Literature update week 30 (2018)

[1] *Zarei L, Bahrami M, Farhad N et al.* **All-trans retinoic acid effectively reduces atheroma plaque size in a rabbit model of high-fat-induced atherosclerosis**. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30048051
ABSTRACT
BACKGROUND: Atherosclerosis (AS) is one of the most prevalent causes of death around the world. Since there are different types of risk factors, different types of medications focus on preventing atheromas and plaques from establishing or on preventing established plaques from growing. OBJECTIVES: The aim of this study was to evaluate the effect of all-trans retinoic acid (atRA) on AS in a rabbit model of fat-induced AS. MATERIAL AND METHODS: Atherosclerosis was induced by a high-fat diet (HFD) for 75 days. Thirty rabbits were randomly divided into 5 groups. Group 1 was the negative control group and received a normal diet. The animals in the other groups were fed a HFD. Group 2 (the AS positive control group) received no drugs, Group 3 received atorvastatin orally (20 mg/kg/day), Group 4 received atRA (5 mg/kg/day, orally), and Group 5 received both drugs. All medications were started on day 45 and continued until the end of the study. Fasting blood samples were obtained for lipid profile evaluation. The aorta sections were evaluated for maximum wall and intima thickness. RESULTS: Oral administration of atRA, atorvastatin or their combination significantly improved serum lipid profile ($p < 0.001$). Atorvastatin and atRA significantly decreased serum total cholesterol and LDL-cholesterol levels in HFD ($p < 0.001$). No difference was found in serum HDL-cholesterol levels among the studied groups. The HFD group (Group 2 - positive control) showed significant intima irregularities with fat deposition and foamy macrophage accumulation (atheroma). Administration of atRA and atorvastatin significantly decreased the size of atherosclerotic plaques (intima thickness). The maximum vessel wall and intima thickness were significantly decreased after atRA and atorvastatin administration ($p < 0.001$). No difference was found between atRA and atorvastatin effectiveness, but combination therapy significantly decreased AS size in comparison to using either of the drugs alone ($p < 0.001$). CONCLUSIONS: In reducing AS plaque size, atRA is as effective as atorvastatin. Additionally, the combination therapy of atRA and atorvastatin decreased AS size much more effectively, showing their synergistic effect. atRA can also improve the serum lipid profile.

[2] *Kerkhof PLM, Khamaganova I*. **Sex-Specific Cardiovascular Comorbidities with Associations in Dermatologic and Rheumatic Disorders**. Advances in experimental medicine and biology 2018; 1065:489-509.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30051403
ABSTRACT
Cardiology, dermatology, and rheumatology form a fascinating triad. Many skin and joint disorders are associated with cardiovascular comorbidities because they share etiologic elements. Female predominance is often remarkable and likely related to autoimmune pathology. Although studies have shown that X-encoded genes may be involved in the differences in immunity between males and females, other studies have also shown that sex chromosomes are irrelevant and that estrogens and androgens are responsible for the differences. The elevated immune activity in females provides a beneficial position in coping with a pathogenic stimulus but may also enhance their susceptibility to autoimmunity. The

complexity of the immune system and its role as a defensive force against infection requires an armamentarium to precisely identify and selectively control inflammatory processes or cells which promote atherosclerosis. On the other hand, the inflammation in skin diseases seems to be an active source of diverse proinflammatory cytokines and chemokines which can predispose to cardiovascular comorbidities. Also, it has been shown that comorbidity disproportionately accelerates risk in women.The skin offers a readily available window to facilitate detection of risk factors or even to assist the diagnostic process regarding a variety of disorders, including those with cardiovascular involvement. Current imaging techniques provide exquisite capabilities for diagnosing and possibly even counteracting atherosclerotic plaque formation, before serious cardiovascular events occur. Combining imaging approaches (such as videocapillaroscopy, intravascular ultrasound, and FDG positron emission tomography) with insights based on immunology will likely accelerate advances in this area.We review major dermatologic manifestations and rheumatologic disorders which are associated with cardiac and vascular abnormalities. In particular we discuss sex-specific aspects concerning incidence and severity of cardiovascular disease associated with systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, atopic dermatitis, and hidradenitis suppurativa.

[3] *Raggi P, Genest J, Giles JT et al.* **Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions**. Atherosclerosis 2018; 276:98-108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30055326
ABSTRACT
Rudolph Virchow (1821-1902) recognized inflammation in histological preparations of coronary arteries and proposed that inflammation plays a causal role in atherosclerosis. Despite this seminal observation, the main focus of research and drug development programs has been cholesterol alone, and inflammation received less attention over time. However, during the past several decades extensive observations supported the importance of inflammation in the development and destabilization of atherosclerosis. Studies in patients affected by rheumatological diseases suggested an interaction between chronic inflammation and atherosclerotic cardiovascular disease. Randomized clinical studies with lipid lowering agents suggested that part of the beneficial effect may have been related to reduction in inflammation. More recently, a few studies were designed to directly address the role of anti-inflammatory treatments in reducing risk of atherosclerotic heart disease beyond traditional risk factors. In this article, we review the pathophysiologic contribution of inflammation to atherosclerosis, biomarkers of inflammation and the evidence collected in observational studies regarding the role of chronic inflammation in the development of atherosclerotic heart disease. Finally, we discuss the most recent randomized clinical trials of anti-inflammatory agents directed at stemming atherosclerotic cardiovascular disease.

[4] *Essalmani R, Weider E, Marcinkiewicz J et al.* **A single domain antibody against the Cys- and His-rich domain of PCSK9 and evolocumab exhibit different inhibition mechanisms in humanized PCSK9 mice**. Biological chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30044755
ABSTRACT

Literature update week 30 (2018)

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein that binds and escorts the low density lipoprotein receptor (LDLR) into the lysosomal degradation pathway. Prescribed monoclonal antibodies (mAbs) against PCSK9 prevent its binding to the LDLR, and result in ~60% lower LDL cholesterol (LDLc) levels. Although efficient, mAbs are expensive. Hence other PCSK9 inhibitors are needed. For screening purpose, we developed C57BL/6J mice expressing the human PCSK9 gene under the control of its own promoter, but lacking endogenous mouse PCSK9. All lines recapitulate the endogenous PCSK9 expression pattern. The Tg2 line that expresses physiological levels of human PCSK9 (hPCSK9) was selected to characterize the inhibitory properties of a previously reported single domain antibody (sdAb), PKF8-mFc, which binds the C-terminal domain of PCSK9. Upon intraveinous injection of 10 mg/kg, PKF8-mFc and the mAb evolocumab neutralized ~50% and 100% of the hPCSK9 impact on total cholesterol (TC) levels, respectively, but PKF8- mFc had a more sustained effect. PKF8-mFc barely affected hPCSK9 levels, whereas evolocumab promoted a 4-fold increase 3 days post-injection, suggesting very different inhibitory mechanisms. The present study also shows that the new transgenic mice are well suited to screen a variety of hPCSK9 inhibitors.

[5] *Subhan M, Faryal R, Macreadie I*. **Statin resistance in Candida glabrata**. Biotechnology letters 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30054755
ABSTRACT
OBJECTIVES: Reduced efficacy of statins has been observed in people but the mechanism of this resistance is unclear and no statin-resistance mutations in the catalytic domain of HMGCR have been reported. The present study focused on looking for statin-resistance mutations and examining the mechanism of statin resistance using Candida glabrata as a model organism. RESULTS: C. glabrata was cultured in media containing lovastatin, simvastatin or atorvastatin to obtain lovastatin-, simvastatin- and atorvastatin-resistant mutants. A single mutant from each was purified for further analysis. In each mutant, gene sequencing showed there were no changes in the catalytic domain of HMGCR. HMGCR was overexpressed in two resistant isolates suggesting that increased production of HMGCR can lead to resistance. In a third mutant, HMGCR activity was unaltered, suggesting a non-HMGCR related mechanism, such as increased drug efflux, could be operating. CONCLUSIONS: Candida glabrata is a useful model organism for examining resistance to statins. Further studies are warranted to examine the precise molecular mechanisms of statin resistance.

[6] *Nasiri-Ansari N, Dimitriadis GK, Agrogiannis G et al.* **Canagliflozin attenuates the progression of atherosclerosis and inflammation process in APOE knockout mice**. Cardiovascular diabetology 2018; 17:106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30049285
ABSTRACT
BACKGROUND: Sodium glucose co-transporter2 inhibitors reduce the incidence of cardiovascular events in patients with type 2 diabetes mellitus based on the results of recent cardiovascular outcome studies. Herein, we investigated the effects of long-term treatment with canagliflozin on biochemical and immunohistochemical markers related to atherosclerosis and atherosclerosis development in the aorta of apolipoprotein E knockout (Apo-E((-/-))) mice.

METHODS: At the age of 5 weeks, mice were switched from normal to a high-fat diet. After 5 weeks, Apo-E((-/-)) mice were divided into control-group (6 mice) treated with 0.5% hydroxypropyl methylcellulose and Cana-group (7 mice) treated with canagliflozin (10 mg/kg per day) per os. After 5 weeks of intervention, animals were sacrificed, and heart and aorta were removed. Sections stained with hematoxylin-eosin (H&E) were used for histomorphometry whereas Masson's stained tissues were used to quantify the collagen content. Immunohistochemistry to assess MCP-1, CD68, a-smooth muscle actin, MMP-2, MMP-9, TIMP-1 and TIMP-2 expression was carried out and q-PCR experiments were performed to quantify mRNA expression. RESULTS: Canagliflozin-group mice had lower total-cholesterol, triglycerides and glucose levels ($P < 0.01$), while heart rate was significantly lower ($P < 0.05$). Histomorphometry revealed that one in seven Cana-group mice versus four in six control mice developed atheromatosis, while aortic root plaque was significantly less, and collagen was 1.6 times more intense in canagliflozin-group suggesting increased plaque stability. Immunohistochemistry revealed that MCP-1 was significantly less expressed ($P < 0.05$) in the aortic root of canagliflozin-group while reduced expression of a-actin and CD68 was not reaching significance ($P = 0.15$). VCAM-1 and MCP-1 mRNA levels were lower ($P = 0.02$ and $P = 0.07$, respectively), while TIMP-1/MMP-2 ratio expression was higher in canagliflozin-group approaching statistical significance ($P = 0.07$). CONCLUSIONS: Canagliflozin attenuates the progression of atherosclerosis, reducing (1) hyperlipidemia and hyperglycemia, and (2) inflammatory process, by lowering the expression of inflammatory molecules such as MCP-1 and VCAM-1. Moreover, canagliflozin was found to increase the atherosclerotic plaque stability via increasing TIMP-1/MMP-2 ratio expression.

[7] *van Koeverden ID, de Bakker M, Haitjema S et al.* **Testosterone to estradiol ratio reflects systemic and plaque inflammation and predicts future cardiovascular events in men with severe atherosclerosis**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30052805
ABSTRACT
Aims: The effects of testosterone on cardiovascular disease (CVD) as reported in literature have been ambiguous. Recently, the interplay between testosterone and estradiol as assessed by testosterone/estradiol (T/E2) ratio was suggested to be better informative on the normal physiological balance. Considering the role in CVD, we hypothesized that a low T/E2 ratio in men with CVD is associated with increased inflammation, a more unstable plaque and a worse cardiovascular outcome. Methods and results: Testosterone and estradiol concentrations were determined in blood samples of 611 male carotid endarterectomy patients included in the Athero-Express Biobank Study. T/E2 ratio was associated with baseline characteristics, atherosclerotic plaque specimens, inflammatory biomarkers and three-year follow-up information. Patients with low T/E2 ratio had more unfavorable inflammatory profiles compared to patients with high T/E2 as observed by higher levels of C-reactive protein (CRP) (2.81 mug/mL vs. 1.22 mug/mL ($p < 0.001$)) and higher leukocyte counts (8.98*109/L vs. 7.75*109/L ($p = 0.001$)) in blood. In atherosclerotic plaques, a negative association between T/E2 ratio and number of neutrophils (B=-0.366($p = 0.012$), plaque calcifications (OR: 0.816($p = 0.044$)), interleukin-6 (IL-6) (B=-0.15 $p = 0.009$) and Il-6receptor (B=-0.13 $p = 0.024$) was found. Furthermore, in multivariate Cox regression analysis, low T/E2 ratio was independently

associated with an increased risk for major cardiovascular events (MACE) during three-year follow-up (HR 1.67(95%CI: 1.02-2.76) p = 0.043). In men with elevated body mass index, these effects were strongest. Conclusions: In male patients with manifest atherosclerotic disease, low T/E2 ratio was associated with increased systemic inflammation, increased inflammatory plaque proteins and an increased risk of future major cardiovascular events as compared to men with normal T/E2 ratio. These effects are strongest in men with elevated body mass index and are expected to be affected by aromatase activity in white fat tissues. Normalization of T/E2 ratio may be considered as target for the secondary prevention of CVD in men.

[8] *Gao H, Song Z, Zhao Q et al.* **Pharmacological Effects of EGLP-1, a Novel Analog of Glucagon-Like Peptide-1, on Carbohydrate and Lipid Metabolism**. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2018; 48:1112-1122.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30041175
ABSTRACT
BACKGROUND/AIMS: Abnormal glucose metabolism and lipid metabolism are two key issues in Type 1 diabetes mellitus (T1DM). Insulin can control carbohydrate metabolism adequately, but cannot regulate lipid metabolism well in patients with T1DM. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have cured type 2 diabetes mellitus in clinical trials and have improved T1DM glycemic control in preclinical studies. However, previous studies have not reported whether GLP-1 can lower the serum concentration of non-esterified fatty acids (NEFAs). In this study, we examine whether GLP-1 can affect serum NEFA levels. METHODS: The bioactivity of EGLP-1 (a novel GLP-1 analog) in vitro was analyzed in CG-HEK293 cells and with high-performance liquid chromatography. An intraperitoneal glucose tolerance test (IPGTT) was used to analyze the acute and sustained hypoglycemic effects of EGLP-1 in normal C57BL/6J mice. Streptozotocin-induced hyperglycemic mice were used to study the effects of EGLP-1 on blood glucose and NEFAs as well as its mechanism. RESULTS: EGLP-1 activated GLP-1R and resisted dipeptidyl peptidase-IV digestion in vitro. Additionally, EGLP-1 had an insulinotropic action in vivo that lasted for approximately 6 h. In Streptozotocin-induced hyperglycemic mice, EGLP-1 improved hyperglycemia, inhibited food intake, and increased beta-cell area. Serum physiological indexes showed that insulin and C-peptide levels were increased, while NEFA and triacylglycerol concentrations were decreased. Western blot analysis revealed that EGLP-1 significantly reduced phosphorylated-hormone sensitive lipase (pHSL) levels in white adipose tissue. CONCLUSIONS: EGLP-1 can improve hyperglycemia by increasing islet beta-cell area and improving beta-cell function, possibly due to reduced NEFA content in serum by lowering pHSL levels.

[9] *Kodera S, Morita H, Kiyosue A et al.* **Cost-Effectiveness of PCSK9 Inhibitor Plus Statin in Patients With Triple-Vessel Coronary Artery Disease in Japan**. Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30033948
ABSTRACT
BACKGROUND: The addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to statin therapy reduces the rate of cardiovascular events. This study examined the cost-

effectiveness of PCSK9 inhibitor+statin compared with standard therapy (statin monotherapy) in the treatment of triple-vessel coronary artery disease (CAD) in Japan.Methods and Results:A Markov model was applied to assess the costs and benefits associated with PCSK9 inhibitor+statin over a projected 30-year period from the perspective of a public healthcare payer in Japan. The incremental cost-effectiveness ratio (ICER), expressed as the quality-adjusted life-years (QALYs), was estimated. The effects on survival and numbers of events were based on the FOURIER trial and the CREDO Kyoto registry. The ICER of PCSK9 inhibitor+statin over standard therapy was 13.5 million (95% confidence interval 7.6-23.5 million) Japanese Yen (JPY) per QALY gained for triple-vessel CAD. The probability of the cost-effectiveness of PCSK9 inhibitor+statin vs. standard therapy was 0.0008% at a cost-effectiveness threshold of 5 million JPY. In patients with poorly controlled familial hypercholesterolemia (FH) with triple-vessel CAD, the ICER was 3.4 million JPY per QALY gained. CONCLUSIONS: PCSK9 inhibitor plus statin did not show good cost-effectiveness for triple-vessel CAD; however, it showed good cost-effectiveness for patients with triple-vessel CAD and poorly controlled FH in Japan.

[10] *De Luca L, Arca M, Temporelli PL et al.* **Prevalence and Pharmacologic Management of Familial Hypercholesterolemia in an Unselected Contemporary Cohort of Patients With Stable Coronary Artery Disease**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30039543
ABSTRACT
INTRODUCTION: Familiar hypercholesterolemia (FH) is an inherited disorder characterized by elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) associated with premature cardiovascular disease. METHODS: Using the data from the START (STable Coronary Artery Diseases RegisTry) study, a nationwide, prospective survey on patients with stable coronary artery disease (CAD), we described prevalence and lipid lowering strategies commonly employed in these patients. The study population was divided into 'definite/probable FH', defined as a Dutch Lipid Clinic Network (DLCN) score >/=6, 'possible FH' with DLCN 3-5, and 'unlikely FH' in presence of a DLCN<3. RESULTS: Among the 4030 patients with the DLCN score available, 132 (3.3%) were classified as FH (2.3% with definite/probable and 1.0% with possible FH) and 3898 (96.7%) had unlikely FH. Patients with both definite/probable and possible FH were younger compared to patients not presenting FH. Mean on-treatment LDL cholesterol levels were 107.8+/-41.5, 84.4+/-40.9 and 85.8+/-32.3 (p<0.0001) and a target of </=70 mg/dl was reached in 10.9%, 30.0% and 22.0% (p<0.0001) of patents with definite/probable, possible FH and unlikely FH, respectively. Statin therapy was prescribed in 85 (92.4%) patients with definite/probable FH, in 38 (95.0%) with possible FH and in 3621 (92.9%) with unlikely FH (p=0.86). The association of statin and ezetimibe, in absence of other lipid-lowering therapy, was more frequently used in patients with definite/probable FH compared to patients without FH (31.5% vs 17.5% vs 9.5%; p<0.0001). CONCLUSIONS: In this large cohort of consecutive patients with stable CAD, FH was highly prevalent and generally undertreated with lipid lowering therapies.

[11] *Gurgoze MT, Muller-Hansma AH, Schreuder MM et al.* **Adverse events associated with PCSK9 inhibitors: A real-world experience**. Clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30053327

ABSTRACT
In randomized clinical trials (RCTs) pro-protein convertase subtilisin/kexin 9 (PCSK9) inhibitors showed a favorable safety profile, however "real-world" data on adverse events (AEs) is scarce. Three datasets, a hospital registry (n=164) and two Pharmacovigilance databases, Lareb (n=149) and VigiLyze (n=15,554), reporting AEs attributed to PCSK9 inhibitors (alirocumab or evolocumab) prescribed in clinical practice were analyzed. In the hospital registry 41.5% of the patients reported any AE, most often injection-site reactions (33.8%) and influenza like illness (27.9%). Twelve patients (7%) discontinued PCSK9 inhibitor treatment. Most common AE reported in the Lareb and VigiLyze database was myalgia (12.8% and 8.3% respectively). No clinically relevant differences in gender or between drugs were observed. No specific subgroup of patients could be identified at risk of developing AEs. During follow-up, AEs resolved in most patients (71.1%). In real-world setting, PCSK9 inhibitors are well tolerated with an overall safety profile comparable to RCTs.

[12] *Kong R, Zhu X, Meteleva ES et al.* **Atorvastatin calcium inclusion complexation with polysaccharide arabinogalactan and saponin disodium glycyrrhizate for increasing of solubility and bioavailability**. Drug delivery and translational research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30039497
ABSTRACT
The aim of the present investigation was to enhance the solubility and dissolution of atorvastatin calcium (ATV), a poorly water-soluble drug with larch polysaccharide arabinogalactan (AG) and disodium glycyrrhizate (Na2GA) as carriers of drug delivery systems for improving its bioavailability. The interactions of ATV with AG or Na2GA were investigated by DSC, XRD, SEM, and NMR techniques. The molecular weights of supramolecular systems-inclusion complexes and micelles-which are the hosts for ATV molecules were measured. On the other hand, the rapid storage assay (+ 40 degrees C for 3 months) showed that the chemical stability of ATV/AG and ATV/Na2GA complexes had been enhanced compared with pure ATV. In vitro drug release showed a significant increase in ATV's dissolution rate after formation of a complex with Na2GA or AG. Pharmacokinetic tests in vivo on laboratory animals showed a significant increase in ATV's bioavailability after its introduction as a complex with Na2GA or AG. Moreover, ATV/AG and ATV/Na2GA complexes showed a more prominent decrease of total cholesterol (TC) level compared to net ATV. Therefore, the novel mechanochemically synthesized complexes of ATV with AG or Na2GA as drug delivery systems might be potential and promising candidates for hypercholesterolemia treatment and deserved further researches.

[13] *Bittencourt MS, Blankstein R, Blaha MJ et al.* **Implications of coronary artery calcium testing on risk stratification for lipid-lowering therapy according to the 2016 European Society of Cardiology recommendations: The MESA study**. European journal of preventive cardiology 2018:2047487318788930.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30043629
ABSTRACT
Aims The European Society of Cardiology (ESC) guideline on cardiovascular risk assessment considers coronary artery calcium a class B indication for risk assessment. We evaluated the

degree to which coronary artery calcium can change the recommendation for individuals based on a change in estimated risk. Methods and results We stratified 5602 MESA participants according to the ESC recommendation as: no lipid-lowering treatment recommended (N = 2228), consider lipid-lowering treatment if uncontrolled (N = 1686), or lipid-lowering treatment recommended (N = 1688). We evaluated the ability of coronary artery calcium to reclassify cardiovascular risk. Among the selected sample, 54% had coronary artery calcium of zero, 25% had coronary artery calcium of 1-100 and 21% had coronary artery calcium greater than 100. In the lipid-lowering treatment recommended group 31% had coronary artery calcium of zero, while in the lipid-lowering treatment if uncontrolled group about 50% had coronary artery calcium of zero. The cardiovascular mortality rate was 1.7%/10 years in the lipid-lowering treatment if uncontrolled, and 7.0%/10 years in the lipid-lowering treatment recommended group. The absence of coronary artery calcium was associated with 1.4%/10 years in the lipid-lowering treatment if uncontrolled group and 3.0%/10 years in the lipid-lowering treatment recommended group. Compared with coronary artery calcium of zero, any coronary artery calcium was associated with significantly higher cardiovascular mortality in the lipid-lowering treatment recommended group (9.0%/10 years), whereas only coronary artery calcium greater than 100 was significantly associated with a higher cardiovascular mortality in the lipid-lowering treatment if uncontrolled group (3.2%/10 years). Conclusion The absence of coronary artery calcium is associated with a low incidence of cardiovascular mortality or coronary heart disease events even in individuals in whom lipid-lowering therapy is recommended. A significant proportion of individuals deemed to be candidates for lipid-lowering therapy might be reclassified to a lower risk group with the use of coronary artery calcium.

[14] *Murtola TJ, Syvala H, Tolonen T et al.* **Atorvastatin Versus Placebo for Prostate Cancer Before Radical Prostatectomy-A Randomized, Double-blind, Placebo-controlled Clinical Trial**. European urology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30031572
ABSTRACT
We tested whether intervention with atorvastatin affects the prostate beneficially compared with placebo in men with prostate cancer in a randomized clinical trial. A total of 160 statin-naive prostate cancer patients scheduled for radical prostatectomy were randomized to use 80mg atorvastatin or placebo daily from recruitment to surgery for a median of 27 d. Blinding was maintained throughout the trial. In total, 158 men completed the follow-up, with 96% compliance. Overall, atorvastatin did not significantly lower tumor proliferation index Ki-67 or serum prostate-specific antigen (PSA) compared with placebo. In subgroup analyses, after a minimum of 28 d of atorvastatin use, Ki-67 was 14.1% lower compared with placebo (p = 0.056). Among high-grade cases (International Society of Urological Pathology Gleason grade 3 or higher), atorvastatin lowered PSA compared with placebo: median change -0.6 ng/ml; p = 0.024. Intraprostatic inflammation did not differ between the study arms (p = 0.8). Despite a negative overall result showing no effect of statins on Ki67 or PSA overall, in post hoc exploratory analyses, there appeared to be benefit after a minimum duration of 28 d. Further studies are needed to verify this. PATIENT SUMMARY: Cholesterol-lowering atorvastatin does not lower prostate cancer proliferation rate compared with placebo overall, but exploratory analyses suggest a benefit in longer exposure.

[15] *Yuan X, Liu X, McClements DJ et al.* **Enhancement of phytochemical bioaccessibility from plant-based foods using excipient emulsions: impact of lipid type on carotenoid solubilization from spinach**. Food & function 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30043000
ABSTRACT
Effects of lipid type in excipient emulsions on the bioaccessibility of carotenoids (lutein and beta-carotene) in spinach were studied using a simulated gastrointestinal tract (GIT). Results showed that the lipid type only had a minor impact on the physical and structural characteristics of the spinach/emulsion mixtures as they passed through simulated mouth, stomach, and small intestine phases. However, a significant effect was observed on lipid digestion, mixed micelle formation, and carotenoid bioaccessibility. Excipient emulsions containing mainly medium chain triacylglycerols (MCTs) (MCT and coconut oils) had faster initial lipid digestion rates, higher overall digestibility, smaller mixed micelle sizes, and higher lutein bioaccessibilities than those containing mainly long chain triacylglycerols (LCTs) (corn, olive, and fish oils). Excipient emulsions rich in long chain monounsaturated fatty acids (MUFAs) (corn and olive oils) formed larger mixed micelles and gave higher beta-carotene bioaccessibilities than those rich in either medium chain saturated fatty acids (SFAs) (MCT and coconut oils) or long chain polyunsaturated fatty acids (PUFAs) (fish oil). These differences in bioaccessibility were attributed to differences in micelle size and solubilization capacity, as well as carotenoid dimensions. Finally, emulsions containing a mixed oil phase (MCT oil : corn oil = 1 : 1, w/w) appreciably increased both lutein (from 21% to 42%) and beta-carotene (from 6.8% to 25%) bioaccessibility from spinach compared to a control (no oil). These results suggest that mixed LCT-MCT oil phases may be useful for the design of excipient emulsions for improving the bioaccessibility of various hydrophobic nutraceuticals.

[16] *Mirhosseini N, Rainsbury J, Kimball SM*. **Vitamin D Supplementation, Serum 25(OH)D Concentrations and Cardiovascular Disease Risk Factors: A Systematic Review and Meta-Analysis**. Frontiers in cardiovascular medicine 2018; 5:87.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30050908
ABSTRACT
Background: Cardiovascular disease (CVD) risk factors are associated with low serum 25 hydroxyvitamin D (25(OH)D) concentrations in observational studies; however, clinical trial findings are inconsistent. Objective: We assessed the effect of vitamin D supplementation and increased serum 25(OH)D concentrations on CVD risk factors in a systemic review and meta-analysis of randomized controlled trials (RCTs). Design: MEDLINE, CINAHL, EMBASE, and Google Scholar were searched for RCTs that evaluated vitamin D supplementation and cardiovascular outcomes [blood pressure, parathyroid hormone (PTH), serum high-sensitivity C-reactive protein (hs-CRP), total cholesterol, high and low density lipoprotein (HDL and LDL, respectively), triglycerides, peak wave velocity (PWV) and Augmentation Index (AI)] from 1992 through 2017. Meta-analysis was based on a random-effects model and inverse variance method to calculate standardized mean difference (SMD) as effect sizes, followed by a leave-one-out method for sensitivity analysis. Risk of publication bias was assessed using Cochrane checklist and Begg funnel plots. The systematic review is registered as CRD42015025346. Results: We identified

2341 studies from which 81 met inclusion criteria. The meta-analysis indicated a significant reduction in systolic blood pressure (SMD = -0.102 +/- 0.04 mmHg, 95% confidence interval (CI), -0.20 to -0.03), diastolic blood pressure (SMD = -0.07 +/- 0.03 mmHg, 95% CI, -0.14 to -0.006), serum PTH (SMD = -0.66 +/- 0.08 ng/L, 95% CI, -0.82 to -0.49), hs-CRP (SMD = -0.20 +/- 0.07 mg/L, 95% CI, -0.34 to -0.06), total cholesterol (SMD = -0.15 +/- 0.06 mmol/L, 95% CI, -0.25 to -0.04), LDL (SMD = -0.10 +/- 0.05 mmol/L, 95% CI, -0.20 to -0.003), triglycerides (SMD = -0.12 +/- 0.06 mmol/L, 95% CI, -0.23 to -0.003) and a significant increase in HDL (SMD = 0.09 +/- 0.04 mmol/L, 95% CI, 0.00 to 0.17) with vitamin D supplementation. These findings remained significant in sensitivity analyses for blood pressure, lipid profile, serum PTH, and serum hs-CRP. There was no significant effect of vitamin D supplementation on PWV (SMD = -0.20 +/- 0.13 m/s, 95% CI, -0.46 to 0.06, p = 0.14) and AI (SMD = -0.09 +/- 0.14%, 95% CI, -0.37 to 0.19, p = 0.52) for vitamin D supplemented groups. Conclusion: These findings suggest that vitamin D supplementation may act to protect against CVD through improving risk factors, including high blood pressure, elevated PTH, dyslipidemia, and inflammation.

[17] *Mytilinaiou M, Kyrou I, Khan M et al.* **Familial Hypercholesterolemia: New Horizons for Diagnosis and Effective Management**. Frontiers in pharmacology 2018; 9:707.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30050433
ABSTRACT
Familial hypercholesterolemia (FH) is a common genetic cause of premature cardiovascular disease (CVD). The reported prevalence rates for both heterozygous FH (HeFH) and homozygous FH (HoFH) vary significantly, and this can be attributed, at least in part, to the variable diagnostic criteria used across different populations. Due to lack of consistent data, new global registries and unified guidelines are being formed, which are expected to advance current knowledge and improve the care of FH patients. This review presents a comprehensive overview of the pathophysiology, epidemiology, manifestations, and pharmacological treatment of FH, whilst summarizing the up-to-date relevant recommendations and guidelines. Ongoing research in FH seems promising and novel therapies are expected to be introduced in clinical practice in order to compliment or even substitute current treatment options, aiming for better lipid-lowering effects, fewer side effects, and improved clinical outcomes.

[18] *Tripathi DM, Vilaseca M, Lafoz E et al.* **Simvastatin Prevents Progression of Acute on Chronic Liver Failure in Rats With Cirrhosis and Portal Hypertension**. Gastroenterology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30055171
ABSTRACT
BACKGROUND & AIMS: Cirrhosis and its clinical consequences can be aggravated by bacterial infections, ultimately leading to the development of acute on chronic liver failure (ACLF), characterized by acute decompensation, organ failure, and high mortality within 28 days. Little is known about cellular and molecular mechanisms of ACLF in patients with cirrhosis, so no therapeutic options are available. We developed a sepsis-associated pre-clinical model of ACLF to facilitate studies of pathogenesis and evaluate the protective effects of simvastatin. METHODS: Male Wistar rats inhaled CCl4 until they developed cirrhosis (at 10 weeks) or cirrhosis with ascites (at 15-16 weeks). Male Sprague-Dawley rats received bile-duct ligation for 28 days or intraperitoneal thioacetamide for 10 weeks to induce cirrhosis. After induction of

cirrhosis, some rats received a single injection of lipopolysaccharide (LPS) to induce ACLF; some were given simvastatin or vehicle (control) 4h or 24h before induction of ACLF. We collected data on changes in hepatic and systemic hemodynamics, hepatic microvascular phenotype and function, and survival times. Liver tissues and plasma were collected and analyzed by immunoblots, quantitative PCR, immuno(fluoro)histochemistry and immunoassays. RESULTS: Administration of LPS aggravated portal hypertension in rats with cirrhosis, by increasing the severity of intrahepatic microvascular dysfunction, exacerbating hepatic inflammation, increasing oxidative stress, and recruiting hepatic stellate cells and neutrophils. Rats with cirrhosis given LPS had significantly shorter survival times than rats with cirrhosis given the control. Simvastatin prevented most of ACLF-derived complications and increased survival times. Simvastatin appeared to increase hepatic sinusoidal function and reduce portal hypertension and markers of inflammation and oxidation. The drug significantly reduced levels of transaminases, total bilirubin, and ammonia, as well as LPS-mediated activation of HSCs in liver tissues of rats with cirrhosis. CONCLUSIONS: In studies of rats with cirrhosis, we found administration of LPS to promote development of ACLF, aggravating the complications of chronic liver disease and decreasing survival times. Simvastatin reduced LPS-induced inflammation and liver damage in rats with ACLF, supporting its use in treatment of patients with advanced chronic liver disease.

[19] *Karsanidze A, Antelava N, Gorgasledze N et al.* **STATIN-ASSOCIATED INTOLERANCE AND ITS PREVENTION**. Georgian medical news 2018:155-161.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30035739
ABSTRACT
The review analyzes the literature data, which covers the intolerance of statins associated with myopathy. The article gives a definition of statin intolerance, analyzed data from a randomized, controlled trials, where are indicated frequency of statin-associated myopathy, its symptoms in juxtaposition with an increase in creatine kinase activity. It is noted that the frequency of complications depends on the applied statin, its dose, duration, the use of other risk factors that contribute to the development of myopathy. It is indicated that polypharmacy - the joint use of statins with such drugs as anti-inflammatory (glucocorticoids), immunosuppressants (cyclosporine), antipsychotics, antiviral (protease inhibitors), macrolides, antifungal, lipid modifying (gemfibrozole), cytochrome P450 inhibitors and substances causing dependence (alcohol, opioids) may contribute to the development of statin-associated myopathy. Risk factors are also age over 75 years, low body mass index, female gender, high level of physical activity, multi-system diseases - hypothyroidism, diabetes, infections, hepatic dysfunction, biliary obstruction, organ transplantation, severe injuries, hypovitaminosis D, metabolic lesions, etc. Methods of therapy of patients with statin-associated myopathy, namely, dose changes, duration of administration, regimen of application (twice a week instead of daily), replacement of the drug and the use of other lipid-lowering agents, as well as nutritional and complementary therapy are considered.

[20] *Voloshchuk N, Melnik A, Danchenko O et al.* **THE STATE OF THE CYSTATHIONINE GAMMA-LYASE / H2S SYSTEM IN THE LIVER AND SKELETAL MUSCLES OF RATS WITH**

HYPERCHOLESTEROLEMIA UNDER SIMVASTATIN ADMINISTRATION. Georgian medical news 2018:150-155.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30035738
ABSTRACT
In studies on 94 male Wistar rats changes in the hydrogen sulfide content (H2S) and cystathionine gamma-lyase (CSE) in the liver and skeletal muscles in hypercholesterolemia under simvastatin treatment were assessed, as well as the effect of propargylglycine (PAG) on hepato- and myotoxicity of simvastatin. It was determined, that simvastatin inhibited the CSE-mediated synthesis of H2S in the main target organs. This negatively affected their biochemical and functional status. The use of PAG significantly suppressed the H2S deficiency induced by simvastatin, and also was accompanied by a significant increase in the activity of cytolysis markers in the serum, which significantly and negatively correlated with the activity of CSE and H2S in organs. Thus, formation of H2S deficiency due to simvastatin intake is probably one of the molecular mechanisms for the realization of hepato- and myotoxicity of this drug.

[21] *Seyam E, Hefzy E*. **Long-term effects of combined simvastatin and metformin treatment on the clinical abnormalities and ovulation dysfunction in single young women with polycystic ovary syndrome**. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2018:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30044162
ABSTRACT
The aim of the current work was to investigate the value of the long term effects of combined use of simvastatin and metformin treatment for a year versus the effects of their individual treatment on the clinical, biochemical abnormalities, and ovulation dysfunction in young single women with polycystic ovary syndrome (PCOS). It was a randomized, double-blind controlled study. Where two hundreds (n = 200) single young women with PCOS were randomized into seventy (n = 70) women using simvastatin 20 mg daily combined with metformin 500 mg three times daily considered as group A (study group), and another 2 sixty five (n = 65) women groups using simvastatin and metformin individually as a single treatment use, and considered as groups (B & C), respectively. Medications period extended for twelve months treatment period. The primary outcome measures were the changes in serum androgen levels (testosterone, androstendione, and dehydro-epiandrostenion sulfate-DHEAS), LH, FSH, LH/FSH ratio, and insulin resistance (IR), in addition to menstrual regularity, hirsutism, BMI, and W/H ratio. Spontaneous ovulation, confirmed with both trans-abdominal sonography (TAS) and luteal serum progesterone as well had been also evaluated. After 12 months' treatment, in group A serum testosterone showed significant decline by 37%, with significant drop in LH serum level (51%) and a marked decline of the LH/FSH ratio (53%). IR showed a significant improvement in groups A and C but still relatively higher in group B. There was also a clear decrease of total cholesterol (36%), low-density lipoprotein (LDL; 48%), and triglycerides (26%), and increased high-density lipoprotein (HDL) by 24% in groups A and B. Improved menstrual regularity and decreased hirsutism, acne, ovarian volume, and BMI had been significantly noticed in the study groups A and C, although still relatively higher in group C. Spontaneous ovulation had been confirmed in group A: songoraphically (TAS), and biochemically (progesterone >10 ng) in 10 women after the first six months treatment, and 26 at the end of 12 months treatment,

compared to 5 & 8 in group B, and 2 & 5 in group C, respectively. Combined simvastatin and metformin treatment showed significant improvement of PCOS clinical and ovarian dysfunction abnormalities much better than their individual treatment.

[22] *Lim JW, Jeong HS, Hong SJ et al.* **Effects of lowest-dose vs. highest-dose pitavastatin on coronary neointimal hyperplasia at 12-month follow-up in type 2 diabetic patients with non-ST elevation acute coronary syndrome: an optical coherence tomography analysis**. Heart Vessels 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30047013
ABSTRACT
Current ACC/AHA guidelines recommend high-dose statin therapy after coronary stenting, especially in diabetic patients; however, pitavastatin 4 mg or pitavastatin 1 mg are frequently used after coronary stenting in Asia, even in patients with acute coronary syndrome. We compared the effects of highest-dose and lowest-dose pitavastatin therapy on coronary neointimal hyperplasia at 12-month follow-up in diabetic patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) using optical coherence tomography. A total of 72 diabetic patients with NSTE-ACS were randomized to lowest-dose pitavastatin [1 mg (n = 36)] or highest-dose pitavastatin [4 mg (n = 36)] after everolimus-eluting stent implantation. The primary endpoint was to compare the normalized neointimal volume at 12-month follow-up. Normalized neointimal volume was significantly lower in the pitavastatin 4 mg group (4.00 +/- 2.80 vs. 8.24 +/- 2.83 mm(3)/mm, p < 0.01) at 12-month follow-up. There was also significant difference in neointimal area between the pitavastatin 4 mg group and pitavastatin 1 mg group (0.41 +/- 0.28 vs. 0.74 +/- 0.23 mm(2), p < 0.01). Improvement of brachial artery flow-mediated dilation (baFMD) was significantly higher in the pitavastatin 4 mg group than in pitavastatin 1 mg group (0.15 +/- 0.15 vs. - 0.03 +/- 0.19 mm, p < 0.001). In addition, the improvement of adiponectin levels was significantly greater in the pitavastatin 4 mg group than in the pitavastatin 1 mg group (2.97 +/- 3.98 vs. 0.59 +/- 2.80 mug/mL, p < 0.05). Pitavastatin 4 mg significantly improved inflammatory cytokines and lipid profiles compared to pitavastatin 1 mg during the 12-month follow-up, contributing to the reduction of neointimal hyperplasia and to the improvement of baFMD in diabetic patients with NSTE-ACS requiring coronary stenting. Thus, the administration of pitavastatin 4 mg can be safely and effectively used in high-risk patients requiring coronary stenting. Trial registration NCT02545231 (Clinical Trial registration information: https://clinicaltrials.gov/ct2/show/NCT02545231).

[23] *Breuker C, Clement F, Mura T et al.* **Non-achievement of LDL-cholesterol targets in patients with diabetes at very-high cardiovascular risk receiving statin treatment: Incidence and risk factors**. International journal of cardiology 2018; 268:195-199.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30041785
ABSTRACT
BACKGROUND: Cardiovascular diseases are the first cause of mortality in patients with diabetes, and LDL-cholesterol is a well-established cardiovascular risk factor. This study aimed to assess rate of LDL-cholesterol target attainment among patients with diabetes at very-high cardiovascular risk treated with statins, and to identify predictive factors of non-attainment of target in this population. METHODS: Patients were recruited in the Nutrition-Diabetes unit of

Montpellier University Hospital, France, from 2014 to 2017. We included all consecutive patients with type 1 or type 2 diabetes receiving statin treatment and at very-high cardiovascular risk according to 2016 ESC guidelines, therefore having a LDL-cholesterol target of <1.8mmol/L. LDL-cholesterol levels were measured upon admission. Variables independently associated with non-attainment of LDL-Cholesterol target were assessed using multivariable logistic regression. RESULTS: 654 patients were included. Mean age was 63.8years (SD 11.0), 41.9% were women and 42.3% had a history of cardiovascular disease. 59% of patients did not achieve LDL-cholesterol target, with a median value (interquartile range) of 2.4mmol/L (2.1-2.9) versus 1.4mmol/L (1.1-1.6) in patients at target. Risk of non-attainment of LDL-cholesterol target value was increased in women (odds ratio [95% confidence interval]: 2.27 [1.62-3.17]) and decreased in patients with history of coronary artery disease (0.64 [0.45-0.89]) or history of stroke or transient ischemic attack (0.59 [0.33-1.07]). CONCLUSIONS: Management of dyslipidemia is suboptimal, even in very-high risk patients with diabetes under statins. Lipid-lowering treatment should be intensified, in particular in very high risk patients with diabetes who are women or in primary cardiovascular prevention. Clinical Trial number: NCT03449784.

[24] *Fukumoto Y*. **Impact of statin-ezetimibe combination in chronic kidney disease**. International journal of cardiology 2018; 268:36-37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30041796
ABSTRACT

[25] *Das UN*. **Ageing: Is there a role for arachidonic acid and other bioactive lipids? A review**. Journal of advanced research 2018; 11:67-79.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30034877
ABSTRACT
Ageing is inevitable. Recent studies suggest that it could be delayed. Low-grade systemic inflammation is seen in type 2 diabetes mellitus, hypertension and endothelial dysfunction that are common with increasing age. In all these conditions, an alteration in arachidonic acid (AA) metabolism is seen in the form of increased formation of pro-inflammatory eicosanoids and decreased production of anti-inflammatory lipoxins, resolvins, protectins and maresins and decreased activity of desaturases. Calorie restriction, exercise and parabiosis delay age-related changes that could be related to enhanced proliferation of stem cells, decrease in inflammation and transfer of GDF-11 (growth differentiation factor-11) and other related molecules from the young to the old, increase in the formation of lipoxin A4, resolvins, protectins and maresins, hydrogen sulfide (H2S) and nitric oxide (NO); inhibition of ageing-related hypothalamic or brain IKK-beta and NF-kB activation, decreased gonadotropin-releasing hormone (GnRH) release resulting in increased neurogenesis and consequent decelerated ageing. This suggests that hypothalamus participates in ageing process. N-acylethanolamines (NAEs) and lipid-derived signalling molecules can be tuned favorably under dietary restriction to extend lifespan and/or prevent advanced age associated diseases in an mTOR dependent pathway manner. Sulfur amino acid (SAA) restriction increased hydrogen sulfide (H2S) production and protected tissues from hypoxia and tissue damage. Anti-inflammatory metabolites formed from AA such as LXA4, resolvins, protectins and maresins enhance production of NO, CO, H2S; suppress NF-kB expression and alter mTOR expression and thus, may aid in delaying ageing process. Dietary

restriction and exercise enhance AA metabolism to form LXA4, resolvins, protectins and maresins that have anti-inflammatory actions. AA and their metabolites also influence stem cell biology, enhance neurogenesis to improve memory and augment autophagy to prolong life span. Thus, AA and other PUFAs and their anti-inflammatory metabolites inhibit inflammation, augment stem cell proliferation, restore to normal lipid-derived signaling molecules and NO and H2S production, enhance autophagy and prolong life span.

[26] *Das UN*. **Arachidonic acid and other unsaturated fatty acids and some of their metabolites function as endogenous antimicrobial molecules: A review**. Journal of advanced research 2018; 11:57-66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30034876
ABSTRACT
Our body is endowed with several endogenous anti-microbial compounds such as interferon, cytokines, free radicals, etc. However, little attention has been paid to the possibility that lipids could function as antimicrobial compounds. In this short review, the antimicrobial actions of various polyunsaturated fatty acids (PUFAs, mainly free acids) and their putative mechanisms of action are described. In general, PUFAs kill microbes by their direct action on microbial cell membranes, enhancing generation of free radicals, augmenting the formation of lipid peroxides that are cytotoxic, and by increasing the formation of their bioactive metabolites, such as prostaglandins, lipoxins, resolvins, protectins and maresins that enhance the phagocytic action of leukocytes and macrophages. Higher intakes of alpha-linolenic and cis-linoleic acids (ALA and LA respectively) and fish (a rich source of eicosapentaenoic acid and docosahexaenoic acid) might reduce the risk pneumonia. Previously, it was suggested that polyunsaturated fatty acids (PUFAs): linoleic, alpha-linolenic, gamma-linolenic (GLA), dihomo-GLA (DGLA), arachidonic (AA), eicosapentaenoic (EPA), and docosahexaenoic acids (DHA) function as endogenous anti-bacterial, anti-fungal, anti-viral, anti-parasitic, and immunomodulating agents. A variety of bacteria are sensitive to the growth inhibitory actions of LA and ALA in vitro. Hydrolyzed linseed oil can kill methicillin-resistant Staphylococcus aureus. Both LA and AA have the ability to inactivate herpes, influenza, Sendai, and Sindbis virus within minutes of contact. AA, EPA, and DHA induce death of Plasmodium falciparum both in vitro and in vivo. Prostaglandin E1 (PGE1) and prostaglandin A (PGA), derived from DGLA, AA, and EPA inhibit viral replication and show anti-viral activity. Oral mucosa, epidermal cells, lymphocytes and macrophages contain and release significant amounts of PUFAs on stimulation. PUFAs stimulate NADPH-dependent superoxide production by macrophages, neutrophils and lymphocytes to kill the invading microorganisms. Cytokines induce the release of PUFAs from cell membrane lipid pool, a potential mechanism for their antimicrobial action. AA, EPA, and DHA give rise to lipoxins (LXs), resolvins, protectins, and maresins that limit and resolve inflammation and have antimicrobial actions. Thus, PUFAs and their metabolites have broad antimicrobial actions.

[27] *Shanab SMM, Hafez RM, Fouad AS*. **A review on algae and plants as potential source of arachidonic acid**. Journal of advanced research 2018; 11:3-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30034871
ABSTRACT

Some of the essential polyunsaturated fatty acids (PUFAs) as ARA (arachidonic acid, n-6), EPA (eicosapentaenoic acid, n-3) and DHA (Docosahexaenoic acid, n-3) cannot be synthesized by mammals and it must be provided as food supplement. ARA and DHA are the major PUFAs that constitute the brain membrane phospholipid. n-3 PUFAs are contained in fish oil and animal sources, while the n-6 PUFAs are mostly provided by vegetable oils. Inappropriate fatty acids consumption from the n-6 and n-3 families is the major cause of chronic diseases as cancer, cardiovascular diseases and diabetes. The n-6: n-3 ratio (lower than 10) recommended by the WHO can be achieved by consuming certain edible sources rich in n-3 and n-6 in daily food meal. Many researches have been screened for alternative sources of n-3 and n-6 PUFAs of plant origin, microbes, algae, lower and higher plants, which biosynthesize these valuable PUFAs needed for our body health. Biosynthesis of C18 PUFAs, in entire plant kingdom, takes place through certain pathways using elongases and desaturases to synthesize their needs of ARA (C20-PUFAs). This review is an attempt to highlight the importance and function of PUFAs mainly ARA, its occurrence throughout the plant kingdom (and others), its biosynthetic pathways and the enzymes involved. The methods used to enhance ARA productions through environmental factors and metabolic engineering are also presented. It also deals with advising people that healthy life is affected by their dietary intake of both n-3 and n-6 FAs. The review also addresses the scientist to carry on their work to enrich organisms with ARA.

[28] *Freeman AM, Morris PB, Aspry K et al.* **A Clinician's Guide for Trending Cardiovascular Nutrition Controversies: Part II**. Journal of the American College of Cardiology 2018; 72:553-568.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30049315
ABSTRACT
The potential cardiovascular (CV) benefits of many trending foods and dietary patterns are still incompletely understood, and scientific inquiry continues to evolve. In the meantime, however, a number of controversial dietary patterns, foods, and nutrients have received significant media attention and are mired by "hype." This second review addresses some of the more recent popular foods and dietary patterns that are recommended for CV health to provide clinicians with current information for patient discussions in the clinical setting. Specifically, this paper delves into dairy products, added sugars, legumes, coffee, tea, alcoholic beverages, energy drinks, mushrooms, fermented foods, seaweed, plant and marine-derived omega-3-fatty acids, and vitamin B12.

[29] *Dagenais GR, Jung H, Lonn E et al.* **Effects of Lipid-Lowering and Antihypertensive Treatments in Addition to Healthy Lifestyles in Primary Prevention: An Analysis of the HOPE-3 Trial**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30033433
ABSTRACT
BACKGROUND: It is not clear whether the effects of lipid-lowering or antihypertensive medications are influenced by adherence to healthy lifestyle factors. We assessed the effects of both drug interventions in subgroups by the number of healthy lifestyle factors in participants in the HOPE-3 (Heart Outcomes Prevention Evaluation) trial. METHODS AND RESULTS: In this primary prevention trial, 4 healthy lifestyle factors (nonsmoking status, physical activity,

optimal body weight, and healthy diet) were recorded in 12 521 participants who were at intermediate risk of cardiovascular disease (CVD) and were randomized to rosuvastatin, candesartan/hydrochlorothiazide, their combination, or matched placebos. Median follow-up was 5.6 years. The outcome was a composite of CVD events. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models. Participants with >/=2 healthy lifestyle factors had a lower rate of CVD compared with those with fewer factors (HR: 0.85; 95% CI, 0.73-1.00). Rosuvastatin reduced CVD events in participants with >/=2 healthy lifestyle factors (HR: 0.74; 95% CI, 0.62-0.90) and in participants with <2 factors (HR: 0.79; 95% CI, 0.61-1.01). Consistent results were observed with combination therapy (>/=2 factors: HR: 0.74; 95% CI, 0.57-0.97; <2 factors: HR: 0.61; 95% CI, 0.43-0.88). Candesartan/hydrochlorothiazide tends to reduce CVD only in participants with <2 healthy lifestyle factors (HR: 0.78; 95% CI, 0.61-1.00). CONCLUSIONS: Healthy lifestyles are associated with lower CVD. Rosuvastatin alone and combined with candesartan/hydrochlorothiazide is beneficial regardless of healthy lifestyle status; however, the benefit of antihypertensive treatment appears to be limited to patients with less healthy lifestyles. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00239681.

[30] *Tada H, Nohara A, Inazu A et al.* **Sitosterolemia, Hypercholesterolemia, and Coronary Artery Disease**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30033951
ABSTRACT
Sitosterolemia is a rare inherited disease characterized by increased levels of plant sterols, such as sitosterol. The cause of this disease is ATP-binding cassette (ABC) subfamily G member 5 or member 8 (ABCG5 or ABCG8, respectively) gene mutations. Recent advances in genetics have revealed that the prevalence of subjects with deleterious mutations in ABCG5 and/or ABCG8 genes could be more than 1 in ~200,000 individuals among the general population. Furthermore, accumulated evidence, including infantile cases exhibiting progression/regression of systemic xanthomas associated with LDL cholesterol levels, have shown that the elevation of LDL cholesterol seems to be the major cause of development of atherosclerosis and not the elevation of sitosterol. Regarding therapies, LDL apheresis, as well as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, could be useful for sitosterolemia, in addition to ezetimibe and/or colestimide. In this study, we provide the current understanding and future perspectives of sitosterolemia, which is currently considered an extremely rare disorder but is expected to be much more prevalent in clinical settings.

[31] *Xu B, Wu C, Wu W et al.* **Study of Serum CD147 Level in Patients with Transient Ischemic Attack and CD147 Expression in Atherosclerotic Plaque**. Journal of cardiovascular translational research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30039437
ABSTRACT
There is growing evidence that highlighted the potential effects of CD147 in atherosclerosis, but the potential implication of CD147 in diagnosis and treatment of transient ischemic attack (TIA) and acute cerebral infarction (ACI) is still unclear. In this work, we investigated the serum level of CD147 in patients with TIA and ACI, and CD147 expression in atherosclerotic plaque. The

result showed significantly increasing serum level of CD147 in patients with TIA and ACI, and increasing amount of CD147 in vulnerable plaque compared with that in migrating plaque. The serum level of CD147 was correlation with risk of stroke after an episode of TIA. These results together suggest a potential involvement of CD147 in the development and progression of TIA and ACI and CD147 as a potential biomarker for stroke prediction.

[32] *Gazzola K, Snijder MB, Hovingh GK et al.* **Ethnic differences in plasma lipid levels in a large multiethnic cohort: The HELIUS study**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30054248
ABSTRACT
BACKGROUND: There is limited information on differences in plasma lipid levels among the major ethnic groups in Europe. OBJECTIVE: We investigated ethnic differences in plasma lipid levels in a large multiethnic cohort and explored the contribution of obesity and other determinants to ethnic differences in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels. METHODS: We compared lipid profiles among 21,617 participants (aged 18 to 70 years) of Moroccan, Ghanaian, South Asian Surinamese, African Surinamese, Turkish and Dutch ethnic origin, living in Amsterdam, the Netherlands. Fasting total cholesterol, HDL-C, and TG were measured while fasting. LDL-C was calculated using the Friedewald formula and corrected for lipid-lowering therapy. RESULTS: Mean LDL-C ranged from 2.84 +/- 0.22 mmol/L in Moroccans to 3.13 +/- 0.06 mmol/L in South Asian Surinamese participants. Mean HDL-C ranged from 1.30 +/- 0.15 mmol/L in Turkish to 1.62 +/- 0.10 mmol/L in Ghanaian participants. Mean TG ranged from 0.64 +/- 1.18 mmol/L in Ghanaian to 1.00 +/- 1.18 mmol/L in South Asian Surinamese and 1.00 +/- 1.27 mmol/L in Turkish origin participants. The differences in LDL-C, HDL-C, and TG levels remained present after adjustment for age and sex. Differences between ethnic groups were significantly attenuated after adjustment for other determinants, including body mass index, diabetes and use of lipid-lowering drugs but remained significant. CONCLUSION: Large ethnic differences exist in lipid components, especially HDL-C and TG levels with a higher HDL-C and lower TG levels among African (Ghanaian and Surinamese) origin participants and the most unfavorable lipid profiles among individuals of South Asian Surinamese and Turkish origin.

[33] *Mateo-Gallego R, Lacalle L, Perez-Calahorra S et al.* **Efficacy of repeated phlebotomies in hypertriglyceridemia and iron overload: A prospective, randomized, controlled trial**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30049591
ABSTRACT
BACKGROUND: High ferritin concentration is associated with hypertriglyceridemia, although it is not elucidated if iron overload has a causal role. OBJECTIVE: To evaluate the efficacy of repeated phlebotomies in patients with iron overload and hypertriglyceridemia. METHODS: Twelve weeks, 1:1 randomized, parallel-groups trial conducted at a University Hospital Lipid Clinic, including 86 subjects aged 18-70 years with serum ferritin >300 ng/mL in men or >200 ng/mL in women and triglycerides >200 mg/dL. Participants underwent: (1) three phlebotomies (every 3 weeks) and lipid-lowering dietary counseling or (2) lipid-lowering dietary counseling. The main outcome measured was the mean difference in percent change in triglyceride

concentration between groups after the intervention. The mean differences in percent change of other clinical and biochemical variables (including cytokines and proinflammatory markers) after the intervention were also evaluated. RESULTS: Subjects who received phlebotomies showed a significant improvement in iron metabolism. The mean percent change in triglycerides between groups was -4.68 [-20.8, 11.4]%, P = .721. Retinol-binding protein 4 decreased by 9.98 +/- 21.7% after phlebotomies, with a mean percent change between groups of -14.2 [-25.8, -2.73]%, P = .017, and correlated to gamma glutamyl transferase, alanine aminotransferase and aspartate aminotransferase change. Subjects with a large reduction in hepcidin showed a large improvement in liver enzymes and proinflammatory markers. CONCLUSIONS: A lipid-lowering diet plus a substantial reduction in iron deposits with repeated phlebotomies in subjects with hyperferritinemia and hypertriglyceridemia did not reduce triglyceride concentration in comparison with a lipid-lowering diet. Iron depletion for lipid management in these patients is not supported.

[34] *Mashayekhi S, Ziaee M, Garjani A et al.* **Prognostic Value of sLOX-1 Level in Acute Coronary Syndromes Based on Thrombolysis in Myocardial Infarction Risk Score and Clinical Outcome**. The Journal of emergency medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30049431
ABSTRACT
BACKGROUND: Biomarkers possess important diagnostic and prognostic value in acute coronary syndromes (ACSs). Soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) is one of the markers involved in atherosclerotic plaque vulnerability and rupture. OBJECTIVE: This study aimed to evaluate the prognostic value of sLOX-1 through its correlation with Thrombolysis in Myocardial Infarction (TIMI) risk score and its possible association with clinical outcomes in 2 major spectrums of ACS. METHODS: A prospective cross-sectional study was planned, and 320 patients who underwent diagnostic coronary angiography were selected (in first 24 h after coronary angiography): those with documented ST elevation myocardial infarction or unstable angina/non-ST elevation myocardial infarction. sLOX-1 was measured immediately after administration in the emergency department. The TIMI risk score was calculated separately for both groups. In hospital death, heart failure and recurrent infarction were considered major adverse cardiac events. RESULTS: There was a significant positive correlation between sLOX-1, TIMI risk score, major adverse cardiac events, and heart failure. The optimal cutoff value of sLOX-1 to predict clinical endpoints was 1.75 ng/mL in patients with ST elevation myocardial infarction and 1.35 ng/mL in patients with unstable angina/non-ST elevation myocardial infarction. CONCLUSIONS: Circulating sLOX-1 could be used as a biomarker to predict major adverse cardiac events in patients with ACS and may be clinically useful in the triage and management of these patients.

[35] *Luque A, Farwati A, Krupinski J, Aran JM*. **Association between low levels of serum miR-638 and atherosclerotic plaque vulnerability in patients with high-grade carotid stenosis**. Journal of neurosurgery 2018:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30052155
ABSTRACT

OBJECTIVE Carotid artery atherosclerosis is a major cause of ischemic stroke. However, reliable criteria to identify patients with high-risk carotid plaques beyond the severity of stenosis are still lacking. Circulating microRNAs (miRNAs) are being postulated as biomarkers for a variety of vascular immune-inflammatory diseases. The authors investigated whether cell-free circulating miR-638, highly expressed in vascular smooth muscle cells and implicated in proliferative vascular diseases, is associated with vulnerable atherosclerotic plaques in high-risk patients with advanced carotid artery stenosis undergoing carotid endarterectomy (CEA). METHODS The authors conducted a prospective study in 22 consecutive symptomatic patients with high-grade carotid stenosis undergoing CEA and 36 age- and sex-matched patients without ischemic stroke history or carotid atherosclerosis (control group). In addition, they reviewed data from a historical group of 9 CEA patients who underwent long-term follow-up after revascularization. Total RNA was isolated from all serum samples, and relative miR-638 expression levels were detected by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and compared among groups. A correlation analysis of serum miR-638 levels with vascular risk factors and treatments, and with plaque features, was performed. The ability of serum miR-638 to discriminate between the non-CEA control group and the different CEA groups was assessed by receiver operating characteristic evaluation. A logistic regression model was employed to examine the association between stratified CEA patients and serum miR-638 levels. RESULTS Serum levels of miR-638 were significantly lower in symptomatic CEA patients ($p = 0.009$) and particularly in the subgroup of CEA patients who had experienced stroke ($p = 0.0006$) than in non-CEA controls. Discrimination of high-risk plaques was accurate (area under the curve [AUC] 0.66 for symptomatic CEA patients in general and 0.76 for those who had experienced stroke). When only patients with high cardiovascular risk were considered, the diagnostic value of serum miR-638 from symptomatic CEA patients and CEA patients who had experienced stroke improved (AUC 0.79 and 0.85). Moreover, serum miR-638 was negatively correlated with the occurrence of stroke, smoker status, presence of bilateral pathology, coronary artery disease, and cholesterol treatment; and with the high-risk fibroatheroma plaques extracted from CEA patients. Multivariate logistic regression analysis demonstrated that serum miR-638 was an independent predictor of plaque instability. Furthermore, serum miR-638 appeared to attain good discrimination for atherosclerotic stenosis in CEA patients based on analysis of blood samples obtained in the historical group before and 5 years after intervention ($p = 0.04$) (AUC = 0.79). CONCLUSIONS According to this preliminary proof-of-concept study, serum miR-638 might constitute a promising noninvasive biomarker associated with plaque vulnerability and ischemic stroke, particularly in individuals with elevated cardiovascular risk.

[36] *Bakhshi H, Meyghani Z, Kishi S et al.* **Comparative Effectiveness of CT-Derived Atherosclerotic Plaque Metrics for Predicting Myocardial Ischemia**. JACC. Cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30031705
ABSTRACT
OBJECTIVES: This study sought to investigate the performance of various cardiac computed tomography (CT)-derived atherosclerotic plaque metrics for predicting provocable myocardial ischemia. BACKGROUND: The association of coronary arterial diameter stenosis with myocardial ischemia is only modest, but cardiac CT provides several other, readily available

atherosclerosis metrics, which may have incremental value. METHODS: The study analyzed 873 nonstented coronary arteries and their myocardial perfusion territories in 356 patients (mean 62 years of age) enrolled in the CORE320 (Coronary Artery Evaluation using 320-row Multidetector Computed Tomography Angiography and Myocardial Perfusion) study. Myocardial perfusion defects in static CT perfusion imaging were graded at rest and after adenosine in 13 myocardial segments using a 4-point scale. The summed difference score was calculated by subtracting the summed rest score from the summed stress score. Reversible ischemia was defined as summed difference score >/=1. In a sensitivity analysis, results were also provided using single-photon emission computed tomography (SPECT) as the reference standard. Vessel based predictor variables included maximum percent diameter stenosis, lesion length, coronary calcium score, maximum cross-sectional calcium arc, percent atheroma volume (PAV), low-attenuation atheroma volume, positive (external) vascular remodeling, and subjective impression of "vulnerable plaque." The study used logistic regression models to assess the association of plaque metrics with myocardial ischemia. RESULTS: In univariate analysis, all plaque metrics were associated with reversible ischemia. In the adjusted logistic model, only maximum percent diameter stenosis (1.26; 95% confidence interval: 1.15 to 1.38) remained an independent predictor. With SPECT as outcome variable, PAV and "vulnerable" plaque remained predictive after adjustment. In vessels with intermediate stenosis (40% to 70%), no single metric had clinically meaningful incremental value. CONCLUSIONS: Various plaque metrics obtained by cardiac CT predict provocable myocardial ischemia by CT perfusion imaging through their association with maximum percent stenosis, while none had significant incremental value. With SPECT as reference standard, PAV and "vulnerable plaque" remained predictors of ischemia after adjustment but the predictive value added to stenosis assessment alone was small.

[37] *Bathina S, Das UN*. **Dysregulation of PI3K-Akt-mTOR pathway in brain of streptozotocin-induced type 2 diabetes mellitus in Wistar rats**. Lipids in health and disease 2018; 17:168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30041644

ABSTRACT

BACKGROUND: Proteins of the insulin signaling pathway are needed for cell proliferation and development and glucose homeostasis. It is not known whether insulin signalling markers (Foxo1, Gsk3beta) can be correlated with the expression on PI3K-Akt-mTOR pathway, which are needed for cell survival and maintenance of glucose homeostasis. In the present study, we studied the expression of Foxo1, Gsk3beta and PI3K-Akt-mTOR in the brain of streptozotocin-induced type 2 diabetes mellitus Wistar rats. METHODS: The study was performed both in vitro (RIN5F cells) and in vivo (male Wistar rats). Gene expression of Nf-kB, IkB, Bax, Bcl-2 and Pdx1 gene was studied invitro by qRT-PCR in RIN5F cells. In STZ (65 mg/kg i.p.)-induced type 2 DM Wistar rats, blood glucose and insulin levels, iNOS, Foxo1, NF-kappaB, pGsk3beta and PPAR-gamma1 levels along with PI3k-Akt-mTOR were measured in brain tissue. RESULTS: RIN5F cells treated with STZ showed increase in the expression of NF-kB and Bax and decrease in IkB, Bcl-2 and PDX1. Brain tissue of STZ-induced type 2 DM animals showed a significant reduction in secondary messengers of insulin signalling (Foxo1) ($P < 0.001$) and Gsk3beta ($P < 0.01$) and a significant alteration in the expression of phosphorylated-Akt ($P < 0.001$) mTOR ($P < 0.01$) and PI3K. CONCLUSION: These results suggest that STZ induces pancreatic beta cell apoptosis by

enhancing inflammation. Significant alterations in the expression brain insulin signaling and cell survival pathways seen in brain of STZ-treated animals implies that alterations neuronal apoptosis may have a role in altered glucose homeostasis seen in type 2 DM that may also explain the increased incidence of cognitive dysfunction seen in them.

[38] *Liu H, Li X, Song Y, Wang Z*. **MicroRNA-217 attenuates intima-media complex thickness of ascending aorta measured by ultrasound bio-microscopy and inhibits inflammation and lipid metabolism in atherosclerotic models of ApoE(-/-) mice**. Lipids in health and disease 2018; 17:170.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30041636
ABSTRACT
BACKGROUND: Little investigation was done to test the efficiency of microRNA-217 (miR-217) on atherosclerosis in vivo. METHODS: ApoE(-/-) mice were used to construct atherosclerotic models and ultrasound bio-microscopy (UBM) was applied to detect the intima-media thickness (IMT) of the ascending aorta. The serum level of miR-217 and correlation with IMT was investigated. After miR-217 mimic administration, the IMT, inflammation, and lipid-associated molecules were assayed. RESULTS: The serum level of miR-217 was reduced in ApoE(-/-) mice and showed a negative correlation with the IMT of the ascending aorta ($r(2) = 0.5899$, $p < 0.0001$). miR-217 mimic administration attenuated IMT and down-regulated the level of serum triglyceride (TG), total cholesterol (TC), and low-density-lipoprotein cholesterol (LDL-C), while it could up-regulate high-density lipoprotein cholesterol (HDL-C). Inflammation relevant genes, such as F4/80, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-6, and monocyte chemoattractant protein (MCP)-1, and lipid metabolism associated gene, such as LDL receptor, class A scavenger receptors (SR-A), scavenger receptor class B type I (SR-BI), CD36, ATP binding cassette subfamily A member 1 (ABCA1), and ATP binding cassette subfamily G member 1 (ABCG1) in the aorta were significantly down-regulated in miR-217 group when compared with atherosclerosis group. CONCLUSION: miR-217 could down-regulate IMT and modulate the inflammation and lipid metabolism process, which indicates that miR-217 could be a potential treatment option.

[39] *Zhou Z, Chen H, Ju H, Sun M*. **Circulating chemerin levels and gestational diabetes mellitus: a systematic review and meta-analysis**. Lipids in health and disease 2018; 17:169.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30041634
ABSTRACT
BACKGROUND: Chemerin is a novel adipokine which is associated with metabolic syndrome and type 2 diabetes mellitus. However, recent investigations regarding circulating chemerin levels in gestational diabetes mellitus (GDM) are conflicting. This meta-analysis is to evaluate and determine their associations. METHODS: A systematic literature search was performed in PubMed, EMBASE and Web of Science up to 13 December 2017. Pooled standardized mean differences (SMD) and 95% confidence interval (CI) were calculated using a random-effect model. RESULTS: Eleven studies comprising 742 GDM patients and 840 normal pregnant women were included. Circulating chemerin levels were increased in GDM patients compared with healthy pregnant women (SMD: 1.16; 95% CI: 0.29, 2.04; P = 0.009). Subgroup analyses revealed such difference was especially available in the groups of the second trimester (SMD:

1.47; 95% CI: 0.28, 2.67) and mean age < 30 years (SMD: 2.30; 95% CI: 0.69, 3.91) of GDM patients. There was significant heterogeneity among studies (I(2) = 98.0%, P < 0.001); however, heterogeneity disappeared or markedly decreased in the subgroups of European populations (I(2) = 0.0%, P = 0.531), age >/= 30 years (I(2) = 28.2%, P = 0.223) and WHO diagnostic criteria (I(2) = 0.0%, P = 0.490) when stratifying by study location, trimester of chemerin measurement and the diagnostic criteria of GDM. CONCLUSIONS: The elevated levels of circulating chemerin were associated with GDM, which suggests it might play an important role in the pathogenetic mechanism of GDM.

[40] *Zhou Z, Zhong W*. **Targeting the gut barrier for the treatment of alcoholic liver disease**. Liver research 2017; 1:197-207.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30034913
ABSTRACT
Alcohol consumption remains one of the predominant causes of liver disease and liver-related death worldwide. Intriguingly, dysregulation of the gut barrier is a key factor promoting the pathogenesis of alcoholic liver disease (ALD). A functional gut barrier, which consists of a mucus layer, an intact epithelial monolayer and mucosal immune cells, supports nutrient absorption and prevents bacterial penetration. Compromised gut barrier function is associated with the progression of ALD. Indeed, alcohol consumption disrupts the gut barrier, increases gut permeability, and induces bacterial translocation both in ALD patients and in experimental models with ALD. Moreover, alcohol consumption also causes enteric dysbiosis with both numerical and proportional perturbations. Here, we review and discuss mechanisms of alcohol-induced gut barrier dysfunction to better understand the contribution of the gut-liver axis to the pathogenesis of ALD. Unfortunately, there is no effectual Food and Drug Administration-approved treatment for any stage of ALD. Therefore, we conclude with a discussion of potential strategies aimed at restoring the gut barrier in ALD. The principle behind antibiotics, prebiotics, probiotics and fecal microbiota transplants is to restore microbial symbiosis and subsequently gut barrier function. Nutrient-based treatments, such as dietary supplementation with zinc, niacin or fatty acids, have been shown to regulate tight junction expression, reduce intestinal inflammation, and prevent endotoxemia as well as liver injury caused by alcohol in experimental settings. Interestingly, saturated fatty acids may also directly control the gut microbiome. In summary, clinical and experimental studies highlight the significance and efficacy of the gut barrier in treating ALD.

[41] *Kuhnl A, Musiol A, Heitzig N et al.* **Late Endosomal/Lysosomal Cholesterol Accumulation Is a Host Cell-Protective Mechanism Inhibiting Endosomal Escape of Influenza A Virus**. mBio 2018; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30042202
ABSTRACT
To transfer the viral genome into the host cell cytoplasm, internalized influenza A virus (IAV) particles depend on the fusion of the IAV envelope with host endosomal membranes. The antiviral host interferon (IFN) response includes the upregulation of interferon-induced transmembrane protein 3 (IFITM3), which inhibits the release of the viral content into the cytosol. Although IFITM3 induction occurs concomitantly with late endosomal/lysosomal (LE/L)

cholesterol accumulation, the functional significance of this process is not well understood. Here we report that LE/L cholesterol accumulation itself plays a pivotal role in the early antiviral defense. We demonstrate that inducing LE/L cholesterol accumulation is antiviral in non-IFN-primed cells, restricting incoming IAV particles and impairing mixing of IAV/endosomal membrane lipids. Our results establish a protective function of LE/L cholesterol accumulation and suggest endosomal cholesterol balance as a possible antiviral target.IMPORTANCE With annual epidemics occurring in all parts of the world and the risk of global outbreaks, influenza A virus (IAV) infections remain a major threat to public health. Infected host cells detect viral components and mount an interferon (IFN)-mediated response to restrict virus propagation and spread of infection. Identification of cellular factors and underlying mechanisms that establish such an antiviral state can provide novel strategies for the development of antiviral drugs. The contribution of LE/L cholesterol levels, especially in the context of the IFN-induced antiviral response, has remained controversial so far. Here, we report that accumulation of cholesterol in the LE/L compartment contributes to the IFN-induced host cell defense against incoming IAV. Our results establish cholesterol accumulation in LE/L per se as a novel antiviral barrier and suggest the endosomal cholesterol balance as a putative druggable host cell factor in IAV infection.

[42] *Zhou R, Luo Y, Fenster A et al.* **Fractal dimension based carotid plaque characterization from three-dimensional ultrasound images**. Medical & biological engineering & computing 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30046955
ABSTRACT
Irregularity of the plaque surface associated with previous plaque rupture plays an important role in the risk estimation of stroke caused by carotid atherosclerotic lesions. Thus, the aim of this study is to develop and validate novel vulnerability biomarkers from three-dimensional ultrasound (3DUS) images by analyzing the surface morphological characteristics of carotid plaque using fractal geometry features. In the experiments, a total of 38 3DUS plaque images were obtained from two groups of patients treated with 80 mg of atorvastatin or placebo daily for 3 months respectively. Two types of 3D fractal dimensions (FDs) were used to describe the smoothness of plaque surface morphology and the roughness from intensity of 3DUS images. Student's t test showed that the two fractal features were effective for detecting the statin-related changes in carotid atherosclerosis with $p < 0.00023$ and $p < 0.0113$ respectively. It was concluded that the 3D FD measurements were effective for analyzing carotid plaque characteristics and especially effective for evaluating the impact of atorvastatin treatment. Graphical abstract .

[43] *Jeong S, Lee J, Kwon O et al.* **A randomized, double-blind, placebo-controlled trial investigating cholesterol-lowering effects and safety of yellow yeast rice in adults with mild to moderate hypercholesterolemia: A study protocol**. Medicine (Baltimore) 2018; 97:e11634.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30045307
ABSTRACT
BACKGROUND: Elevated levels of blood lipids are well-documented risk factors for cardiovascular disease. For cardiovascular risk reduction, preventive strategies to lower blood

cholesterol levels are essential, and these strategies include lifestyle modification and cholesterol-lowering agents. We aim to investigate the cholesterol-lowering effects and safety of yellow yeast rice in a randomized, controlled, double-blind, and parallel group study. METHODS: Participants for this study will be selected based on the following inclusion criteria:Participants are randomly allocated to the placebo or yellow-yeast-rice-treated group. Participants with mild to moderately elevated LDL-C levels will consume 1 pouch of yellow yeast rice powder (containing monacolin K) or placebo twice daily for 8 weeks. Next, the lipid profiles will be evaluated. RESULTS: The number of participants required for this study is 68, and is currently recruiting participants. Participants are randomly assigned to control group and intervention group. CONCLUSION: This is the first human intervention study to investigate the cholesterol-lowering effects and safety of yellow yeast rice in adults with mild to moderate hypercholesterolemia. Also, this is a randomized, double-blind, placebo-controlled trial that considers confounders, such as dietary habits, lifestyle factors, and genetic factors.

[44] *Sun PP, Feng PY, Wang Q, Shen SS*. **Angiography with the 256-multislice spiral computed tomography and its application in evaluating atherosclerotic plaque and cerebral ischemia**. Medicine (Baltimore) 2018; 97:e11408.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30045262
ABSTRACT
Ulceration of carotid arterial plaque is associated with cerebral events. Detection of ulcerated plaques will benefit patient from stroke and other ischemic events. The aim of this study was to evaluate morphology of atherosclerotic plaques in the carotid arteries and to assess its clinical impact in predicting cerebral events.A total of 386 patients were examined with 256-multislice spiral computed tomographic angiography (MSCTA).It was found that 356 of the 386 patients had cerebral ischemic symptoms. Specifically, 35 patients had amaurosis fugax (AmF), 178 had transient ischemic attack (TIA), and 143 had ischemic stroke. Abnormal images were found in 658 carotid arteries by MSCTA. Of the 658 abnormal images of carotid arteries, besides the 34 cases of carotid arterial occlusion, 624 cases were atherosclerotic plaques. Of the 624 plaques, 394 (63.2%) were smooth surface plaques, 161 (25.8%) were irregular surface plaques, and 69 (11.1%) were ulcerated plaques. Incidence of ulcerated plaque was higher in the ischemic stroke patients (13.1%) compared with that in the TIA group (10.3%), AmF group (6.6%), or symptom-free group (9.4%) although it was not statistically significant (P = .288). However, there was significant difference in the incidence of ischemic stroke between the ulcerated (20/69, 28.9%) and nonulcerated groups (69/555, 12.4%, P < .05, odds ratio = 2.875).These findings suggested that 256-MSCTA is an advanced imaging tool to determine not only arterial stenosis but also morphologic assessment of atherosclerotic plaques, which will benefit the patients by predicting the cerebral events in advance.

[45] *Garbacz WG, Uppal H, Yan J et al.* **Chronic Activation of LXR Sensitizes Mice to High Cholesterol Diet Induced Gut Toxicity**. Molecular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30045953
ABSTRACT
Cholesterol is essential for numerous biological functions and processes, but an excess of intracellular cholesterol can be toxic. Intestinal cholesterol absorption is a major determinant of

plasma cholesterol level. The liver X receptor (LXR) is a nuclear receptor known for its activity in cholesterol efflux and reverse cholesterol transport (RCT). In this study, we uncovered a surprising function of LXR in intestinal cholesterol absorption and toxicity. Genetic or pharmacological activation of LXRalpha sensitized mice to high cholesterol diet (HCD) induced intestinal toxicity and tissue damage including the disruption of enterocyte tight junctions, whereas the same HCD caused little toxicity in the absence of LXR activation. The gut toxicity in HCD-fed LXR-KI mice may have been accounted for by the increased intestinal cholesterol absorption and elevation of enterocyte and systemic levels of free cholesterol. The increased intestinal cholesterol absorption preceded the gut toxicity, suggesting that the increased absorption was not secondary to tissue damage. Interestingly, the heightened sensitivity to HCD in the HCD-fed LXRalpha-activated mice appeared to be intestine specific, because the liver was not affected despite the activation of the same receptor in this tissue. Moreover, the heightened sensitivity to HCD cannot be reversed by ezetimibe, a Niemann-Pick C1-Like 1 (NPC1L1) inhibitor that inhibits intestinal cholesterol absorption, suggesting that the increased cholesterol absorption in LXR-activated intestine is mediated by a yet to be defined mechanism.

[46] *Gomez D, Baylis RA, Durgin BG et al.* **Interleukin-1beta has atheroprotective effects in advanced atherosclerotic lesions of mice**. Nat Med 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30038218
ABSTRACT
Despite decades of research, our understanding of the processes controlling late-stage atherosclerotic plaque stability remains poor. A prevailing hypothesis is that reducing inflammation may improve advanced plaque stability, as recently tested in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial, in which post-myocardial infarction subjects were treated with an IL-1beta antibody. Here, we performed intervention studies in which smooth muscle cell (SMC) lineage-tracing Apoe(-/-) mice with advanced atherosclerosis were treated with anti-IL-1beta or IgG control antibodies. Surprisingly, we found that IL-1beta antibody treatment between 18 and 26 weeks of Western diet feeding induced a marked reduction in SMC and collagen content, but increased macrophage numbers in the fibrous cap. Moreover, although IL-1beta antibody treatment had no effect on lesion size, it completely inhibited beneficial outward remodeling. We also found that SMC-specific knockout of Il1r1 (encoding IL-1 receptor type 1) resulted in smaller lesions nearly devoid of SMCs and lacking a fibrous cap, whereas macrophage-selective loss of IL-1R1 had no effect on lesion size or composition. Taken together, these results show that IL-1beta has multiple beneficial effects in late-stage murine atherosclerosis, including promotion of outward remodeling and formation and maintenance of an SMC- and collagen-rich fibrous cap.

[47] *Chung CP, Chou KH, Peng LN et al.* **Associations between low circulatory low-density lipoprotein cholesterol level and brain health in non-stroke non-demented subjects**. NeuroImage 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30053515
ABSTRACT
Low-density lipoprotein cholesterol (LDL-C) and hypertension have independent and synergistic effects on atherosclerotic cardiovascular disease. However, the role of circulatory LDL-C and its

possible interactions with hypertension in brain health have been poorly investigated. The study aimed to investigate the relationship between the circulatory LDL-C level and (1) brain structures, grey-matter volume (GMV) and white matter hyperintensity (WMH) and (2) cognitive functions, and whether hypertension plays a role in these relationships. Subjects who were non-stroke and non-demented were prospectively recruited from the community-based I-Lan Longitudinal Aging Study. High-resolution 3T MRI was performed with GM and WMH segmentation. GMVs, total and regional including Alzheimer's disease-susceptible area, and WMH volumes were measured. Neurological tests including verbal memory, visuospatial, and verbal executive functions were assessed. Eight-hundred-and-two participants(59.2+/-5.7 years; 44% men) were included. Multivariate linear regression analyses showed that low circulatory LDL-C levels (<98mg/dL) were significantly associated with reduced GMVs in frontal (standardized beta=-0.130; p=0.003) and posterior cingulate (beta=-0.113; p=0.032) regions in hypertensive but not normotensive subjects. In addition, low circulatory LDL-C levels, combined with hypertension, had the lowest posterior cingulate GMV (beta=-0.073; p=0.021), highest periventricular WMH (beta=0.089; p=0.011) and lowest verbal memory test scores (beta=-0.088; p=0.035) compared with neither low circulatory LDL-C level nor hypertension, and either hypertension or low circulatory LDL-C level. Age, sex, total intracranial volume, vascular risk factors, level of other circulatory lipids, and the taking of anti-hypertensive and lipid-lowering medications were adjusted. In conclusion, the role of circulatory LDL-C level and its interactive effect with hypertension on brain health are firstly demonstrated. A low circulatory LDL-C level was associated with reduced regional brain GMVs in hypertensive but not normotensive subjects. In addition, there seems a combined detrimental-effect of low circulatory LDL-C levels with hypertension on posterior cingulate GMV, WMH, and verbal memory.

[48] *Badescu C, Rezus E, Badescu L et al.* **New Drugs for Lowering LDL-Cholesterol**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 2016; 120:485-490.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30044561

ABSTRACT

LDL-Cholesterol (LDL-C) is a well-known risk factor for cardiovascular disease. Although statins are the mainstream treatment for lowering LDL-C level, additional LDL-lowering therapies are needed to reduce residual cardiovascular risk, especially in patients at very high risk, or with hereditary lipid disorderes or statin intolerance. The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator for LDL-Receptor activity and an attractive target for the treatment of hypercholesterolaemia. From its discovery in 2003, several therapeutic approaches to the inhibition of PCSk9 have been proposed. Monclonal antibodies that bind to PCSJ9 received marketing approval in 2015 (alirocumab and evolucumab) or are being evaluated in phase III trials (bococizumab). Many other molecules are in preclinical studies, phase I or II clinical trials. Another point of interest carefully investigated is the cardiovascular benefit of reducing LDL-C using these new molecules. High hopes are invested in them.