 0.017). Ubiquinol significantly ameliorated dyslipidemia-related endothelial dysfunction. This effect was strongly related to increased nitric oxide bioavailability and was partly mediated by enhanced LDL antioxidant protection.

[40] *Ingersgaard MV, Helms Andersen T, Norgaard O et al.* **Reasons for Nonadherence to Statins - A Systematic Review of Reviews**. Patient preference and adherence 2020; 14:675-691.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32308373
ABSTRACT
Purpose: Lipid-lowering medications are often prescribed to decrease the risk of micro- and macro-cardiovascular complications related to dyslipidaemia. Despite widespread prescription of lipid-lowering drugs, including statins, adherence to therapy is a challenge worldwide. This systematic review of reviews aimed to conduct a critical appraisal and synthesis of review findings and to provide an overview of the factors that were found to affect adherence to lipid-

lowering drugs, focusing on statins, in the reviews. Patients and Methods: A systematic review methodology was used. MEDLINE, Embase, and Epistemonikos databases were searched for relevant publications. AMSTAR 2 criteria were used to assess the quality of the selected publications. Results: From a total of 763 screened publications, 9 met all inclusion criteria and were included in this synthesis. Several factors were identified as being associated with adherence to lipid-lowering agents. Among them, high socio-economic and educational position, and middle age had a positive effect on adherence to lipid-lowering agents. Contrary, female sex, older and younger age, non-white race, low socio-economic position, high co-payments, being a new statin user, comorbidities, side effects, regimen complexity, type and intensity of statin dose, smoking, alcohol consumption, imperceptible benefits, and medical distrust contributed to non-adherence. The overall quality of the included reviews was considered critically low to moderate. Conclusion: This review of reviews has evaluated the impact of factors on adherence statins. Further research related to modifiable predictors for non-adherence is warranted.

[41] *Salazar-Tortosa DF, Pascual-Gamarra JM, Labayen I et al.* **Association between LPL gene polymorphisms and cardiovascular disease risk factors in European adolescents: The HELENA study**. Pediatric diabetes 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32333632
ABSTRACT
OBJECTIVES: To examine the association of lipoprotein lipase (LPL) polymorphisms with cardiovascular disease (CVD) risk factors in European adolescents, along with the influence of physical activity on these associations. METHODS: A total of 13 LPL polymorphisms were genotyped in 1.057 European adolescents (12-18 years old) from the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study. Serum lipids, glucose, insulin and leptin levels were measured and a CVD risk score was computed. We also measured body weight and height, waist and hip circumferences, and triceps and subscapular skinfold thickness. Physical activity was objectively measured by accelerometry for 7 days. RESULTS: The rs1534649, rs258, rs320 and rs328 polymorphisms were associated with several CVD risk factors (i.e., body mass index [BMI], Triglycerides [TG], Leptin, and cholesterol/High density lipoprotein [HDL], Low density lipoprotein [LDL]/HDL, TG/HDL ratios). TG and TG/HDL were associated with haplotype blocks 3 (rs282, rs285 polymorphisms) and 4 (rs3126, rs320, rs328, rs10099160 polymorphisms), being the latter also associated with the CVD risk score. Physical activity modulated the association of adiposity with rs1534649 and rs258 polymorphisms. CONCLUSIONS: Polymorphisms rs1534649, rs258, rs320 and rs328, and two haplotypes of LPL were significantly associated with CVD risk factors in European adolescents. Higher levels of moderate to vigorous physical activity may attenuate the effects of rs1534649 and rs258 polymorphisms on adiposity.

[42] *So HC, Chau CK, Cheng YY, Sham PC*. **Causal relationships between blood lipids and depression phenotypes: a Mendelian randomisation analysis**. Psychological medicine 2020:1-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32329708
ABSTRACT

BACKGROUND: The etiology of depression remains poorly understood. Changes in blood lipid levels were reported to be associated with depression and suicide, however study findings were mixed. METHODS: We performed a two-sample Mendelian randomisation (MR) analysis to investigate the causal relationship between blood lipids and depression phenotypes, based on large-scale GWAS summary statistics (N = 188 577/480 359 for lipid/depression traits respectively). Five depression-related phenotypes were included, namely major depression (MD; from PGC), depressive symptoms (DS; from SSGAC), longest duration and number of episodes of low mood, and history of deliberate self-harm (DSH)/suicide (from UK Biobank). MR was conducted with inverse-variance weighted (MR-IVW), Egger and Generalised Summary-data-based MR (GSMR) methods. RESULTS: There was consistent evidence that triglyceride (TG) is causally associated with DS (MR-IVW beta for one-s.d. increase in TG = 0.0346, 95% CI 0.0114-0.0578), supported by MR-IVW and GSMR and multiple r2 clumping thresholds. We also observed relatively consistent associations of TG with DSH/suicide (MR-Egger OR = 2.514, CI 1.579-4.003). There was moderate evidence for positive associations of TG with MD and the number of episodes of low mood. For HDL-c, we observed moderate evidence for causal associations with DS and MD. LDL-c and TC did not show robust causal relationships with depression phenotypes, except for weak evidence that LDL-c is inversely related to DSH/suicide. We did not detect significant associations when depression phenotypes were treated as exposures. CONCLUSIONS: This study provides evidence to a causal relationship between TG, and to a lesser extent, altered cholesterol levels with depression phenotypes. Further studies on its mechanistic basis and the effects of lipid-lowering therapies are warranted.

[43] *Sia CH, Zheng H, Ho AF et al.* **The Lipid Paradox is present in ST-elevation but not in non-ST-elevation myocardial infarction patients: Insights from the Singapore Myocardial Infarction Registry**. Scientific reports 2020; 10:6799.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32321961

ABSTRACT

Lowering low-density lipoprotein (LDL-C) and triglyceride (TG) levels form the cornerstone approach of cardiovascular risk reduction, and a higher high-density lipoprotein (HDL-C) is thought to be protective. However, in acute myocardial infarction (AMI) patients, higher admission LDL-C and TG levels have been shown to be associated with better clinical outcomes - termed the 'lipid paradox'. We studied the relationship between lipid profile obtained within 72 hours of presentation, and all-cause mortality (during hospitalization, at 30-days and 12-months), and rehospitalization for heart failure and non-fatal AMI at 12-months in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) patients treated by percutaneous coronary intervention (PCI). We included 11543 STEMI and 8470 NSTEMI patients who underwent PCI in the Singapore Myocardial Infarction Registry between 2008-2015. NSTEMI patients were older (60.3 years vs 57.7 years, $p < 0.001$) and more likely to be female (22.4% vs 15.0%, $p < 0.001$). In NSTEMI, a lower LDL-C was paradoxically associated with worse outcomes for death during hospitalization, within 30-days and within 12-months (all $p < 0.001$), but adjustment eliminated this paradox. In contrast, the paradox for LDL-C persisted for all primary outcomes after adjustment in STEMI. For NSTEMI patients, a lower HDL-C was associated with a higher risk

of death during hospitalization but in STEMI patients a lower HDL-C was paradoxically associated with a lower risk of death during hospitalization. For this endpoint, the interaction term for HDL-C and type of MI was significant even after adjustment. An elevated TG level was not protective after adjustment. These observations may be due to differing characteristics and underlying pathophysiological mechanisms in NSTEMI and STEMI.

[44] Shah N, Nagalli S. Cholesterol Emboli (Atheroembolism, Blue or Purple Toe Syndrome). In: StatPearls. Treasure Island (FL): StatPearls Publishing
StatPearls Publishing LLC.; 2020.
[45] *Alberts MJ, Thompson PD*. **PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibition and Stroke Prevention: Another Step Forward**. Stroke 2020; 51:1361-1362.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32312221
ABSTRACT

[46] *Giugliano RP, Pedersen TR, Saver JL et al.* **Stroke Prevention With the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Evolocumab Added to Statin in High-Risk Patients With Stable Atherosclerosis**. Stroke 2020; 51:1546-1554.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32312223
ABSTRACT
Background and Purpose- The PCSK9 (proprotein convertase subtilisin-kexin type 9) monoclonal antibody evolocumab lowered LDL (low-density lipoprotein) cholesterol by 59% to 0.8 (0.5-1.2) mmol/L and significantly reduced major vascular events in the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk). Herein, we report the results of a prespecified analysis of cerebrovascular events in the overall trial population and in patients stratified by prior stroke. Methods- FOURIER was a randomized, double-blind trial comparing evolocumab versus placebo in patients with established atherosclerosis, additional risk factors, and LDL cholesterol levels >/=1.8 (or non-HDL [high-density lipoprotein] >/=2.6 mmol/L) on statin therapy. The median follow-up was 2.2 years. We analyzed the efficacy of evolocumab to reduce overall stroke and stroke subtypes, as well as the primary cardiovascular composite end point by subgroups according to a history of stroke. Results- Among the 27 564 patients, 469 (1.7%) experienced a total of 503 strokes of which 421 (84%) were ischemic. Prior ischemic stroke, diabetes mellitus, elevated CRP (C-reactive protein), history of heart failure, older age, nonwhite race, peripheral arterial disease, and renal insufficiency were independent predictors of stroke. Evolocumab significantly reduced all stroke (1.5% versus 1.9%; hazard ratio, 0.79 [95% CI, 0.66-0.95]; P=0.01) and ischemic stroke (1.2% versus 1.6%; hazard ratio, 0.75 [95% CI, 0.62-0.92]; P=0.005), with no difference in hemorrhagic stroke (0.21% versus 0.18%; hazard ratio, 1.16 [95% CI, 0.68-1.98]; P=0.59). These findings were consistent across subgroups, including among the 5337 patients (19%) with prior ischemic stroke in whom the hazard ratios (95% CIs) were 0.85 (0.72-1.00) for the cardiovascular composite, 0.90 (0.68-1.19) for all stroke, and 0.92 (0.68-1.25) for ischemic stroke (P interactions, 0.91, 0.22, and 0.09, respectively, compared with patients without a prior ischemic stroke). Conclusions- Inhibition of PCSK9 with evolocumab added to statin in patients with established atherosclerosis reduced ischemic stroke and cardiovascular events in

the total population and in key subgroups, including those with prior ischemic stroke. Registration- URL: https://www.clinicaltrials.gov; Unique identifier: NCT01764633.

[47] *Kwon TG, Jang AY, Kim SW et al.* **Design and rationale of a randomized control trial testing the effectiveness of combined therapy with STAtin plus FENOfibrate and statin alone in non-diabetic, combined dyslipidemia patients with non-intervened intermediate coronary artery disease - STAFENO study**. Trials 2020; 21:353.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32321551
ABSTRACT
BACKGROUND: Despite the chronicled success of low-density lipoprotein cholesterol (LDLc)-lowering statin therapy, substantial residual cardiovascular (CV) disease risk remains a problem worldwide, highlighting the need to for combination therapies targeting non-LDLc factors, such as with fenofibrate. METHODS/DESIGN: The STAFENO trial is a prospective, randomized, open-label, multi-center trial to compare the effect of statin plus fenofibrate with statin alone on the reduction and stabilization of plaque in non-diabetic, combined dyslipidemia patients with non-intervened, intermediate coronary artery disease (CAD) using virtual histology-intravascular ultrasound at 12 months. A total of 106 eligible patients are planned to be randomized to receive either a combination therapy (rosuvastatin 10 mg plus fenofibrate 160 mg/day) or monotherapy (rosuvastatin 10 mg/day) for 12 months. The primary endpoint of this study is the percentage change in the necrotic core volume. Secondary endpoints include changes in tissue characteristics and 1-year major CV events, including all-cause mortality, CV mortality, nonfatal myocardial infarction, stroke, and revascularization of the intervened and non-intervened lesions. DISCUSSION: The STAFENO trial will address whether combination treatment of statin and fenofibrate has an additive beneficial effect compared to statin alone on the reduction and stabilization of plaque and CV events in non-diabetic, combined dyslipidemia patients with non-intervened intermediate CAD. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02232360. Registered 9 February 2014.
https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0004ULE&selectaction=Edit&uid=U00023SZ&ts=2&cx=juppd2.

[48] *Poltavskaya TS, Bazhenov VA, Volojanin AV*. **[The efficacy of metabolic treatment in the early recovery period of patients with ischemic stroke]**. Zh Nevrol Psikhiatr Im S S Korsakova 2020; 120:49-53.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32307430
ABSTRACT
AIM: To evaluate the efficacy of including cytoflavin in rehabilitation measures in the early recovery period of patients with ischemic stroke. MATERIAL AND METHODS: Results of rehabilitation measures of 100 patients (50 women and 50 men, aged 18 to 85 years) in the early recovery period of ischemic stroke were analyzed. Psychological testing included NIHSS, MMSE, Rankin scale, Rivermead mobility index, exercise tolerance test. Depending on the rehabilitation scheme, patients were divided into the main group (n=50), who received a verticalization course and cytoflavin (intravenously, drip 20.0 ml in 250.0 ml 5% glucose for 14 days). The control group (n=50) included patients who received standard treatment. RESULTS AND CONCLUSION: Inclusion of cytoflavin in the rehabilitation scheme for patients with

ischemic stroke increased the effectiveness of treatment, which was manifested by a decrease in the severity of neurological disorders assessed with NIHSS by 17.6% in the main group versus 10.8% in the control group ($p<0.05$) and recovery of cognitive functions assessed with MMSE by 5.8% versus 1.6%, respectively ($p<0.05$). In addition, there was a positive dynamics in the restoration of blood pressure (by 37.1% in the main group versus 30.6% in the control group ($p<0.05$)).

[49] *Tmoyan NA, Ezhov MV, Afanasieva OI et al.* **[Association of lipoprotein (a) with ischemic stroke and stenotic carotid atherosclerosis]**. Zh Nevrol Psikhiatr Im S S Korsakova 2020; 120:42-48.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32307429

ABSTRACT
INTRODUCTION: Lipoprotein(a) [Lp(a)] is a genetically determined risk factor of coronary heart disease and its complications. Meanwhile data about the role of Lp(a) in development of ischemic stroke are controversial. AIM: To investigate the association of Lp(a) with atherothrombotic ischemic stroke and stenotic (>/=50%) atherosclerosis of carotid arteries. MATERIAL AND METHODS: The study included 490 patients (mean age 60 years, 53% male). The first group comprised 157 patients with ischemic stroke, the second group 68 patients with isolated stenotic atherosclerosis of carotid arteries, but without significant lesion of coronary and low limbs arteries. The control group included 265 patients without stroke, myocardial infarction, stenotic atherosclerosis of coronary, carotid and low limbs arteries according to instrumental examinations. The levels of Lp(a) and lipids were measured in blood serum of all patients. RESULTS: Lp(a) concentration was significantly higher in patients of the first and second groups in comparison with the control group (median [interquartile range]): 24 [9; 48], 20 [8; 55] vs 13 [5; 27] mg/dl, respectively ($p<0,05$ in both cases). Hyperlipoproteinemia(a) (Lp(a) >/=30 mg/dl) was more frequent in the group with stroke, stenotic atherosclerosis of carotid arteries, than in the control group: 43%, 40% vs 22% ($p<0.01$ in all cases). In patients with hyperlipoproteinemia(a), odds ratio (OR) for ischemic stroke was 2.7 (95% confidence interval (CI) 1.7-4.1), and OR for stenotic atherosclerosis of carotid arteries was 2.3 (95% CI 1.3-4.0) compared to the patients with Lp(a) level <30 mg/dl ($p<0.01$ in both cases). In logistic regression analysis adjusted for age, sex, hypertension, type 2 diabetes, smoking and Lp(a) concentration, the hyperlipoproteinemia(a) was associated with ischemic stroke and isolated stenotic carotid atherosclerosis. In the group with severe carotid atherosclerosis, 16 patients (24%) had ischemic stroke. Lp(a) concentration in these patients was higher 36 [20; 59] mg/dl, than in the patients with isolated carotid atherosclerosis without stroke 15 [7; 54] mg/dl ($p=0.04$). Other risk factors of atherosclerosis did not differ in patients with or without ischemic stroke. CONCLUSION: The study shows the association of elevated level of Lp(a) with ischemic stroke and isolated stenotic atherosclerosis of carotid arteries. In the presence of isolated stenotic carotid atherosclerosis, the median of Lp(a) concentration was significantly higher in patients with ischemic stroke than in patients without stroke.