Literature update week 26 (2019)

[1] *Oh TK, Song IA, Lee JH et al.* **Preadmission Statin Use and 90-day Mortality in the Critically Ill: A Retrospective Association Study**. Anesthesiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31246609
ABSTRACT
WHAT WE ALREADY KNOW ABOUT THIS TOPIC: Randomized controlled trials evaluating the potential value of statin administration for intensive care unit patients have not observed a benefitHowever, the chronic preadmission use of statins among patients admitted to the intensive care unit has not been robustly studied WHAT THIS ARTICLE TELLS US THAT IS NEW: Single-center retrospective data suggest that preadmission statin use may be associated with decreased 90-day mortality among some intensive care unit patientsSpecific statin agents and noncardiovascular mortality may demonstrate a stronger signal for further study BACKGROUND:: This study aimed to examine the association between preadmission statin use and 90-day mortality in critically ill patients and to investigate whether this association differed according to statin type and dose. We hypothesized that preadmission statin use was associated with lower 90-day mortality. METHODS: This retrospective cohort study analyzed the medical records of all adult patients admitted to the intensive care unit in a single tertiary academic hospital between January 2012 and December 2017. Data including preadmission statin use, statin subtype, and daily dosage were collected, and the associations between these variables and 90-day mortality after intensive care unit admission were examined. The primary endpoint was 90-day mortality. RESULTS: A total of 24,928 patients (7,396 statin users and 17,532 non-statin users) were included. After propensity score matching, 5,354 statin users and 7,758 non-statin users were finally included. The 90-day mortality rate was significantly higher in non-statin users (918 of 7,758; 11.8%) than in statin users (455 of 5,354; 8.5%; $P < 0.001$). In Cox regression analysis, the 90-day mortality rate was lower among statin users than among non-statin users (hazard ratio: 0.70, 95% CI: 0.63 to 0.79; $P < 0.001$). Rosuvastatin use was associated with 42% lower 90-day mortality (hazard ratio: 0.58, 95% CI: 0.47 to 0.72; $P < 0.001$). There were no specific significant differences in the association between daily statin dose and 90-day mortality. In competing risk analysis, the risk of noncardiovascular 90-day mortality in statin users was 32% lower than that in non-statin users (hazard ratio: 0.68, 95% CI: 0.60 to 0.78; $P < 0.001$). Meanwhile, cardiovascular 90-day mortality was not significantly associated with statin use. CONCLUSIONS: Preadmission statin use was associated with a lower 90-day mortality. This association was more evident in the rosuvastatin group and with noncardiovascular 90-day mortality; no differences were seen according to daily dosage intensity.

[2] *Hyafil F, Vigne J*. **Nuclear Imaging**. Arteriosclerosis, thrombosis, and vascular biology 2019; 39:1369-1378.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31242032
ABSTRACT
Noninvasive imaging technologies offer to identify several anatomic and molecular features of high-risk plaques. For the noninvasive molecular imaging of atherosclerotic plaques, nuclear medicine constitutes one of the best imaging modalities, thanks to its high sensitivity for the detection of probes in tissues. 18F-fluorodeoxyglucose (FDG) is currently the most widely used radiopharmaceutical for molecular imaging of atherosclerotic plaques with positron emission

tomography. The intensity of FDG uptake in the vascular wall correlates closely with the degree of macrophage infiltration in atherosclerotic plaques. FDG positron emission tomographic imaging has become a powerful tool to identify and monitor noninvasively inflammatory activities in atherosclerotic plaques over time. This review examines how FDG positron emission tomographic imaging has given us deeper insight into the role of inflammation in atherosclerotic plaque progression and discusses perspectives for alternative radiopharmaceuticals to FDG that could provide a more specific and simple identification of high-risk lesions and help improve risk stratification of atherosclerotic patients. Visual Overview- An online visual overview is available for this article.

[3] *Masana L, Ibarretxe D, Rodriguez-Borjabad C et al.* **Toward a new clinical classification of patients with familial hypercholesterolemia: One perspective from Spain**. Atherosclerosis 2019; 287:89-92.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31238171
ABSTRACT
The introduction of singular therapies, such as proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), to lower high cholesterol levels requires better classification of patients eligible for intensive lipid lowering therapy. According to the European Medicines Administration, PCSK9i are recommended in primary prevention only in familial hypercholesterolemia (FH) patients. Therefore, an FH diagnosis is not simply an academic issue, because it has many clinical implications. The bases of a diagnosis of FH are not entirely clear. The availability of genetic testing, including large genome-wide association analyses and whole genome studies, has shown that some patients with a clinical diagnosis of definite FH have no mutations in the genes associated with the disease. This fact does not exclude the very high cardiovascular risk of these patients, and an early and intensive lipid lowering therapy is recommended in all FH patients. Because an FH diagnosis is a cornerstone for decisions about therapies, a precise definition of FH is urgently required. This is an expert consensus document from the Spanish Atherosclerosis Society. We propose the following classification: familial hypercholesterolemia syndrome integrated by (1) heterozygous familial hypercholesterolemia: patients with clinically definite FH and a functional mutation in one allele of the LDLR, ApoB:100, and PCSK9 genes; (2) homozygous familial hypercholesterolemia: mutations affect both alleles; (3) polygenic familial hypercholesterolemia: patients with clinically definite FH but no mutations associated with FH are found (to be distinguished from non-familial, multifactorial hypercholesterolemia); (4) familial hypercholesterolemia combined with hypertriglyceridemia: a subgroup of familial combined hyperlipidaemia patients fulfilling clinically definite FH with associated hypertriglyceridemia.

[4] *Ray KK, Vallejo-Vaz AJ, Ginsberg HN et al.* **Lipoprotein(a) reductions from PCSK9 inhibition and major adverse cardiovascular events: Pooled analysis of alirocumab phase 3 trials**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31253441
ABSTRACT
BACKGROUND AND AIMS: Elevated lipoprotein(a) [Lp(a)] levels are considered a causal factor for cardiovascular disease. In phase 3 ODYSSEY trials, alirocumab reduced levels of low-density

lipoprotein cholesterol (LDL-C) and Lp(a), with concomitant reductions in the risk of major adverse cardiovascular events (MACE). We assessed whether lower on-study and greater percentage reductions in Lp(a) are associated with a lower risk of MACE. METHODS: Post-hoc analysis of data pooled from 10 phase 3 ODYSSEY trials comparing alirocumab with control (placebo or ezetimibe) in patients (n=4983) with cardiovascular disease and/or risk factors, and hypercholesterolemia despite statin/other lipid-lowering therapies. RESULTS: Median (Q1, Q3) baseline Lp(a) levels were 23.5 (8.0, 67.0) mg/dL. Median Lp(a) changes from baseline with alirocumab were -25.6% vs. -2.5% with placebo (absolute reductions 6.8 vs. 0.5mg/dL) in placebo-controlled trials, and -21.4% vs. 0.0% with ezetimibe (4.5 vs. 0.0mg/dL) in ezetimibe-controlled trials. During follow-up (6699 patient-years), 104 patients experienced MACE. A 12% relative risk reduction in MACE per 25% reduction in Lp(a) (p=0.0254) was no longer significant after adjustment for LDL-C changes: hazard ratio per 25% reduction: 0.89 (95% confidence interval, 0.79-1.01; p=0.0780). In subgroup analysis, the association between Lp(a) reduction and MACE remained significant in a fully adjusted model among participants with baseline Lp(a) >/=50mg/dL (p-interaction vs. Lp(a)<50mg/dL: 0.0549). CONCLUSIONS: In this population, Lp(a) reductions were not significantly associated with MACE independently of LDL-C reductions. Reducing the risk of MACE by targeting Lp(a) may require greater reductions in Lp(a) with more potent therapies and/or higher initial Lp(a) levels.

[5] *Bogomolova AM, Shavva VS, Nikitin AA et al.* **Hypoxia as a Factor Involved in the Regulation of the apoA-1, ABCA1, and Complement C3 Gene Expression in Human Macrophages**.
Biochemistry. Biokhimiia 2019; 84:529-539.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31234767

ABSTRACT

Hypoxia plays a critical role in progression of atherosclerosis. Local oxygen deficiency in a plaque creates a specific microenvironment that alters the transcriptome of resident cells, particularly of macrophages. Reverse cholesterol transport from plaque to liver is considered a main mechanism for regression of atherosclerosis. Ubiquitously expressed ATP-binding cassette transporter A1 (ABCA1) and liver- and small intestine-derived apolipoprotein A-1 (ApoA-1) are two main actors in this process. We recently reported endogenous apoA-1 expression in human macrophages. While ABCA1 and ApoA-1 have antiatherogenic properties, the role of complement factor C3 is controversial. Plasma C3 level positively correlates with the risk of cardiovascular diseases. On the other hand, C3 gene knockout in a murine atherosclerosis model increases both plaque size and triglycerides level in blood. In the present study, we show for the first time that a hypoxia-mimicking agent, CoCl2, induces the upregulation of the apoA-1 and C3 genes and the accumulation of intracellular and membrane protein ApoA-1 in THP-1 macrophages. The MEK1/2-Erk1/2 and MKK4/7-JNK1/2/3 cascades are involved in upregulation of ABCA1 and C3 via activation of transcription factor NF-kappaB, which interacts with the HIF-1alpha subunit of hypoxia-inducible factor 1 (HIF-1). The three major MAP-kinase cascades (Erk1/2, JNK1/2/3, and p38) and the NF-kappaB transcription factor are involved in the hypoxia-induced expression of the apoA-1 gene in THP-1 macrophages.

[6] *Fernandes BS, Dias O, Costa G et al.* **Genome-wide sequencing and metabolic annotation of Pythium irregulare CBS 494.86: understanding Eicosapentaenoic acid production**. BMC biotechnology 2019; 19:41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31253157
ABSTRACT
BACKGROUND: Pythium irregulare is an oleaginous Oomycete able to accumulate large amounts of lipids, including Eicosapentaenoic acid (EPA). EPA is an important and expensive dietary supplement with a promising and very competitive market, which is dependent on fish-oil extraction. This has prompted several research groups to study biotechnological routes to obtain specific fatty acids rather than a mixture of various lipids. Moreover, microorganisms can use low cost carbon sources for lipid production, thus reducing production costs. Previous studies have highlighted the production of EPA by P. irregulare, exploiting diverse low cost carbon sources that are produced in large amounts, such as vinasse, glycerol, and food wastewater. However, there is still a lack of knowledge about its biosynthetic pathways, because no functional annotation of any Pythium sp. exists yet. The goal of this work was to identify key genes and pathways related to EPA biosynthesis, in P. irregulare CBS 494.86, by sequencing and performing an unprecedented annotation of its genome, considering the possibility of using wastewater as a carbon source. RESULTS: Genome sequencing provided 17,727 candidate genes, with 3809 of them associated with enzyme code and 945 with membrane transporter proteins. The functional annotation was compared with curated information of oleaginous organisms, understanding amino acids and fatty acids production, and consumption of carbon and nitrogen sources, present in the wastewater. The main features include the presence of genes related to the consumption of several sugars and candidate genes of unsaturated fatty acids production. CONCLUSIONS: The whole metabolic genome presented, which is an unprecedented reconstruction of P. irregulare CBS 494.86, shows its potential to produce value-added products, in special EPA, for food and pharmaceutical industries, moreover it infers metabolic capabilities of the microorganism by incorporating information obtained from literature and genomic data, supplying information of great importance to future work.

[7] *MacAskill MG, Newby DE, Tavares AAS*. **Frontiers in PET imaging of the vulnerable atherosclerotic plaque**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31233100
ABSTRACT
Rupture of vulnerable atherosclerotic plaques leading to an atherothrombotic event is the primary driver of myocardial infarction and stroke. The ability to detect non-invasively the presence and evolution of vulnerable plaques could have a huge impact on the future identification and management of atherosclerotic cardiovascular disease. Positron imaging tomography (PET) imaging with an appropriate radiotracer has the potential to achieve this goal. This review will discuss the biological hallmarks of plaque vulnerability before going on to evaluate and to present PET imaging approaches which target these processes. The focus of this review will be on techniques beyond [18F]FDG imaging, some of which are clinically advanced, and others which are on the horizon. As inflammation is the primary driving force behind

atherosclerotic plaque development, we will predominantly focus on approaches which either directly, or in directly, target this process.

[8] *Trueck C, Hsin CH, Scherf-Clavel O et al.* **A Clinical DDI Study Assessing a Novel Drug Transporter Phenotyping Cocktail with Adefovir, Sitagliptin, Metformin, Pitavastatin and Digoxin**. Clinical pharmacology and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31247117
ABSTRACT
A new probe drug cocktail containing substrates of important drug transporters was tested for mutual interactions in a clinical trial. The cocktail consisted of (predominant transporter; primary phenotyping metric): 10 mg adefovir-dipivoxil (OAT1; renal clearance [CLR]), 100 mg sitagliptin (OAT3; CLR), 500 mg metformin (several renal transporters; CLR), 2 mg pitavastatin (OATP1B1; clearance/F) and 0.5 mg digoxin (intestinal P-gp, renal P-gp and OATP4C1; Cmax and CLR). Using a randomized six-period, open change-over design, single oral doses were administrated either concomitantly or separately to 24 healthy male and female volunteers. Phenotyping metrics were evaluated by noncompartmental analysis and compared between periods by the standard average bioequivalence approach (boundaries for ratios 0.80-1.25). Primary metrics supported the absence of relevant interactions, while secondary metrics suggested that mainly adefovir was a victim of minor DDIs. All drugs were well tolerated. This cocktail may be another useful tool to assess transporter based DDIs in vivo. This article is protected by copyright. All rights reserved.

[9] *Wang J, Chen HW, Fang XM et al.* **Myocardial CT perfusion imaging and atherosclerotic plaque characteristics on coronary CT angiography for the identification of myocardial ischaemia**. Clinical radiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31239108
ABSTRACT
AIM: To investigate the value of myocardial computed tomography (CT) perfusion imaging (CTP) and atherosclerotic plaque characteristics (APCs) identified on coronary CT angiography (CCTA) for the detection of myocardial ischaemia by using single-photon-emission CT (SPECT) as a reference. MATERIALS AND METHODS: Thirty-six patients (63.9% males) undergoing combined stress dynamic CTP and CCTA were enrolled and analysed. Myocardial blood flow (MBF) from CTP was quantified and compared between normal and abnormal segments. The ability of CTP and APCs to detect ischaemia was compared to that of SPECT. RESULTS: Nineteen patients with 78 segments had perfusion abnormalities on CTP. A significant difference was seen in MBF values between normal (118.51+/-27.86 ml/100 ml/min) and hypoperfused (79.60+/-21.35 ml/100 ml/min) segments ($t=15.832$, $p<0.05$). The sensitivity and specificity for identifying ischaemia were 90.91% and 94.97%, respectively, on a per-segment basis, resulting in a r value of 0.737 ($p<0.05$). On a per-vessel basis, the sensitivity and specificity for detecting ischaemia were 86.67% and 84.62%, respectively, for CTP; 93.33% and 58.97%, respectively, for CCTA; and 86.67% and 87.18%, respectively, for CTP combined with CTA, with an area under the receiver-operator characteristic curve (AUC) being 0.87 ($p<0.05$) and 0.887 ($p<0.05$) for CTP and its combination with CTA, respectively. On CCTA, 55 vessels with APCs were detected, with an AUC of 0.737 ($p<0.05$) for APCs combined with CCTA stenosis and 0.802 ($p<0.05$) for APCs combined

with CTP. CONCLUSIONS: Dynamic stress CTP shows good correlation with SPECT for the detection of ischaemia. Additionally, combining APCs with CCTA stenosis has the ability to discriminate ischaemic stenosis.

[10] *Ali S, Dave N, Virani SS, Navaneethan SD*. **Primary and Secondary Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease**. Current atherosclerosis reports 2019; 21:32.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31230129
ABSTRACT
PURPOSE OF REVIEW: Non-dialysis-dependent chronic kidney disease (NDD-CKD) patients are at an increased risk of cardiovascular disease (CVD)-related deaths in comparison with the general population. This review summarizes recent guideline recommendations and studies on primary and secondary prevention of traditional cardiovascular (CV) risk factors in those with NDD-CKD. RECENT FINDINGS: The use of antiplatelet agents for primary prevention in CKD is not supported by clinical trial evidence; however, they offer potential benefits when used for secondary prevention of CVD in the absence of an elevated bleeding risk. Lipid-lowering therapy reduces CV risk and is recommended for all NDD-CKD patients. In light of recent clinical trial findings, current clinical practice guidelines recommend a blood pressure (BP) goal < 130/80 mmHg and support the use of renin-angiotensin-aldosterone system inhibitors. Evidence supporting intensive glycemic control is limited in those with diabetes and CKD. Newer oral glycemic agents such as sodium-glucose co-transporter type 2 (SGLT2) inhibitors and glucagon-like-peptide-1 (GLP-1) receptor agonists reduce urinary albumin excretion, slow kidney disease progression, and reduce CV events. Despite the absence of dedicated clinical trials in the CKD population, lifestyle modifications including smoking cessation, intentional weight loss, and regular physical activity should be recommended to those with CKD. Patients with NDD-CKD should be treated with statins and a BP target of 130/80 mmHg should be aimed for. Limited data exists for interventions targeting other CV risk factors in CKD patients. Future studies examining the impact of various interventions targeting different primary and secondary CV prevention strategies are needed to fill knowledge gaps and improve CV outcomes.

[11] *Ceska R, Latkovskis G, Ezhov MV et al.* **The Impact of the International Cooperation On Familial Hypercholesterolemia Screening and Treatment: Results from the ScreenPro FH Project**. Current atherosclerosis reports 2019; 21:36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31230174
ABSTRACT
PURPOSE OF REVIEW: Familial hypercholesterolemia (FH) is often perceived and described as underdiagnosed and undertreated, though effective treatment of FH is available. Owing to the mentioned facts, it is ever more imperative to screen and treat FH patients. Subsequent to the identification of patients, the project focuses on the improvement of their prognoses. The ScreenPro FH project was established as a functional international network for the diagnosis, screening, and treatment of FH. Individual countries were assigned goals, e.g., to define the actual situation and available treatment. With "central support," more centers and countries participated in the project. Subsequently, individual countries reported the results at the

beginning and end of the project. Collected data were statistically evaluated. RECENT FINDINGS: The increasing number of patients in databases, from 7500 in 2014 to 25,347 in 2018, demonstrates the improvement in overall effectiveness, as well as an increase in the number of centers from 70 to 252. Before all, LDL-C decreased by 41.5% and total cholesterol by 32.3%. As data from all countries and patients were not available at the time of the analysis, only those results from 10 countries and 5585 patients at the beginning of the project and at the time of writing are included. Our data are quite positive. However, our results have only limited validity. Our patients are far from the target levels of LDL-C. The situation can be improved with the introduction of new therapy, PCSK9-i, evolocumab, and alirocumab. International cooperation improved the screening of FH and finally led to an improvement in cardiovascular risk.

[12] *Qamar A, Libby P*. **Low-Density Lipoprotein Cholesterol After an Acute Coronary Syndrome: How Low to Go?** Current cardiology reports 2019; 21:77.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31250329
ABSTRACT
PURPOSE OF REVIEW: Recent advances in low-density lipoprotein cholesterol (LDL-C) lowering therapy have now enabled reducing LDL-C safely to very low levels. This review summarizes evidence from recent randomized clinical trials of intensive LDL-C lowering in patients with acute coronary syndrome (ACS) and provides a practical approach for LDL-C lowering to reduce the risk of recurrent ischemic events in this population. RECENT FINDINGS: The risk of atherothrombotic events falls linearly with LDL-C level extending to very low achieved LDL-C levels (< 10 mg/dL) without apparent safety concerns. The addition of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (i.e., evolocumab or alirocumab) to statin therapy lowers LDL-C to very low levels (</= 30-50 mg/dL) with safety under the conditions studied and reduces the risk of recurrent cardiovascular events in patients with atherosclerotic cardiovascular disease. Current data support LDL-C lowering to levels below 70 mg/dL in patients post-ACS. Combination of high-intensity statins, ezetimibe, and if needed PCSK9 inhibitors merits consideration in such patients with ACS to optimize outcomes.

[13] *Mahmood T, Shapiro MD*. **Future role of proprotein convertase subtilisin/kexin type 9 inhibitors in preventive cardiology**. Current opinion in cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31246589
ABSTRACT
PURPOSE OF REVIEW: The use of therapeutic monoclonal antibodies to target proprotein convertase subtilisin/kexin type 9 (PCSK9) represents a novel approach to the management of hypercholesteremia and prevention of atherosclerotic cardiovascular disease. We review the most recent literature relevant to PCSK9 inhibition with emphasis on how recent results and ongoing trials have and will continue to shape the use of this new therapeutic class in preventive cardiology. RECENT FINDINGS: PCSK9 inhibitors reduce plasma lipoprotein(a) concentrations but a mechanistic understanding remains elusive. Evaluation of evolocumab for use in patients without prior myocardial infarction or stroke is underway (NCT03872401). Concerns regarding the cost-effectiveness of PCSK9 inhibitors have continued to thwart access to these drugs, though innovative models of care delivery and price reductions have improved

this situation. Inclisiran, a small interfering ribonucleic acid (siRNA), reduces translation of PCSK9 and demonstrates more durable reductions in low-density lipoprotein-cholesterol (LDL-C). It is currently evaluated in the context of a phase III cardiovascular outcome trial in patients with established vascular disease (NCT03705234). SUMMARY: The current scope of PCSK9 inhibitor therapy in preventive cardiology is limited to patients with familial hypercholesterolemia and/or established atherosclerotic cardiovascular disease. Future cardiovascular outcome trial results with PCSK9 blocking antibodies in primary prevention and with siRNA to PCSK9 in secondary prevention, improved understanding of the drivers of lipoprotein(a) reduction with PCSK9 inhibition, and cost-effectiveness will determine the future role of this therapeutic class.

[14] *Hwang YC, Kim JH, Lee BW, Lee WJ*. **A Lower Baseline Urinary Glucose Excretion Predicts a Better Response to the Sodium Glucose Cotransporter 2 Inhibitor**. Diabetes Metab J 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31237132

ABSTRACT

We aimed to identify the clinical variables associated with a better glucose-lowering response to the sodium glucose cotransporter 2 inhibitor ipragliflozin in people with type 2 diabetes mellitus (T2DM). We especially focused on urinary glucose excretion (UGE). This was a single-arm multicenter prospective study. A total of 92 people with T2DM aged 20 to 70 years with glycosylated hemoglobin (HbA1c) levels >/=7.0% and </=9.5% were enrolled. Ipragliflozin (50 mg) was added to the background therapy for these people for 12 weeks. After 3 months treatment with ipragliflozin, the mean HbA1c levels were decreased from 7.6% to 6.9% and 62.0% of the people reached the HbA1c target of less than 7.0% (P<0.001). In addition, body weight, blood pressure, and lipid parameters were improved after ipragliflozin treatment (all P<0.001). The baseline HbA1c (r=0.66, P<0.001) and morning spot urine glucose to creatinine ratio (r=-0.30, P=0.001) were independently associated with the HbA1c reduction. Ipragliflozin treatment for 12 weeks improves glycemic control and other metabolic parameters. A higher HbA1c and lower UGE at baseline predicts a better glucose-lowering efficacy of ipragliflozin.

[15] *Jun JE, Jeong IK, Yu JM et al.* **Efficacy and Safety of Omega-3 Fatty Acids in Patients Treated with Statins for Residual Hypertriglyceridemia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial**. Diabetes Metab J 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31237134

ABSTRACT

BACKGROUND: Cardiovascular risk remains increased despite optimal low density lipoprotein cholesterol (LDL-C) level induced by intensive statin therapy. Therefore, recent guidelines recommend non-high density lipoprotein cholesterol (non-HDL-C) as a secondary target for preventing cardiovascular events. The aim of this study was to assess the efficacy and tolerability of omega-3 fatty acids (OM3-FAs) in combination with atorvastatin compared to atorvastatin alone in patients with mixed dyslipidemia. METHODS: This randomized, double-blind, placebo-controlled, parallel-group, and phase III multicenter study included adults with fasting triglyceride (TG) levels >/=200 and <500 mg/dL and LDL-C levels <110 mg/dL. Eligible subjects were randomized to ATOMEGA (OM3-FAs 4,000 mg plus atorvastatin calcium 20 mg) or atorvastatin 20 mg plus placebo groups. The primary efficacy endpoints were the percent

changes in TG and non-HDL-C levels from baseline at the end of treatment. RESULTS: After 8 weeks of treatment, the percent changes from baseline in TG (-29.8% vs. 3.6%, P<0.001) and non-HDL-C (-10.1% vs. 4.9%, P<0.001) levels were significantly greater in the ATOMEGA group (n=97) than in the atorvastatin group (n=103). Moreover, the proportion of total subjects reaching TG target of <200 mg/dL in the ATOMEGA group was significantly higher than that in the atorvastatin group (62.9% vs. 22.3%, P<0.001). The incidence of adverse events did not differ between the two groups. CONCLUSION: The addition of OM3-FAs to atorvastatin improved TG and non-HDL-C levels to a significant extent compared to atorvastatin alone in subjects with residual hypertriglyceridemia.

[16] *Shayo SC*. **Strategies to ameliorate endothelial dysfunction associated with metabolic syndrome, where are we?** Diabetes & metabolic syndrome 2019; 13:2164-2169.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31235152
ABSTRACT
There is a paucity of aggregated clinical trials on strategies of ameliorating endothelial dysfunction associated with Metabolic Syndrome (MS). We reviewed clinical trials conducted between 2008 and 2017, reporting on strategies of improving endothelial function in patients with MS. A comprehensive search of published articles by the Google Scholar and PubMed were carried out. Only studies involving non-invasive, objective measurement of endothelial function were included. Thirty (30) studies were selected for analysis, in which physical exercise training, diet modification, calcium channel blockers + alpha-lipoic acid, bezafibrate, allopurinol, mesoglycan, and l-arginine supplementation significantly improved Endothelial-Dependent Vasodilation (EDV) in patients with MS but without cardiovascular diseases. Large multicenter clinical trials are required to address the question of generalizability of these findings.

[17] *Gebhardt A, Fichtenbaum CJ*. **Current pharmacotherapy for the treatment of dyslipidemia associated with HIV infection**. Expert opinion on pharmacotherapy 2019:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31232617
ABSTRACT
Introduction: Cardiovascular disease is an important cause of morbidity and mortality in persons with human immunodeficiency virus (PWH). The risk of atherosclerotic cardiovascular disease (ASCVD) is higher in PWH compared to uninfected persons. Dyslipidemia is a critical link in the pathogenesis of ASCVD in PWH. Chronic inflammation associated with HIV infection may drive both dyslipidemia and ASCVD. Areas covered: The authors review the evidence for using lipid-lowering therapy in PWH and includes an overview of the utility and complexity of using statins in PWH, in particular, drug interactions, safety, and efficacy. In addition, data covering alternate therapies like omega-3 fatty acids, fibrates, niacin, ezetimibe, and PCSK-9 inhibitors are reviewed. Expert opinion: Dyslipidemia is a common problem in PWH. The risk of ASCVD is higher in PWH. Lipid-lowering therapy reduces the risk of ASCVD, but clinical endpoint trials are lacking in PWH. Statin therapy is the mainstay of primary prevention for ASCVD. The timing of when to initiate primary prevention with statins in PWH is unclear. Beyond statins, there are limited data that other lipid-lowering agents have utility in PWH. Ongoing trials like the REPRIEVE trial will inform the community about the optimal approach to lipid-lowering therapy in PWH.

[18] *Dou X, Yang R*. **Current and emerging treatments for immune thrombocytopenia**. Expert review of hematology 2019:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31237783
ABSTRACT
Introduction: Immune thrombocytopenia (ITP) is an autoimmune disease. Even though there are many treatments available, some patients remain resistant to multiple treatments. Therefore, it is very important to develop new treatment options. Areas covered: Here, the authors summarize several current and emerging treatments developed for ITP in recent years. They include a summary of their mechanisms of action and clinical trial results. Expert opinion: At present, the first-line treatment of ITP is glucocorticoid and intravenous immunoglobulin (IVIg). Other traditional therapies include splenectomy, thrombopoietin (TPO), rituximab and other immunosuppressive agents. The several emerging treatments developed recently for ITP may change the treatment pattern in the future.

[19] *Zhang LY, Ding L, Shi HH et al.* **Eicosapentaenoic acid in the form of phospholipids exerts superior anti-atherosclerosis effects to its triglyceride form in ApoE(-/-) mice**. Food & function 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31246210
ABSTRACT
Dietary eicosapentaenoic acid (EPA), a main component of fish oil, has been proved to reduce the risk of cardiovascular disease. The purpose of this study was to investigate whether the anti-atherosclerosis effect of fish oil enriched with EPA partially relied on its chemical groups at the sn-3 position. Male ApoE-/- mice were divided into three groups and were fed a high-fat diet (Model) or a high-fat diet containing EPA incorporated into phospholipids (EPA-PL) or triglycerides (EPA-TG), respectively. Compared with the model group, a decrease in the area of atherosclerosis lesions at the aorta was observed in both EPA-treated groups, in which EPA-PL was superior to EPA-TG. Notably, EPA-PL exhibited lower serum and hepatic lipid levels than the model group, whereas EPA-TG only reduced the hepatic triglyceride level. Interestingly, only EPA-PL treatment regulated the expression of genes involved in cholesterol metabolism. In addition, EPA-PL and EPA-TG suppressed the inflammation markers in the aorta and circulation. In conclusion, EPA-PL was superior to EPA-TG in reducing lesion progression by modulating the hepatic lipid metabolism, as well as decreasing the inflammation in the artery wall and circulatory system, which might be attributed to their structural differences at the sn-3 position.

[20] *Wa Y, Yin B, He Y et al.* **Effects of Single Probiotic- and Combined Probiotic-Fermented Milk on Lipid Metabolism in Hyperlipidemic Rats**. Frontiers in microbiology 2019; 10:1312.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31249562
ABSTRACT
Previous studies have shown that probiotics have positive effects on hyperlipidemia by lowering the serum lipid concentration and improving the lipid profile. To explore the mechanism by which probiotic-fermented milk improves lipid metabolism, the transcription of genes regulated by liver X receptors (LXRs), 5'-AMP-activated protein kinase, and the farnesoid

X receptor (FXR), which play integral roles in lipid metabolism, was investigated in hyperlipidemic rats. Compared with rats fed a high-fat diet, the administration of probiotic-fermented milk significantly lowered the levels of total cholesterol (TC) and total triglycerides (TG) in rat serum and viscera ($P < 0.05$) and significantly increased the level of total bile acid in the rat liver and small intestine ($P < 0.05$). The quantitative PCR results showed that the probiotics ameliorated the TC levels in the rats by activating the transcription of genes involved in the LXR axis, which promoted TC reverse transport and increased the conversion of TC to bile acids. The level of TG in the hyperlipidemic rats was ameliorated by the inhibition of the transcription of carbohydrate reaction element binding protein genes and activation of the transcription of PPARalpha genes. The regulation of lipid metabolism-related gene transcription by the single probiotic (Lactobacillus rhamnosus LV108)-fermented milk was more effective than that by the combined probiotic (L. rhamnosus LV108, Lactobacillus casei grx12, and Lactobacillus fermentum grx08)-fermented milk ($P < 0.05$).

[21] *Despas F, Rousseau V, Lafaurie M et al.* **Are Lipid-lowering drugs associated with a risk of cataract? A pharmacovigilance study**. Fundamental & clinical pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31251421

ABSTRACT

Some reports have raised concerns regarding a potential risk of cataracts associated with statins. However, clinical and observational studies evaluating the risk led to conflicting results. We assessed whether lipid-lowering drugs (LLD) use is associated with an increased risk of cataract using the WHO individual case safety reports database, VigiBase(R). We performed a disproportionality analysis with all reports between 1/1/1988 and 31/12/2018 to measure the reporting risk of "cataract" in patients >/=45 years. Primary analysis compared LLD users to non-users. To mitigate some potential confounding bias, we performed several sensitivity analyses excluding reports 1) with an association of at least two LLD, 2) with antidiabetic and glucocorticoids, 3) with lovastatin. We also analyzed the data according to the different classes of age and limiting the period of study to years 2002-2012. We identified 14,664 reports of cataract (3,049 in LLD users, 66% women, 66+/-20 years). Statins (84%, atorvastatin, simvastatin, rosuvastatin and lovastatin) were mostly reported, followed by fibrates (5.7%), nicotinic acid (3%), bile acid sequestrants (2%), herbal cholesterol and triglyceride reducers (2%) and others (ezetimibe, PCSK9 inhibitors, 15%). LLD users were associated with a greater risk of reports than non-users (ROR 2.47, 95% CI 2.37-2.57). This association was also found for statins in general, fibrates, bile sequestrants, nicotinic acid, herbal drugs and others. Similar trends were observed in sensitivity analyses (except for fibrates and nicotinic acid after exclusion of reports with at least two LLD or in older patients >/= 75 years). Using a large real life database (> 18.5 million reports), we found a signal of cataract for LLD as a whole and statins, bile sequestrants and herbal drugs in particular. The signal disappeared for fibrates and nicotinic acid in older patients. No definite conclusions can be made for ezetimibe or PCSK9 inhibitors (evolocumab and alirocumab). This suggests that a decrease in cholesterol could be important in the pathophysiology of cataract in patients exposed to the main LLD.

Literature update week 26 (2019)

[22] *Oster H*. **Circadian enhancer profiling in diet-induced obese mice reveals a critical time window for lipid-lowering therapies**. Hepatobiliary surgery and nutrition 2019; 8:280-282.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31245414
ABSTRACT

[23] *Del Pinto R, Grassi D, Properzi G et al.* **Low Density Lipoprotein (LDL) Cholesterol as a Causal Role for Atherosclerotic Disease: Potential Role of PCSK9 Inhibitors**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2019; 26:199-207.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31236902
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9)-related discoveries of the turn of the century have translated into substantial novelty in dyslipidemia treatment in the last 5 years. With chronic preventable atherosclerotic cardiovascular diseases (ASCVD) representing an epidemic of morbidity and mortality worldwide, low-density lipoprotein cholesterol (LDL-c) reduction represents a public health priority. By overcoming two major statin-related issues, namely intolerance and ineffectiveness, PCSK9 inhibitors have offered a safe and effective option in selected clinical settings where LDL-c reduction is required. Herein, we recapitulate recent findings, clinical applications, and ASCVD prevention potential of PCSK9 inhibition, with focus on anti-PCSK9 monoclonal antibodies, evolocumab and alirocumab.

[24] *Hassan AM, Shawky MAE, Mohammed AQ et al.* **Simvastatin improves the eradication rate of Helicobacter pylori: upper Egypt experience**. Infection and drug resistance 2019; 12:1529-1534.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31239728
ABSTRACT
Background: Helicobacter pylori infection is one of the most prevalent chronic bacterial human infections worldwide. Helicobacter pylori colonizes the gastric mucosa and causes persistent gastritis that may progress to gastric cancer. Increased resistance of H. pylori presents a major problem in most countries. Statins, including simvastatin, which are currently used to treat hypercholesterolemia, appear to have potential synergistic role to antibiotics. This study aimed to assess the value of adding simvastatin as adjuvant to standard triple therapy in patients infected with H. pylori. Methods: This study was conducted on 100 patients diagnosed with H. pylori by the presence of antigen in stools. All patients were randomly subjected either to the standard triple regimen (clarithromycin 500 mg bid + amoxicillin 1 g bid + omeprazole 20 mg bid) (group 1, N=50) or to the standard triple regimen plus simvastatin (clarithromycin 500 mg bid + amoxicillin 1 g bid + omeprazole 20 mg bid + simvastatin 20 mg bid) (group 2, N=50). Both groups were treated for 14 days and eradication of H. pylori was assessed by a stool antigen test 4 weeks after therapy. Results: Eradication of H. pylori infection was significantly higher in patients treated with the standard triple therapy plus simvastatin (n=41, 82%) than in patients treated with the standard triple therapy (n=31, 62%) (P<0.022). Conclusion: Simvastatin significantly improves the H. pylori eradication rate.

Literature update week 26 (2019)

[25] *Deng Y, Zou W, Chen G et al.* **Comparative studies on the effects of different doses of atorvastatin combined with aspirin on inflammatory cytokines and carotid plaques in patients with ischemic cerebrovascular disease**. The International journal of neuroscience 2019:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31232139

ABSTRACT

Objective: To make comparative studies on the effects of different doses of atorvastatin combined with aspirin on inflammatory cytokines, blood lipids, blood glucose, other biochemical indexes and carotid plaques in patients with ischemic cerebrovascular disease (ICVD) and carotid plaques. Method: 120 patients with ICVD and carotid plaques admitted by Renmin Hospital, Hubei University of Medicine Hospital from December 2016 to December 2017 were selected and randomly divided into experimental group and control group, 60 cases in each group. Patients in the control group was asked to orally take standard dose of atorvastatin (20mg/d) combined with aspirin enteric-coated tablets (100mg/d). Patients in the experimental group was asked to orally take high-dose atorvastatin (40mg/d) combined with the same amount of aspirin enteric-coated tablets. Patients in two groups were treated for 6 months averagely. The levels of inflammatory factors, changes in blood biochemical parameters, and carotid plaque degrees of patients in two groups before and after treatment were inspected and compared. Results: The levels of serum high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF-a), interleukin-6 (IL-6) and homocysteine (Hcy) in patients of the experimental group after treatment were higher than those in the control group, difference with statistical significance ($P < 0.05$). The total cholesterol (TC), triglyceride (TG) and low density lipoprotein cholesterol (LDL-C) in patients of the experimental group after treatment were lower than those in the control group and before treatment. The high-density lipoprotein cholesterol (HDL-C) was higher than that of the control group and before treatment, the levels of fasting blood glucose (FBS) and glycosylated hemoglobin (HbAIc) in patients of the experimental group significantly increased compared to those before treatment, difference with statistical significance ($P < 0.05$). There was no significant change in the control group. The carotid intima-media thickness (IMT) and plaque area in patients of the experimental group were lower than those in the control group and before treatment, difference with statistical significance ($P < 0.05$). Conclusion: High-dose atorvastatin combined with aspirin for treatment of patients with ICVD can effectively reduce inflammatory inflammatory cytokine levels in serum and reduce IMT and carotid plaque area. With more obvious effect than lower dose of atorvastatin combined with aspirin, it is easy to cause blood glucose abnormality. So, it is necessary to pay attention to monitoring blood sugar during medication period.

[26] *Lutjohann D.* **[Sitosterolemia (phytosterolemia)]**. Internist (Berl) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31254003

ABSTRACT

Sitosterolemia or phytosterolemia is a rare autosomal recessive hereditary lipid storage disorder. It is caused by homozygous or compound heterozygous mutations in one of the two ABCG5 and ABCG8 genes encoding the intestinal and hepatic heterodimer ABCG5 (sterolin 1)/ABCG8 (sterolin 2) efflux transporters. These mutations lead to intestinal hyperabsorption and reduced hepatic secretion of cholesterol and plant sterols with subsequent accumulation of phytosterols and cholesterol in plasma and deposition in tissue (xanthoma). Phytosterols are

found mainly in vegetable oils, margarine, nuts, grains, soybeans and avocados. Patients with sitosterolemia show extreme phenotypic heterogeneity from almost asymptomatic individuals to those with combined severe hypercholesterolemia at a young age, leading to increased atherosclerosis and premature cardiac death. Early abnormalities include hemolytic anemia with stomatocytosis, macrothrombocytopenia and splenomegaly. In addition to strict avoidance of phytosterol-containing foods, the use of the sterol absorption inhibitor ezetimibe, possibly in combination with the bile acid-binding resin cholestyramine, is the most effective treatment option.

[27] *Koyama S, Horie T, Nishino T et al.* **Identification of Differential Roles of MicroRNA-33a and -33b During Atherosclerosis Progression With Genetically Modified Mice**. Journal of the American Heart Association 2019; 8:e012609.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31242815
ABSTRACT
Background Micro RNA (miR)-33 targets cholesterol transporter ATP -binding cassette protein A1 and other antiatherogenic targets and contributes to atherogenic progression. Its inhibition or deletion is known to result in the amelioration of atherosclerosis in mice. However, mice lack the other member of the miR-33 family, miR-33b, which exists in humans and other large mammals. Thus, precise evaluation and comparison of the responsibilities of these 2 miRs during the progression of atherosclerosis has not been reported, although they are essential. Methods and Results In this study, we performed a comprehensive analysis of the difference between the function of miR-33a and miR-33b using genetically modified mice. We generated 4 strains with or without miR-33a and miR-33b. Comparison between mice with only miR-33a (wild-type mice) and mice with only miR-33b (miR-33a(-/-)/miR-33b(+/+)) revealed the dominant expression of miR-33b in the liver. To evaluate the whole body atherogenic potency of miR-33a and miR-33b, we developed apolipoprotein E-deficient/miR-33a(+/+)/miR-33b(-/-) mice and apolipoprotein E-deficient/miR-33a(-/-)/miR-33b(+/+) mice. With a high-fat and high-cholesterol diet, the apolipoprotein E-deficient/miR-33a(-/-)/miR-33b(+/+) mice developed increased atherosclerotic plaque versus apolipoprotein E-deficient/miR-33a(+/+)/miR-33b(-/-) mice, in line with the predominant expression of miR-33b in the liver and worsened serum cholesterol profile. By contrast, a bone marrow transplantation study showed no significant difference, which was consistent with the relevant expression levels of miR-33a and miR-33b in bone marrow cells. Conclusions The miR-33 family exhibits differences in distribution and regulation and particularly in the progression of atherosclerosis; miR-33b would be more potent than miR-33a.

[28] *Visscher M, Moerman AM, Burgers PC et al.* **Data Processing Pipeline for Lipid Profiling of Carotid Atherosclerotic Plaque with Mass Spectrometry Imaging**. Journal of the American Society for Mass Spectrometry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31250318
ABSTRACT
Atherosclerosis is a lipid and inflammation-driven disease of the arteries that is characterized by gradual buildup of plaques in the vascular wall. A so-called vulnerable plaque, consisting of a lipid-rich necrotic core contained by a thin fibrous cap, may rupture and trigger thrombus

formation, which can lead to ischemia in the heart (heart attack) or in the brain (stroke). In this study, we present a protocol to investigate the lipid composition of advanced human carotid plaques using matrix-assisted laser desorption ionization (MALDI) mass spectrometry imaging (MSI), providing a framework that should enable the discrimination of vulnerable from stable plaques based on lipid composition. We optimized the tissue preparation and imaging methods by systematically analyzing data from three specimens: two human carotid endarterectomy samples (advanced plaque) and one autopsy sample (early stage plaque). We show a robust data reduction method and evaluate the variability of the endarterectomy samples. We found diacylglycerols to be more abundant in a thrombotic area compared to other plaque areas and could distinguish advanced plaque from early stage plaque based on cholesteryl ester composition. We plan to use this systematic approach to analyze a larger dataset of carotid atherosclerotic plaques.

[29] *Makino H, Koezuka R, Tamanaha T et al.* **Familial Hypercholesterolemia and Lipoprotein Apheresis**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31231083
ABSTRACT
Lipoprotein apheresis has been developed as the treatment for refractory familial hypercholesterolemia (FH) to remove low-density lipoprotein (LDL), which is the main pathogenic factor. Currently, three procedures are available in Japan, including the plasma exchange, double-membrane filtration, and selective LDL adsorption. Selective LDL adsorption, which was developed in Japan, has been one of the most common treatment methods in the world. Lipoprotein apheresis enabled the prevention of atherosclerosis progression even in homozygous FH (HoFH) patients. However, in our observational study, HoFH patients who started lipoprotein apheresis in adulthood had a poorer prognosis than those who started in childhood. Therefore, HoFH patients need to start lipoprotein apheresis as early as possible. Although the indication for lipoprotein apheresis in heterozygous FH (HeFH) patients has been decreasing with the advent of strong statins, our observational study showed that HeFH patients who discontinued lipoprotein apheresis had a poorer prognosis than patients who continued apheresis therapy. These results suggest that it is beneficial for very-high-risk HeFH patients to be treated by lipoprotein apheresis even if their LDL cholesterol is controlled well by lipid-lowering agents. Since launching a new class of lipid-lowering agents, proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody and microsome triglyceride transfer protein inhibitors, the indication for lipoprotein apheresis in FH has been changing. However, despite the development of these drugs, lipoprotein apheresis is still an option with a high therapeutic effect for FH patients with severe atherosclerotic cardiovascular disease.

[30] *Peng M, Dong H, Jiang X et al.* **A randomized unblinded trial to compare effects of intensive versus conventional lipid-lowering therapy in patients undergoing renal artery stenting**. J Cardiol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31235418
ABSTRACT
BACKGROUND: Although current guidelines recommend the use of statins for severe atherosclerotic renal artery stenosis (ARAS), the renal protection of intensive lipid-lowering

therapy in patients with ARAS who underwent stent placement remains uncertain. The aim of this study was to compare the renal-protective effect of intensive lipid lowering with that of conventional lipid lowering in patients with ARAS undergoing stent placement. METHODS: A total 150 patients with severe ARAS undergoing stent placement were randomly (1:1) assigned to receive intensive lipid lowering [target low-density lipoprotein cholesterol (LDL-C) <70mg/dL] or conventional lipid lowering (target LDL-C >/=70mg/dL, <128mg/dL). All patients received rosuvastatin. We adjusted LDL-C to the goal within two months after renal stenting and maintained stability. The primary endpoint was the change in estimated glomerular filtration rate (eGFR) at 12 months. RESULTS: During the study period, LDL-C was lower in the patients with intensive lipid lowering than with conventional lipid lowering (at 12 months 58.0+/-11.6 vs 85.1+/-15.5mg/dL, p<0.001). At 12-month follow-up, eGFR (91.8+/-30.2 vs 78.5+/-19.5)mL/min.1.73m(2), p=0.002) and the increase in eGFR compared to baseline [14.8(IQR, 4.1, 26.7) vs -0.4(IQR, -9.5, 8.0)mL/min.1.73m(2), p<0.001] were higher in the patients with intensive lipid lowering than with conventional lipid lowering. Urinary albumin-creatinine ratio [42.2(IQR, 20.0, 60.9) vs 60.8(IQR, 26.8, 121.6)mg/g, p=0.032] was lower and the decrease in urinary albumin-creatinine ratio compared to baseline [27.4(IQR, 3.0, 53.8) vs -3.1(IQR, -17.3, 30.9)mg/g, p=0.001] was higher in the patients with intensive lipid lowering than with conventional lipid lowering. The restenosis rate (3.1% vs 3.4%, p=0.711) and major clinical events (6.8% vs 11.0%, p=0.37) were similar between the two groups. CONCLUSIONS: In patients with severe ARAS undergoing stent placement, intensive lipid lowering showed significant benefits in renal protection over conventional lipid-lowering therapy.

[31] *Chi B, Fan X, Li Z et al.* **Identification of Gli1-interacting proteins during simvastatin-stimulated osteogenic differentiation of bone marrow mesenchymal stem cells**. Journal of cellular biochemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31245876
ABSTRACT
Simvastatin has been shown to promote osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs). Our study aimed to illuminate the underlying mechanism, with a specific focus on the role of Hedgehog signaling in this process. BMSCs cultured with or without 10(-7) mol/L simvastatin were subjected to evaluation of osteogenic differentiation capacity. Osteogenic markers such as type 1 collagen (COL1) and osteocalcin (OCN), as well as key molecules of Hedgehog signaling molecules, were examined by Western blot and real-time polymerase chain reaction (PCR). Co-immunoprecipitation and mass spectrometry assays were applied to screen for Gli1-interacting proteins. Cyclopamine (Cpn) was used as a Hedgehog signaling inhibitor. Our results indicated that simvastatin increased alkaline phosphatase (ALP) activity; mineralization of extracellular matrix; mRNA expression of ALP, COL1, and OCN; and expression and nuclear translocation of Gli1. Contrasting effects were observed in Cpn-exposed groups, but were partially rescued by the simvastatin treatment. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses indicated that Gli1-interacting proteins were primarily associated with mitogen-activated protein kinase (MAPK) (P = 7.04E(-04)), hippo, insulin, and glucagon signaling. Further, hub genes identified by protein-protein interaction network analysis included Gli1-interacting proteins such as Ppp2r1a, Rac1, Etf1, and XPO1/CRM1. In summary, the current study showed that the mechanism by which simvastatin

stimulates osteogenic differentiation of BMSCs involves activation of Hedgehog signaling, as indicated by interactions with Gli1 and, most notably, the MAPK signaling pathway.

[32] *Braun LT, Saseen JJ, Orringer CE et al.* **JCL roundtable. The 2018 AHA/ACC/Multisociety Cholesterol Guidelines: Process and product**. Journal of clinical lipidology 2019; 13:345-355.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31229021
ABSTRACT
In this NLA Roundtable four members of the writing committee join the Editor to discuss the process of developing the AHA/ACC/Multisociety Cholesterol Guidelines, which were unveiled in November 2018. They also provide personal insights on the finished product. Highlights include 1) the committee's decision to summarize 10 take-home messages providing rapid communication of key points, 2) emphasis on clinician -patient discussion, which may bring up issues specific to women or other population groups at risk, 3) personalizing risk with risk-enhancing factors such as LDL-C >/= 160 mg/dl, metabolic syndrome, chronic kidney disease, pre-eclampsia, premature menopause, high risk ethnicity, inflammatory diseases, hypertriglyceridemia and in selected cases, Lp(a), hs-CRP and apoB; 4) using coronary artery calcium scoring when a risk decision is uncertain in intermediate risk patients 5) monitoring for goals of moderate or intensive LDL cholesterol reduction, 6) thresholds for adding nonstatin LDL-lowering therapy in those at very high risk or for heterozygous familial hypercholesterolemia and 7) cost value assessment for expensive treatment.

[33] *Vega GL, Grundy SM*. **Current trends in non-HDL cholesterol and LDL cholesterol levels in adults with atherosclerotic cardiovascular disease**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31248654
ABSTRACT
BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) are targets for prevention of atherosclerotic cardiovascular disease (ASCVD). The American Heart Association and American College of Cardiology recently modified recommendations for clinical management of cholesterol in secondary and primary prevention. Accordingly, the present article examines the need for cholesterol-lowering drugs in the U.S. population with ASCVD. OBJECTIVE: This study examines trends in non-HDL-C and LDL-C levels in a free living population of ASCVD subjects between 1999 and 2016. METHODS: National Health and Nutrition Examination Surveys database included 4920 adults with ASCVD aged 40 to 85 years. Complete data were available for 4226. Trend analysis of changes in lipids is shown in box plots. RESULTS: Mean age was 67 years with 57% males. Over 17 years, LDL-C decreased significantly by 24% and non-HDL-C by 21%. Over the period of study, reported intake of cholesterol-lowering drugs rose from 37% in 1999-2000 to 69% in 2015 to 2016. Over this same period, serum triglycerides decreased by 29% ($P < .001$) and HDL-C rose by 6%. CONCLUSIONS: The changes in LDL-C and non-HDL-C in patients with ASCVD over a 17-year period probably are related to increased treatment with statins. However, the changes are too small to be explained by widespread use of high-intensity statins, which is the current recommendation for patients with ASCVD. These findings pose a challenge for professional education to support implementation of current guidelines for cholesterol-lowering therapies.

[34] *Baggett MC, Nykamp D*. **Statin-Associated Bilateral Foot Myopathy**. Journal of pharmacy practice 2019:897190019857851.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31248326
ABSTRACT
OBJECTIVE: To report a case of statin-induced bilateral foot myopathy that resulted from 2 different statins. CASE SUMMARY: A 44-year-old Caucasian male with a history of ventricular fibrillation cardiac arrest, hyperlipidemia, and coronary artery disease experienced bilateral foot pain, weakness, and soreness while taking atorvastatin 20 mg daily. The pain subsided within weeks of discontinuing atorvastatin but returned years later after the initiation of rosuvastatin. The Naranjo probability scale indicates that this is a definite association between bilateral foot myopathy and statin use. DISCUSSION: There is an association with statin use and lowering cardiovascular risk in patients with dyslipidemia and cardiovascular disease. However, statin metabolites can accumulate in the myocytes of muscle groups to cause a common side effect of myopathy. Statin myopathy typically occurs in large, bilateral, or proximal muscle groups, such as the thighs, back, calves, or buttocks. This patient was unusual in that his muscle symptoms only occurred in his feet and was severe enough to affect his ambulation. CONCLUSION: Stain-associated muscle symptoms have been reported to lessen medication adherence. There is also a risk with muscle symptoms that the patient could develop rhabdomyolysis, a rare but serious condition. Recognizing statin-associated muscle symptoms even in uncommon locations is important, so that alternative lipid-lowering strategies can be implemented to lower cardiovascular risk.

[35] *Walther CP, Erickson KF*. **The cost-effectiveness of lipid lowering for primary cardiovascular prevention in chronic kidney disease: moving beyond statins**. Kidney international 2019; 96:22-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31229030
ABSTRACT
Because of high risk of cardiovascular disease, patients with chronic kidney disease may benefit from cholesterol-lowering therapy beyond statins. A cost-effectiveness analysis of adding ezetimibe to high-dose statins for primary cardiovascular disease prevention in patients with non-dialysis-dependent chronic kidney disease found treatment with ezetimibe to be cost-effective for many patients with chronic kidney disease. We describe the importance of this topic and explain key assumptions necessary for the investigators to arrive at their conclusions.

[36] *Liu SH, Chiu CY, Wang LP, Chiang MT*. **Omega-3 Fatty Acids-Enriched Fish Oil Activates AMPK/PGC-1alpha Signaling and Prevents Obesity-Related Skeletal Muscle Wasting**. Marine drugs 2019; 17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31242648
ABSTRACT
Obesity is known to cause skeletal muscle wasting. This study investigated the effect and the possible mechanism of fish oil on skeletal muscle wasting in an obese rat model. High-fat (HF) diets were applied to induce the defects of lipid metabolism in male Sprague-Dawley rats with or without substitution of omega-3 fatty acids-enriched fish oil (FO, 5%) for eight weeks. Diets supplemented with 5% FO showed a significant decrease in the final body weight compared to

HF diet-fed rats. The decreased soleus muscle weights in HF diet-fed rats could be improved by FO substitution. The decreased myosin heavy chain (a muscle thick filament protein) and increased FOXO3A and Atrogin-1 (muscle atrophy-related proteins) protein expressions in soleus muscles of HF diet-fed rats could also be reversed by FO substitution. FO substitution could also significantly activate adenosine monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation, peroxisome-proliferator-activated receptor-gamma (PPARgamma) coactivator 1alpha (PGC-1alpha), and PPARgamma protein expression and lipoprotein lipase (LPL) mRNA expression in soleus muscles of HF diet-fed rats. These results suggest that substitution of FO exerts a beneficial improvement in the imbalance of lipid and muscle metabolisms in obesity. AMPK/PGC-1alpha signaling may play an important role in FO-prevented obesity-induced muscle wasting.

[37] *Parolini C*. **Effects of Fish n-3 PUFAs on Intestinal Microbiota and Immune System**. Marine drugs 2019; 17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31234533
ABSTRACT
Studies over several decades have documented the beneficial actions of n-3 polyunsaturated fatty acids (PUFAs), which are plentiful in fish oil, in different disease states. Mechanisms responsible for the efficacy of n-3 PUFAs include: (1) Reduction of triglyceride levels; (2) anti-arrhythmic and antithrombotic effects, and (3) resolution of inflammatory processes. The human microbiota project and subsequent studies using next-generation sequencing technology have highlighted that thousands of different microbial species are present in the human gut, and that there has been a significant variability of taxa in the microbiota composition among people. Several factors (gestational age, mode of delivery, diet, sanitation and antibiotic treatment) influence the bacterial community in the human gastrointestinal tract, and among these diet habits play a crucial role. The disturbances in the gut microbiota composition, i.e., gut dysbiosis, have been associated with diseases ranging from localized gastrointestinal disorders to neurologic, respiratory, metabolic, ocular, and cardiovascular illnesses. Many studies have been published about the effects of probiotics and prebiotics on the gut microbiota/microbioma. On the contrary, PUFAs in the gut microbiota have been less well defined. However, experimental studies suggested that gut microbiota, n-3 PUFAs, and host immune cells work together to ensure the intestinal wall integrity. This review discussed current evidence concerning the links among gut microbiota, n-3 PUFAs intake, and human inflammatory disease.

[38] *Wang Y, Shi Y, Xu X et al.* **Effects of probucol on contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention**. Medicine (Baltimore) 2019; 98:e16049.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31232940
ABSTRACT
OBJECTIVE: This study was performed to explore the effects of probucol on contrast-induced acute kidney injury (CIAKI) in patients with coronary heart disease undergoing percutaneous coronary intervention (PCI). METHODS: In total, 220 patients undergoing PCI were randomly assigned to either the control group (hydration from 12 hours before to 12 hours after contrast

administration; n = 110) or the probucol group (hydration plus probucol 500 mg twice daily 1 day before and 3 days after the operation; n = 110). The primary endpoint was the occurrence of serum creatinine (Scr)-based CIAKI, defined as an absolute increase in Scr by 0.5 mg/dl (44.2 mumol/L) or a relative 25% increase from baseline within 48 to 72 hours after exposure to contrast medium. The secondary outcomes were composite variations in Scr, blood urea nitrogen (BUN), creatinine clearance rate (Ccr) within 48 to 72 hours, and major adverse events during hospitalization or the 7-day follow-up period after PCI. RESULTS: The overall incidence of Scr-based CIAKI was 7.3% (16/220): 5.5% (6/110) in the control group and 9.1% (10/110) in the probucol group (chi = 1.078, P = .298). There were no significant differences in the occurrence rate of major adverse events during hospitalization or the 7-day follow-up period after PCI between the groups. Multivariate logistic regression analysis showed that probucol was not an independent protective factor for CIAKI (odds ratio, 1.825; 95% confidence interval, 0.639-5.212; P = .261). However, hydration was an independent protective factor (odds ratio, 0.997; 95% confidence interval, 0.995-0.999; P = .004). CONCLUSION: Probucol cannot effectively reduce the incidence of CIAKI through its anti-inflammatory and antioxidative stress effects.

[39] *Soll D, Spira D, Hollstein T et al.* **Clinical outcome of a patient with lysosomal acid lipase deficiency and first results after initiation of treatment with Sebelipase alfa: A case report**. Molecular genetics and metabolism reports 2019; 20:100479.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31249784

ABSTRACT

We report on a case of very rare autosomal recessive cholesteryl ester storage disease due to lysosomal acid lipase deficiency (LALD). LALD is caused by mutations in the lysosomal acid lipase A (LIPA) gene resulting in cholesteryl ester accumulation in liver, spleen, and macrophages. It can lead to liver failure, accelerated atherosclerosis and premature death. Until recently, treatment options were limited to lipid-lowering medications to control dyslipidemia. Presently, a long-term enzyme replacement therapy with Sebelipase alfa, a recombinant human lysosomal acid lipase, is available for patients with LALD. Our patient's condition became conspicuous at the age of two due to a xanthogranuloma of the chin together with increased lipid levels, elevated liver enzymes and hepatomegaly. It took another five years until our patient was diagnosed with LALD after genetic testing. A bi-weekly therapy with intravenous Sebelipase alfa was started at the age of 26years. It led to normalization of lipid levels, reduction of liver enzymes and beginning regression of hepatomegaly in the absence of adverse drug reactions after 46 infusions. Since LALD can take a fatal course even in patients with a long-term stable condition, it is essential to identify affected patients early and to treat them appropriately by enzyme replacement therapy. LALD should be suspected in patients with low high-density lipoprotein cholesterol (HDL-C) and high low-density lipoprotein cholesterol (LDL-C) in conjunction with elevated liver enzymes or hepatomegaly. A registry for LALD patients shall help to advance our understanding of the disease as well as improve patient care (NCT01633489).

[40] *Basatemur GL, Jorgensen HF, Clarke MCH et al.* **Vascular smooth muscle cells in atherosclerosis**. Nature reviews. Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31243391

ABSTRACT
Vascular smooth muscle cells (VSMCs) are a major cell type present at all stages of an atherosclerotic plaque. According to the 'response to injury' and 'vulnerable plaque' hypotheses, contractile VSMCs recruited from the media undergo phenotypic conversion to proliferative synthetic cells that generate extracellular matrix to form the fibrous cap and hence stabilize plaques. However, lineage-tracing studies have highlighted flaws in the interpretation of former studies, revealing that these studies had underestimated both the content and functions of VSMCs in plaques and have thus challenged our view on the role of VSMCs in atherosclerosis. VSMCs are more plastic than previously recognized and can adopt alternative phenotypes, including phenotypes resembling foam cells, macrophages, mesenchymal stem cells and osteochondrogenic cells, which could contribute both positively and negatively to disease progression. In this Review, we present the evidence for VSMC plasticity and summarize the roles of VSMCs and VSMC-derived cells in atherosclerotic plaque development and progression. Correct attribution and spatiotemporal resolution of clinically beneficial and detrimental processes will underpin the success of any therapeutic intervention aimed at VSMCs and their derivatives.

[41] *Leyrolle Q, Laye S, Nadjar A*. **Direct and indirect effects of lipids on microglia function**. Neurosci Lett 2019:134348.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31238131
ABSTRACT
Microglia are key players in brain function by maintaining brain homeostasis across lifetime. They participate to brain development and maturation through their ability to release neurotrophic factors, to remove immature synapses or unnecessary neural progenitors. They modulate neuronal activity in healthy adult brains and they also orchestrate the neuroinflammatory response in various pathophysiological contexts such as aging and neurodegenerative diseases. One of the main features of microglia is their high sensitivity to environmental factors, partly via the expression of a wide range of receptors. Recent data pinpoint that dietary fatty acids modulate microglia function. Both the quantity and the type of fatty acid are potent modulators of microglia physiology. The present review aims at dissecting the current knowledge on the direct and indirect mechanisms (focus on gut microbiota and hormones) through which fatty acids influence microglial physiology. We summarize main discoveries from in vitro and in vivo models on fatty acid-mediated microglial modulation. All these studies represent a promising field of research that could promote using nutrition as a novel therapeutic or preventive tool in diseases involving microglia dysfunctions.

[42] *Clifton P*. **Metabolic Syndrome-Role of Dietary Fat Type and Quantity**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31247933
ABSTRACT
BACKGROUND: Metabolic syndrome increases the risk of cardiovascular disease (CVD) over and above that related to type 2 diabetes. The optimal diet for the treatment of metabolic syndrome is not clear. MATERIALS AND METHODS: A review of dietary interventions in volunteers with metabolic syndrome as well as studies examining the impact of dietary fat on the separate components of metabolic syndrome was undertaken using only recent meta-

analyses, if available. RESULTS: Most of the data suggest that replacing carbohydrates with any fat, but particularly polyunsaturated fat, will lower triglyceride(TG), increase high density lipoprotein (HDL) cholesterol, and lower blood pressure, but have no effects on fasting glucose in normal volunteers or insulin sensitivity, as assessed by euglycemic hyperinsulinemic clamps. Fasting insulin may be lowered by fat. Monounsaturated fat (MUFA) is preferable to polyunsaturated fat (PUFA) for fasting insulin and glucose lowering. The addition of 3-4 g of N3 fats will lower TG and blood pressure (BP) and reduce the proportion of subjects with metabolic syndrome. Dairy fat (50% saturated fat) is also related to a lower incidence of metabolic syndrome in cohort studies.

[43] *Martin-Acebes MA, Jimenez de Oya N, Saiz JC*. **Lipid Metabolism as a Source of Druggable Targets for Antiviral Discovery against Zika and Other Flaviviruses**. Pharmaceuticals (Basel, Switzerland) 2019; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31234348
ABSTRACT
The Zika virus (ZIKV) is a mosquito-borne flavivirus that can lead to birth defects (microcephaly), ocular lesions and neurological disorders (Guillain-Barre syndrome). There is no licensed vaccine or antiviral treatment against ZIKV infection. The effort to understand the complex interactions of ZIKV with cellular networks contributes to the identification of novel host-directed antiviral (HDA) candidates. Among the cellular pathways involved in infection, lipid metabolism gains attention. In ZIKV-infected cells lipid metabolism attributed to intracellular membrane remodeling, virion morphogenesis, autophagy modulation, innate immunity and inflammation. The key roles played by the cellular structures associated with lipid metabolism, such as peroxisomes and lipid droplets, are starting to be deciphered. Consequently, there is a wide variety of lipid-related antiviral strategies that are currently under consideration, which include an inhibition of sterol regulatory element-binding proteins (SREBP), the activation of adenosine-monophosphate activated kinase (AMPK), an inhibition of acetyl-Coenzyme A carboxylase (ACC), interference with sphingolipid metabolism, blockage of intracellular cholesterol trafficking, or a treatment with cholesterol derivatives. Remarkably, most of the HDAs identified in these studies are also effective against flaviviruses other than ZIKV (West Nile virus and dengue virus), supporting their broad-spectrum effect. Considering that lipid metabolism is one of the main cellular pathways suitable for pharmacological intervention, the idea of repositioning drugs targeting lipid metabolism as antiviral candidates is gaining force.

[44] *Kongpakwattana K, Ademi Z, Chaiyasothi T et al.* **Cost-Effectiveness Analysis of Non-Statin Lipid-Modifying Agents for Secondary Cardiovascular Disease Prevention Among Statin-Treated Patients in Thailand**. PharmacoEconomics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31243736
ABSTRACT
BACKGROUND: Using non-statin lipid-modifying agents in combination with statin therapy provides additional benefits for cardiovascular disease (CVD) risk reduction, but their value for money has only been evaluated in high-income countries (HICs). Furthermore, studies mainly derive effectiveness data from a single trial or older meta-analyses. OBJECTIVES: Our study used data from the most recent network meta-analysis (NMA) and local parameters to assess the

cost effectiveness of non-statin agents in statin-treated patients with a history of CVD. METHODS: A published Markov model was adopted to investigate lifetime outcomes: (1) number of recurrent CVD events prevented, (2) quality-adjusted life-years (QALYs) gained, (3) costs and (4) incremental cost-effectiveness ratios (ICERs) of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) and ezetimibe added to statin therapy. Event rates and effectiveness inputs were obtained from the NMA. Cost and utility data were gathered from published studies conducted in Thailand. A series of sensitivity analyses were performed. RESULTS: Patients receiving PCSK9i and ezetimibe experienced fewer recurrent CVD events (number needed to treat [NNT] 17 and 30) and more QALYs (0.168 and 0.096 QALYs gained per person). However, under the societal perspective and at current acquisition costs in 2018, ICERs of both agents were $US1,223,995 and 27,361 per QALY gained, respectively. Based on threshold analyses, the costs need to be reduced by 97 and 85%, respectively, for PCSK9i and ezetimibe to be cost-effective. CONCLUSIONS: Despite the proven effectiveness of PCSK9i and ezetimibe, the costs of these agents need to reduce to a much greater extent than in HICs to be cost-effective in Thailand.

[45] *Novikova OA, Nazarkina ZK, Cherepanova AV et al.* **Isolation, culturing and gene expression profiling of inner mass cells from stable and vulnerable carotid atherosclerotic plaques**. PloS one 2019; 14:e0218892.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31242269
ABSTRACT
The connective tissue components that form the atherosclerotic plaque body are produced by the plaque inner mass cells (PIMC), located inside the plaque. We report an approach to isolate and culture cells from the connective tissue of stable and vulnerable human atherosclerotic plaques based on elimination of non-connective tissue cells such as blood and non-plaque intima cells with a lysis buffer. The resulting plaque cells were characterized by growth capacity, morphology, transcriptome profiling and specific protein expression. Plaque cells slowly proliferated for up to three passages unaffected by the use of proliferation stimulants or changes of culture media composition. Stable plaques yielded more cells than vulnerable ones. Plaque cell cultures also contained several morphological cellular types. RNA-seq profiles of plaque cells were different from any of the cell types known to be involved in atherogenesis. The expression of the following proteins was observed in cultured plaque cells: smooth muscle cells marker alpha-SMA, macrophage marker CD14, extracellular matrix proteins aggrecan, fibronectin, neovascularisation markers VEGF-A, CD105, cellular adhesion receptor CD31 and progenitor/dedifferentiation receptor CD34. Differential expression of several notable transcripts in cells from stable and vulnerable plaques suggests the value of plaque cell culture studies for the search of plaque vulnerability markers.

[46] *Piran S, Sarmasti S, Shabani M et al.* **Associations between fat-soluble vitamins and lipid profile in overweight population**. Recent patents on food, nutrition & agriculture 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31237223
ABSTRACT
METHODS: A total of 120 overweight subjects participated in this study. The circulating PCSK9 and vitamin D were measured by ELISA technique. The serum vitamin A and vitamin E amounts

were simultaneously measured by HPLC method. The serum small dense LDL-Cholesterol (sdLDL-C) values were evaluated using heparin-Mg2+ precipitation technique. The lipid profile was measured by routine laboratory techniques. RESULTS: The serum vitamin E values correlated significantly to vitamin A (r=0.47, P= 0.0001), VLDL-C (r= 0.30, P= 0.002), total cholesterol (r=0.309, P= 0.001), PCSK9 (r=0.233, P=0.01) and total triglyceride (r= 0.61, P= 0.0001) values. The circulating PCSK9 values correlated significantly to LDL-C (r=0.17, P=0.05) and total cholesterol (r=0.23, P=0.009) values. However, there were not correlations between the levels of serum D and A vitamins, the serum LDL-C, sdLDL-C and total cholesterol values. CONCLUSION: The data showed the correlations between serum vitamin E and PCSK9-related LDL-C values lower than the normal range. Furthermore, the results suggested a nutritional need on the patents considering supplementation or fortification of vitamin E for the overweight subjects with higher LDL-C levels.

[47] *Xu J, Xiong YY, Li Q et al.* **Optimization of Timing and Times for Administration of Atorvastatin-Pretreated Mesenchymal Stem Cells in a Preclinical Model of Acute Myocardial Infarction**. Stem cells translational medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31245934
ABSTRACT
Our previous studies showed that the combination of atorvastatin (ATV) and single injection of ATV-pretreated mesenchymal stem cells (MSCs) ((ATV) -MSCs) at 1 week post-acute myocardial infarction (AMI) promoted MSC recruitment and survival. This study aimed to investigate whether the combinatorial therapy of intensive ATV with multiple injections of (ATV) -MSCs has greater efficacy at different stages to better define the optimal strategy for MSC therapy in AMI. In order to determine the optimal time window for MSC treatment, we first assessed stromal cell-derived factor-1 (SDF-1) dynamic expression and inflammation. Next, we compared MSC recruitment and differentiation, cardiac function, infarct size, and angiogenesis among animal groups with single, dual, and triple injections of (ATV) -MSCs at early (Early1, Early2, Early3), mid-term (Mid1, Mid2, Mid3), and late (Late1, Late2, Late3) stages. Compared with AMI control, intensive ATV significantly augmented SDF-1 expression 1.5 approximately 2.6-fold in peri-infarcted region with inhibited inflammation. (ATV) -MSCs implantation with ATV administration further enhanced MSC recruitment rate by 3.9% approximately 24.0%, improved left ventricular ejection fraction (LVEF) by 2.0% approximately 16.2%, and reduced infarct size in all groups 6 weeks post-AMI with most prominent improvement in mid groups and still effective in late groups. Mechanistically, (ATV) -MSCs remarkably suppressed inflammation and apoptosis while increasing angiogenesis. Furthermore, triple injections of (ATV) -MSCs were much more effective than single administration during early and mid-term stages of AMI with the best effects in Mid3 group. We conclude that the optimal strategy is multiple injections of (ATV) -MSCs combined with intensive ATV administration at mid-term stage of AMI. The translational potential of this strategy is clinically promising. Stem Cells Translational Medicine 2019.

[48] *Barale C, Frascaroli C, Cavalot F, Russo I*. **Hypercholesterolemia impairs the Glucagon-like peptide 1 action on platelets: Effects of a lipid-lowering treatment with simvastatin**. Thrombosis research 2019; 180:74-85.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31229924

ABSTRACT

BACKGROUND: The incretin hormone Glucagon-like peptide 1(GLP-1) plays a pivotal role in maintaining glucose homeostasis with effects also on the cardiovascular system. GLP-1 influences platelet functions by increasing the inhibitory action of nitric oxide (NO) and reducing oxidative stress. To date, the role of hypercholesterolemia (HyC) on platelet GLP-1 effects needs to be elucidated. METHODS: Forty-five subjects with primary HyC and twenty normocholesterolemic controls (NoC) were enrolled. In platelets from all subjects, the native GLP-1 (7-36), the truncated GLP-1 (9-36) and the GLP-1 analogue Liraglutide were evaluated in their ability to interfere with the activation of NO/PKG/VASP, PI-3K/Akt e MAPK/ERK-1/2 pathways and oxidative stress. Furthermore, in HyC subjects the role of a lipid-lowering therapy with statin on GLP-1 related peptide effects on platelet function was evaluated. RESULTS: Unlike in NoC, in platelets from HyC subjects the GLP-1 related peptides GLP-1 (7-36), GLP-1 (9-36) and Liraglutide all failed to: i) increase the antiaggregating effects of NO and the NO-induced VASP-ser239 phosphorylation, ii) decrease phosphorylation levels of Akt and ERK-2 and iii) reduce reactive oxygen species (ROS) generation. The treatment with simvastatin (40mg/die) in HyC (n=18) significantly reduced total and LDL cholesterol levels, platelet aggregability/activation, ROS production and NO action but did not modify platelet sensitivity to the GLP-1 effects. CONCLUSION: Collectively, these results indicate that hypercholesterolemia per se is characterized by a resistance to GLP-1 effects on platelets and this impairment is not corrected by treatment with simvastatin.

[49] *Zhao TY, Li Z, Lei S et al.* **Associations for BCO2, PCSK9, and TR1B1 Polymorphism and Lifestyle Factors with Ischemic Stroke: A Nested Case-Control Study**. Yonsei medical journal 2019; 60:659-666.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31250580

ABSTRACT

PURPOSE: To investigate associations for polymorphisms in beta-carotene 9',10'-oxygenase (BCO2, rs10431036 and rs11214109), proprotein convertase subtilisin kexin type 9 (PCSK9, rs11583680), and tribbles pseudokinase 1 (TRIB1, rs17321515 and rs2954029), as well as lifestyle factors, with ischemic stroke (IS). MATERIALS AND METHODS: This nested case-control study included 161 patients with IS and 483 matched control individuals. We collected medical reports, lifestyle details, and blood samples from individuals and used the PCR-ligase detection reaction method to genotype single nucleotide polymorphisms (SNPs). RESULTS: The GA+AA genotype of rs10431036 ($p<0.001$) and rs17321515 ($p=0.003$), the CT+TT genotype of rs11214109 ($p=0.005$), and the TA+AA genotype of rs2954029 ($p=0.006$) in dominant models increased the risk of IS. In additive models, the GG genotype of rs17321515 ($p=0.005$) and the TT genotype of rs2954029 ($p=0.008$) increased the risk of IS. Adequate intake of fruits/vegetables reduced the risk of IS ($p=0.005$). Although there was no interaction between genes and fruits/vegetables, people with inadequate intake of fruits/vegetables who carried a risk genotype had a higher risk of IS than those only having inadequate fruits/vegetables intake or those only carrying a risk genotype. Also, the haplotypes AC, AT, and GT (comprising rs10431036 and rs11214109) and GT (comprising rs2954029 and rs17321515) were found to be associated with an increased risk of IS ($p<0.05$). CONCLUSION: Polymorphisms in BCO2 and

TRIB1 and fruits/vegetables intake were associated with IS. These results provide the theoretical basis for gene screening to prevent chronic cerebrovascular diseases.