Literature update week 41 (2019)

[1] *Panajatovic MV, Singh F, Roos NJ et al.* **PGC-1alpha plays a pivotal role in simvastatin-induced exercise impairment in mice**. Acta Physiol (Oxf) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31605661
ABSTRACT
AIM: Statins decrease cardiovascular complications, but can induce myopathy. Here, we explored the implication of PGC-1alpha in statin-associated myotoxicity. METHODS: We treated PGC-1alpha knockout (KO), PGC-1alpha over-expression (OE) and wild-type mice (WT) mice orally with 5 mg simvastatin kg(-1) day(-1) for 3 weeks and assessed muscle function and metabolism. RESULTS: In WT and KO mice, but not in OE mice, simvastatin decreased grip strength, maximal running distance and vertical power assessed by ergometry. Post exercise plasma lactate concentrations were higher in WT and KO compared to OE mice. In glycolytic gastrocnemius, simvastatin decreased mitochondrial respiration, increased mitochondrial ROS production and free radical leak in WT and KO, but not in OE mice. Simvastatin increased mRNA expression of Sod1 and Sod2 in glycolytic and oxidative gastrocnemius of WT, but decreased it in KO mice. OE mice had a higher mitochondrial DNA content in both gastrocnemius than WT or KO mice and simvastatin exhibited a trend to decrease the citrate synthase activity in white and red gastrocnemius in all treatment groups. Simvastatin showed a trend to decrease the mitochondrial volume fraction in both muscle types of all treatment groups. Mitochondria were smaller in WT and KO compared to OE mice and simvastatin further reduced the mitochondrial size in WT and KO mice, but not in OE mice. CONCLUSIONS: Simvastatin impairs skeletal muscle function, muscle oxidative metabolism and mitochondrial morphology preferentially in WT and KO mice, whereas OE mice appear to be protected, suggesting a role of PGC-1alpha in preventing simvastatin-associated myotoxicity.

[2] *Huang JL, Yu C, Su M et al.* **Probucol, a "non-statin" cholesterol-lowering drug, ameliorates D-galactose induced cognitive deficits by alleviating oxidative stress via Keap1/Nrf2 signaling pathway in mice**. Aging 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31590160
ABSTRACT
Oxidative stress plays a vital role in the initiation and progression of age-related neurodegenerative diseases. Ameliorating oxidative damage is therefore considered as a beneficial strategy for the treatment of age-related neurodegenerative disorders. Probucol (Prob), a lipid-lowering prototype agent, was reported to treat cardiovascular diseases, chronic kidney disease and diabetes mellitus. However, whether Prob has an effect on age-related neurodegenerative diseases remains unknown. In the study, it was found that Prob ameliorated D-galactose (D-gal) induced cognitive deficits and neuronal loss in the hippocampal CA1 region. Moreover, Prob alleviated ROS and MDA levels by elevating SOD, GSH-PX and HO-1 mRNA and protein expressions, and improving plasmic and cerebral SOD and GSH-PX activities in D-gal treated mice. Furthermore, Prob promoted the dissociation of Keap1/Nrf2 complex leading to the accumulation of Nrf2 in nucleus, implying that the improved anti-oxidant property of Prob is mediated by Keap1/Nrf2 pathway. The study firstly demonstrates the favorable effects of Prob against cognitive impairments in a senescent mouse model, rendering this compound a promising agent for the treatment or prevention of age-related neurodegenerative disease.

[3] *Quan W, Zhang Z, Li P et al.* **Role of Regulatory T cells in Atorvastatin Induced Absorption of Chronic Subdural Hematoma in Rats**. Aging and disease 2019; 10:992-1002.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31595197
ABSTRACT
Chronic subdural hematoma (CSDH) is a neurological disorder with a substantial recurrence rate. Atorvastatin is an effective drug for treating hyperlipidemia and known to improve neurological outcome after intracerebral hemorrhage. Previous studies have reported that atorvastatin treatment promotes hematoma absorption in CSDH, while the underlying mechanisms remain unclear. In this study, we investigated whether the anti-inflammatory effects of atorvastatin mediate absorption of CSDH. 144 male, Wistar rats (6 months old) were randomly divided into the following groups: 1) sham surgery control, 2) treatment: CSDH + atorvastatin, and 3) vehicle control: CSDH + saline. Atorvastatin or saline was orally administered daily for 19 days after CSDH procedure. A T2WI MRI was used to evaluate CSDH volume changes during the time course of the study. Flow cytometry and immunohistochemical staining were used to measure the number of regulatory T cells (Treg). ELISA was used to measure cytokine level in the hematoma border. Neurological function and cognitive outcome were evaluated using Foot-Fault test and Morris Water Maze test, respectively. When compared to saline treatment, atorvastatin treatment accelerated the absorption of CSDH as indicated by decreased hematoma volume in T2WI MRI data on 14(th) and 21(st) day after CSDH ($P<0.05$). Atorvastatin treatment significantly increased the number of Treg in circulation and hematoma border from 3(rd) to 21(st) day after CSDH. Atorvastatin treatment significantly decreased the levels of interleukins (IL-6 and IL-8) and tumor necrosis factor-alpha (TNF-alpha), but increased IL-10 level in the hematoma border. Atorvastatin treatment also improved neurological function and cognitive outcome compared to vehicle treated group. Atorvastatin induced anti-inflammatory responses and increased Treg in circulation and brain which may contribute to the accelerated CSDH absorption in rats.

[4] *Greve AM, Bang CN, Boman K et al.* **Relation of Lipid-Lowering Therapy to Need for Aortic Valve Replacement in Patients With Asymptomatic Mild to Moderate Aortic Stenosis**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31586530
ABSTRACT
In this study, we aimed to determine if pretreatment low-density lipoprotein (LDL) levels and aortic stenosis (AS) severity alter the efficacy of lipid-lowering therapy on reducing aortic valve replacement (AVR). We used 1,687 patients with asymptomatic mild-to-moderate AS, who were randomly assigned (1:1) to 40/10 mg simvastatin/ezetimibe combination versus. placebo in the simvastatin and ezetimibe in aortic stenosis (SEAS) trial. Pretreatment LDL levels (>4 mmol/L) and peak aortic jet velocity (3 m/s) were used to partition study participants into 4 groups, which were followed for a primary endpoint of AVR. Cox regression with tests for interaction was used to study the effect of randomized treatment in each subgroup. During a median follow-up of 4.3 years (IQR 4.2 to 4.7 years; total 7,396 patient-years of follow-up), 478 (28%) patients underwent AVR and 146 (9%) died. A significant risk dependency was detected between simvastatin/ezetimibe combination, LDL levels and mild versus moderate AS on rates of AVR ($p=0.01$ for interaction). In stratified analyses, randomized treatment, therefore,

reduced the rate of AVR in patients with LDL levels >4 mmol and mild AS at baseline (HR 0.4; 95% CI: 0.2 to 0.9). There was no detectable effect of randomized treatment on the need for AVR in the 3 other participants subgroups. We conclude, that in a secondary analysis from a prospective randomized clinical trial, treatment with simvastatin/ezetimibe combination reduced the need for AVR in a subset of patients with mild AS and high pretreatment LDL levels (Unique identifier on clinicaltrials.gov: NCT00092677).

[5] *Pedrosa JF, Ribeiro ALP, Santana PC et al.* **Relation of Thoracic Aortic and Coronary Artery Calcium to Cardiovascular Risk Factors (from The Brazilian Longitudinal Study of Adult Health [ELSA-Brazil])**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31590910
ABSTRACT
Thoracic aortic calcium (TAC) and coronary artery calcium (CAC) are associated with an increased risk of cardiovascular disease (CVD) and death. However, risk factors associated with arterial calcium may vary across vascular beds. We verified whether TAC is associated with the same risk factors as is CAC in adults without established CVD. Cross-sectional analysis including 2,433 participants (aged 38 to 78 years) of ELSA-Brasil cohort in Minas Gerais, Brazil. Nonenhanced ECG-gated multislice computed tomography were performed to detect calcium in the thoracic aorta and the coronaries (2015 to 2016). Multivariate logistic regression evaluated the associations of both TAC and CAC with CVD risk factors (smoking, body mass index, physical activity, alcohol intake, family history of CVD, low-density lipoprotein- and high-density lipoprotein-cholesterol, HbA1c, blood pressure, antidiabetic, antihypertensive, and lipid lowering medications). Overall prevalence of TAC and CAC were 69% and 43%, respectively. CAC prevalence was lower among women (31%) than men (56%) (Adjusted odds ratio [OR] 0.30; 0.24 to 0.38). After adjustments, black individuals were less likely to have any CAC as compared with whites (OR 0.63; 0.47 to 0.86). Neither sex, nor race/skin color were statistically associated with TAC. Use of antidiabetic medications remained associated with CAC (OR 1.80; 1.23 to 2.631.01), but not with TAC. All other risk factors, except education, alcohol, physical activity and HbA1c, persisted statistically associated with both TAC and CAC in the final analysis, with small differences in the magnitudes of the ORs. In conclusion, the only disagreements seen in the risk factors associated with CAC and TAC were sex, race/skin color, and use of antidiabetic medications.

[6] *Bertomeu-Gonzalez V, Soriano Maldonado C, Bleda-Cano J et al.* **Predictive validity of the risk SCORE model in a Mediterranean population with dyslipidemia**. Atherosclerosis 2019; 290:80-86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31593904
ABSTRACT
BACKGROUND AND AIMS: Cholesterol treatment for the primary prevention of cardiovascular disease is based on cardiovascular risk, as assessed by the SCORE (Systematic COronary Risk Evaluation) scale. This study aimed to assess the predictive value and clinical utility of the SCORE scale for preventing cardiovascular events and all-cause mortality in people with dyslipidemia and no lipid-lowering treatment. METHODS: Patients with dyslipidemia and no lipid-lowering treatment were included from the ESCARVAL-RISK cohort. Cardiovascular risk

was calculated by means of the SCORE scale. All deaths and cardiovascular events were recorded for up to five years of follow-up. We calculated sensitivity, specificity and other predictive values for different cut-off points and assessed the effect of different risk factors on the diagnostic accuracy of the SCORE charts. RESULTS: In the final cohort of 18,853 patients, there were 1565 cardiovascular events and 268 deaths. The risk value recommended to initiate pharmacological treatment (5%) presented a specificity of 86% for death and 90% for cardiovascular events, and a sensitivity of 53% for death and 32% for cardiovascular events. In addition, the scale classified as low risk 62.8% of the patients who suffered a cardiovascular event and 46.6% of those who died. Antithrombotic treatment, diabetes, hypertension, heart failure, peripheral artery disease and chronic kidney disease were associated with a reduction in the predictive capability of the SCORE scale, whereas metabolic syndrome was related to better risk prediction. CONCLUSIONS: The predictive capability of the SCORE scale for cardiovascular disease and total mortality in patients with dyslipidemia is limited.

[7] *Rico-Jimenez JJ, Campos-Delgado DU, Buja LM et al.* **Intravascular optical coherence tomography method for automated detection of macrophage infiltration within atherosclerotic coronary plaques**. Atherosclerosis 2019; 290:94-102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31604172
ABSTRACT
BACKGROUND AND AIMS: Significant macrophages infiltration in advanced atherosclerotic plaques promotes acute coronary events. Hence, the clinical imaging of macrophage content in coronary atherosclerotic plaques could potentially aid in identifying patients most at risk of future acute coronary events. The aim of this study was to introduce and validate a simple intravascular optical coherence tomography (IV-OCT) image processing method for automated, accurate and fast detection of macrophage infiltration within coronary atherosclerotic plaques. METHODS: This method calculates the ratio of the normalized-intensity standard deviation (NSD) values estimated over two axially-adjacent regions of interest in an IV-OCT cross-sectional image (B-scan). When applied to entire IV-OCT B-scans, this method highlights plaque areas with high NSD ratio values (NSDRatio), which was demonstrated to be correlated with the degree of coronary plaque macrophage infiltration. RESULTS: Using an optimized NSDRatio threshold value, coronary plaque macrophage infiltration could be detected with ~88% sensitivity and specificity in a database of 28 IV-OCT scans from postmortem coronary segments. For comparison, using an optimized NSD threshold value, considered the standard IV-OCT signature for macrophages, coronary plaque macrophage infiltration could be detected with only ~55% sensitivity and specificity. CONCLUSIONS: The proposed NSDRatio method significantly increases the sensitivity and specificity for the detection of coronary plaque macrophage infiltration compared to the standard NSD method. This computationally efficient method can be seamlessly implemented within standard IV-OCT imaging systems for in-vivo real-time imaging of macrophage content in coronary plaques, which could potentially aid in identifying patients most at risk of future acute coronary events.

[8] *Yang L, Song L, Ma D et al.* **Plasma S100A4 level and cardiovascular risk in patients with unstable angina pectoris**. Biomarkers in medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31596125

ABSTRACT

Aim: We investigated whether S100A4 level is associated with pathophysiology of unstable angina pectoris (UAP), and its potential prognostic value for subsequent cardiovascular events. Methods: We compared plasma levels of S100A4 and a set of clinical markers in three groups (59 with UAP, 32 with stable angina pectoris and 30 healthy controls). Results: S100A4 levels in patients with UAP were significantly elevated. In UAP group, baseline S100A4 levels were significantly higher in patients with subsequent cardiovascular events than those without, a positive correlation was identified between the risk of subsequent cardiovascular events and the plasma levels of S100A4. Conclusion: Elevated S100A4 levels may be involved in the pathogenesis of UAP, and may be a marker predictive of post-treatment cardiovascular events.

[9] *Hussain K, Xavier A*. **Rosuvastatin-related rhabdomyolysis causing severe proximal paraparesis and acute kidney injury**. BMJ case reports 2019; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31601550

ABSTRACT

We describe the case of a 76-year-old man who presented with bilateral lower limb weakness associated with decreased urine output. His initial blood results showed acute kidney injury (AKI) stage 3 with substantially raised serum creatine kinase concentration of 37 950 IU/L (normal range <171 U/L). He had been on high-dose rosuvastatin for 4 years with a recent brand change occurring 1 week prior to onset of symptoms. There was no history of pre-existing neuromuscular disease. Statin-related rhabdomyolysis was suspected and rosuvastatin was withheld. His muscle strength gradually improved. He required haemodialysis for 10 weeks. He was discharged home after a complicated course of hospitalisation. His renal function improved and he became dialysis-independent; however, he was left with residual chronic kidney disease.

[10] *Carroll CB, Webb D, Stevens KN et al.* **Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): protocol for a double-blind, randomised, placebo-controlled futility study**. BMJ open 2019; 9:e029740.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31594876

ABSTRACT

INTRODUCTION: Parkinson's disease (PD) is a progressive neurodegenerative condition affecting approximately 185,000 people in the UK. No drug has been proven to slow disease progression. Epidemiological and pre-clinical data support simvastatin, a widely used cholesterol-lowering drug with a well-established safety profile, having neuroprotective properties. The aim of this study (Simvastatin as a neuroprotective treatment for PD (PD STAT)) is to determine whether simvastatin has the potential to slow PD progression. The study is part of the International Linked Clinical Trials initiative coordinated by The Cure Parkinson's Trust. This paper describes the protocol for the PD STAT study. METHODS AND ANALYSIS: PD STAT is a double-blind, randomised, placebo-controlled, multi-centre, parallel group, futility trial in patients with PD of mild-moderate severity. 235 participants have been recruited and randomly allocated in a 1:1 ratio to receive either oral simvastatin or matched placebo. Treatment involves a 1-month low-dose phase (40 mg daily), followed by a 23-month high-dose phase (80 mg daily) and ends with a 2-month washout period. Participants are reviewed at clinic visits at 1

month, 6, 12, 18, 24 and 26 months post-baseline, with interim telephone follow-up to monitor for adverse events.The primary outcome is the change in the Movement Disorder Society Unified Parkinson's Disease Rating Scale part III motor subscale score in the practically defined OFF medication state (OFF state) between baseline and 24 months. Primary analysis will be on a modified intention to treat basis and will include only those participants who progress to the high-dose phase of the study. ETHICS AND DISSEMINATION: The protocol has been approved by the North East-Newcastle and North Tyneside 2 Research Ethics Committee. The results will be disseminated via research articles in peer-reviewed journals and presentations at local, national and international scientific meetings, as well as disseminated via patient groups, websites and networks. A summary of the study findings will be posted to participants at the end of the study. TRIAL REGISTRATION: ISRCTN16108482 (prospectively registered); EudraCT 2015-000148-40; ClinicalTrials.gov NCT02787590; Pre-results.

[11] *Daghem M, Newby DE*. **Detecting unstable plaques in humans using cardiac CT Can it guide treatments?** Br J Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31596945
ABSTRACT
Advances in imaging technology have driven the rapid expansion in the use of computed tomography in the assessment of coronary atherosclerotic plaque. Current guidelines recommend coronary CT angiography as the first line diagnostic test for patients presenting with stable chest pain based on a rapidly growing evidence base. There is a growing need to refine current methods for diagnosis and risk stratification to better individualise preventative therapies. Imaging assessments of high-risk plaque with computed tomography can be used to differentiate stable from unstable patterns of coronary atherosclerosis and potentially to improve patient risk stratification. This review will focus on coronary imaging with computed tomography with a specific focus on the detection of coronary atherosclerosis, high-risk plaque features, and the implications for patient management.

[12] *Kikuchi M, Nakaya A*. **[Apolipoprotein E4, a Genetic Risk Factor for Alzheimer's Disease]**. Brain and nerve = Shinkei kenkyu no shinpo 2019; 71:1053-1060.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31588049
ABSTRACT
Apolipoprotein E (APOE) is reported to be a strong genetic risk factor for Alzheimer's disease (AD), broadly contributing to the AD pathologies observed in most populations. However, it is difficult to explicate these AD pathologies based only on the known functions of APOE. In this review article, we revisited the histories and functions of APOE and also reviewed its recently elucidated the pleiotropic roles in the brain.

[13] *Poston RN*. **Atherosclerosis: integration of its pathogenesis as a self-perpetuating propagating inflammation: a review**. Cardiovascular endocrinology & metabolism 2019; 8:51-61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31588428
ABSTRACT

This review proposes that the development of the atherosclerotic plaque is critically dependent on its inflammatory components forming a self-perpetuating and propagating positive feedback loop. The components involved are: (1) LDL oxidation, (2) activation of the endothelium, (3) recruitment of inflammatory monocytes, (4) macrophage accumulation, which induces LDL oxidation, and (5) macrophage generation of inflammatory mediators, which also activate the endothelium. Through these stages, the positive feedback loop is formed, which generates and promotes expansion of the atherosclerotic process. To illustrate this dynamic of lesion development, the author previously produced a computer simulation, which allowed realistic modelling. This hypothesis on atherogenesis can explain the existence and characteristic focal morphology of the atherosclerotic plaque. Each of the components contributing to the feedback loop is discussed. Many of these components also contain subsidiary positive feedback loops, which could exacerbate the overall process.

[14] *Liu S, Deng X, Zhang P et al.* **Blood flow patterns regulate PCSK9 secretion via MyD88 mediated proinflammatory cytokines**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31593224
ABSTRACT
AIMS: Blood flow patterns play an important role in the localization of atherosclerosis in the sense that low-flow state is pro-atherogenic, and helical flow is protective against atherosclerosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates cholesterol metabolism via LDL receptor degradation and is highly expressed in the atherosclerotic tissues. This study was designed to investigate the role of different blood flow patterns in the regulation of PCSK9 expression. METHODS AND RESULTS: We designed an experimental model guider to generate stable helical flow. Our data showed that compared with normal flow, low flow state induces while helical flow inhibits PCSK9 expression in the rabbit thoracic aorta in an inflammatory state. Our data also identified that TLR4-MyD88-NF-kappaB signaling plays an important role in PCSK9 expression. On the other hand, TRIF pathway had almost no effect. Further studies showed that the signals downstream of NF-kappaB, such as proinflammatory cytokines (IL-1beta, IL-18, MCP-1, IL-6, TNF-alpha, IL-12, IFNgamma and GM-CSF) directly influence PCSK9 expression. Interestingly, high fat diet further enhanced PCSK9 expression in an inflammatory milieu. CONCLUSIONS: These observations suggest a link between abnormal flow patterns and PCSK9 expression in inflammatory states, which may qualify helical flow and proinflammatory cytokines as potential targets to treat PCSK9 related cardiovascular diseases. TRANSLATIONAL PERSPECTIVE: PCSK9 regulates LDL receptor degradation and plays key roles in hypercholesterolemia and related cardiovascular diseases. In this study, we show that helical flow which is associated with atherosclerosis induces more PCSK9 than linear flow. Further proinflammatory cytokines directly determine PCSK9 levels. As upstream pathway, TLR4-MyD88-NF-kappaB signaling plays an important role in the regulation of PCSK9 expression. TRIF has almost no effect in this signaling. Thus, inhibition of TLR4-MyD88-NF-kappaB signaling may be a novel strategy to attenuate PCSK9 release associated with helical flow.

[15] *Zhou E, Hoeke G, Li Z et al.* **Colesevelam enhances the beneficial effects of brown fat activation on hyperlipidemia and atherosclerosis development**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31589318

ABSTRACT
AIMS: Brown fat activation accelerates the uptake of cholesterol-enriched remnants by the liver and thereby lowers plasma cholesterol, consequently protecting against atherosclerosis development. Hepatic cholesterol is then converted into bile acids (BAs) that are secreted into the intestine and largely maintained within the enterohepatic circulation. We now aimed to evaluate the effects of prolonged brown fat activation combined with inhibition of intestinal BA reabsorption on plasma cholesterol metabolism and atherosclerosis development. METHODS AND RESULTS: APOE*3-Leiden.CETP mice with humanized lipoprotein metabolism were treated for 9 weeks with the selective beta3-adrenergic receptor (AR) agonist CL316,243 to substantially activate brown fat. Prolonged beta3-AR agonism reduced fecal BA excretion (-31%), while markedly increasing plasma levels of total BAs (+258%), cholic acid-derived BAs (+295%) and chenodeoxycholic acid-derived BAs (+217%), and decreasing the expression of hepatic genes involved in BA production. In subsequent experiments mice were additionally treated with the BA sequestrant Colesevelam to inhibit BA reabsorption. Concomitant intestinal BA sequestration increased fecal BA excretion, normalized plasma BA levels and reduced hepatic cholesterol. Moreover, concomitant BA sequestration further reduced plasma total cholesterol (-49%) and non-high-density lipoprotein-cholesterol (-56%), tended to further attenuate atherosclerotic lesion area (-54%). Concomitant BA sequestration further increased the proportion of lesion-free valves (+34%) and decreased the relative macrophage area within the lesion (-26%) thereby further increasing the plaque stability index (+44%). CONCLUSIONS: BA sequestration prevents the marked accumulation of plasma BAs as induced by prolonged brown fat activation thereby further improving cholesterol metabolism and reducing atherosclerosis development. These data suggest that combining brown fat activation with BA sequestration is a promising new therapeutic strategy to reduce hyperlipidemia and cardiovascular diseases. A TRANSLATIONAL PERSPECTIVE: Current therapeutic strategies are unable to prevent the majority of cardiovascular disease (CVD)-relating morbidities and mortalities, illustrating the need for new therapeutic strategies. Brown fat has been shown as an emerging target to combat hyperlipidemia and atherosclerosis. Here we showed that prolonged brown fat activation promotes bile acid (BA) reabsorption, resulting in elevated plasma BA and hepatic cholesterol content, both of which are reversed by additional BA sequestration. Importantly, combining BA sequestration with brown fat activation further lowers plasma cholesterol and reduces atherosclerosis development, indicating the combination therapy as a new therapeutic strategy to treat hyperlipidemia, and ultimately CVD.

[16] *Saad Shaukat MH, Toledo-Garcia A, Torosoff M*. **Recurrent Myocardial Infarction Despite Normal C-reactive Protein in a Patient with Behcet's Disease and Compound Heterozygous Methylenetetrahydrofolate Reductase (MTHFR) Mutations (C677T and A1298C)**. Cureus 2019; 11:e5344.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31602349

ABSTRACT
A 39-year-old diabetic female with Behcet's disease presented with acute inferior wall myocardial infarction and underwent successful angioplasty of the occluded circumflex artery with a bare-metal stent (balancing increased the bleeding risk with Behcet's). Other coronary vessels were free of obstructive atherosclerosis. Optimal coronary artery disease (CAD) therapy

was commenced, and Behcet's disease treatment was intensified with the normalization of C-reactive protein. Two years later, she presented with an acute left anterior descending artery occlusion that was managed with a drug-eluting stent this time. There was no evidence of diffuse atherosclerosis on coronary angiogram or coronary calcifications on the chest computed tomography (CT) scan. Compound heterozygous methylenetetrahydrofolate reductase (MTHFR) mutations (C677T and A1298C) and high-normal plasma homocysteine were detected. With the long-term continuation of dual anti-platelet, lipid-lowering, immunosuppressive, and folic-acid therapies, she did not have cardiac events during the three-year follow-up. This is the first report of recurrent thrombotic acute coronary syndrome (ACS) in a patient with diabetes, compound heterozygous MTHFR mutations, Behcet's disease with normal C-reactive protein (CRP), and no evidence of diffuse coronary artery disease.

[17] *Darnton-Hill I*. **Public Health Aspects in the Prevention and Control of Vitamin Deficiencies**. Current developments in nutrition 2019; 3:nzz075.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31598578
ABSTRACT
Vitamin deficiencies remain major etiological factors in the global burden of disease, especially in low- and middle-income countries. The purpose of this state-of-the-art review was to update current information on deficiencies of vitamins and public health approaches to addressing them. Some stages of life present a higher risk of deficiency than others: risks are higher in pregnant women, children (from conception to young childhood), adolescents, the elderly, and all of the over 800 million people globally who are undernourished. At risk are approximately 125 million preschool children with vitamin A deficiency, as well as sub-populations at risk of deficiencies of folate, thiamin, vitamin B12, niacin, riboflavin, other B vitamins. and vitamin D. Addressing micronutrient deficiencies requires identifying those at risk and then working to prevent and manage that risk. Public health approaches include improved, diversified diets; supplementation; fortification and biofortification; and other supportive public health measures. Historically, as with pellagra and beriberi and, in the last 3 decades, with vitamin A and folic acid, there has been encouraging progress, but much remains to be done.

[18] *Gallo G, Battistoni A, Coluccia R et al.* **Legacy Effect in the Treatment of Hypertension: Persistent Cardiovascular Protection after Conclusion of Randomized Clinical Trials in Hypertension**. Curr Hypertens Rep 2019; 21:85.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31599359
ABSTRACT
RECENT FINDINGS: Essential hypertension is the main determinant of cardiovascular morbidity and mortality worldwide. During the last decades, several antihypertensive drug therapies have been introduced and tested in clinical trials, both as monotherapies and combination therapies. The current recommended therapeutic approaches effectively reduce the lifetime risk of experiencing major cardiovascular outcomes and disabling comorbidities, such as myocardial infarction, stroke, and congestive heart failure. On the basis of multiple proofs, antihypertensive therapy is currently recommended for improving event-free survival rate and quality of life in different clinical settings and conditions. At the same time, other cardiovascular drugs, including novel lipid-lowering, anti-platelet, and anti-coagulation agents, have been

made available and also contribute to reduce the incidence of atherothrombotic diseases. PURPOSE OF REVIEW: Beyond the beneficial aspects obtained by pharmacological treatment of major cardiovascular risk factors and comorbidities, including hypertension, several aspects remain to be defined. One major limitation linked to randomized, controlled clinical trials is represented by the relatively short duration of the studies, which usually ranges between 1 and 5 years. Whether antihypertensive therapy should be maintained for a longer time (after 5 years) and whether this is supported by sufficient evidence of a persisting benefit is supported by limited post-trial observations but mostly by findings derived from large clinical registries. The so-called legacy effect in the treatment of hypertension, in which patients who are treated with a given antihypertensive therapy may derive a long-term benefit after discontinuation of therapy, has been recently proposed on the basis of accumulating evidence and, in particular, on the availability of long-term post-trial observations in randomized controlled clinical trials. In this review, we discuss the evidence witnessing a legacy effect of antihypertensive therapy and whether this supports sufficiently lifetime drug treatment of hypertension.

[19] *Chen Z, Larregina AT, Morelli AE*. **Impact of extracellular vesicles on innate immunity**. Current opinion in organ transplantation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31592838
ABSTRACT
PURPOSE OF REVIEW: Extracellular vesicles released by prokaryote or eukaryote cells are emerging as mechanisms of cell-to-cell communication, by either physically interacting with the surface of target cells or transferring proteins/peptides, lipids, carbohydrates, and nuclei acids to acceptor cells. Accumulating evidence indicates that extracellular vesicles, among other functions, regulate innate and adaptive immune responses. We revisit here the effects that extracellular vesicles of various origins have on innate immunity. RECENT FINDINGS: Extracellular vesicles comprise a heterogeneous group of vesicles with different biogenesis, composition and biological properties, which include exosomes, microvesicles, apoptotic cell-derived extracellular vesicles, and other extracellular vesicles still not well characterized. Extracellular vesicles released by pathogens, leukocytes, nonhematopoietic cells, tumor cells, and likely allografts, can either stimulate or suppress innate immunity via multiple mechanisms. These include transfer to target leukocytes of pro-inflammatory or anti-inflammatory mediators, membrane receptors, enzymes, mRNAs, and noncoding RNAs; and interaction of extracellular vesicles with the complement and coagulation systems. As a result, extracellular vesicles affect differentiation, polarization, activation, tissue recruitment, cytokine and chemokine production, cytolytic and phagocytic function, and antigen transfer ability, of different types of innate immune cells. SUMMARY: The field of intercellular communication via extracellular vesicles is a rapid evolving area and the effects of pathogen-derived and host-derived extracellular vesicles on innate immunity in particular, have received increasing attention during the past decade. Future studies will be necessary to assess the full potential of the crosstalk between extracellular vesicles and the innate immune system and its use for therapeutic applications to treat chronic inflammation-based diseases and cancer growth and dissemination, among the growing list of disorders in which the innate immune system plays a critical role.

[20] *Khoo NKH, Schopfer FJ*. **Nitrated fatty acids: from diet to disease**. Current opinion in physiology 2019; 9:67-72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31598569
ABSTRACT
Fatty acids not only provide caloric energy in our diets and building blocks of lipids but are also precursors of potent signaling molecules. Fatty acids can undergo enzymatic and non-enzymatic transformations to form autocrine and paracrine signaling molecules that regulate energy balance and metabolic homeostasis. A new class of lipid signaling mediators known as nitro-fatty acids (NO2-FAs) has recently been identified. These NO2-FAs are generated endogenously through non-enzymatic reactions of secondary products of nitrite and nitric oxide and are readily detected in human plasma and urine. NO2-FAs are potent anti-inflammatory and antioxidant cell signaling mediators and exert protective effects in numerous pre-clinical animal models of disease including cardiovascular, pulmonary and renal fibrosis. Chronic unresolved inflammation is common key feature underlying most fibrotic disorders. Two pathways that converge on inflammation and oxidative stress are nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and nuclear factor kappa B (NF-kappaB). NO2-FAs are pleiotropic signaling modulators that target both of these pathways providing a therapeutic strategy directed towards an integrated decrease in inflammation. This review summarizes the latest findings and understanding of the formation, signaling and anti-fibrotic effects of NO2-FA.

[21] *Lee N, Maeda K, Fukizawa S et al.* **Microdosing clinical study to clarify pharmacokinetic and pharmacogenetic characteristics of atorvastatin in Japanese hypercholesterolemic patients**. Drug metabolism and pharmacokinetics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31594719
ABSTRACT
The present study investigated whether the clinical pharmacokinetics of atorvastatin can be predicted from the results of microdosing study in Japanese patients with hypercholesterolemia whose SLCO1B1 and ABCG2 polymorphisms were analyzed. Forty seven statin-naive patients clinically indicated to LDL cholesterol-lowering therapy with atorvastatin were enrolled in a two-period crossover study. Microdose (100 mug) of atorvastatin was orally administered followed by therapeutic dose (10 mg) administration. Transport studies were performed with BCRP-expressing membrane vesicles. The dose-normalized plasma AUC following the therapeutic dose of atorvastatin was positively correlated with that following its microdose, but the AUC increased more than dose proportionally from microdose to therapeutic dose. The patients carrying SLCO1B1 c.521TC showed a significantly higher AUC compared with those carrying c.521TT following the microdose (175%) and therapeutic dose (139%). On the other hand, SLCO1B1 c.388G or ABCG2 c.421A variant alleles did not significantly affect the pharmacokinetics of atorvastatin. Atorvastatin showed ATP-dependent transport in BCRP-expressing membrane vesicles and it inhibited rosuvastatin transport with Ki of 6.3 +/- 2.9 muM (mean +/- SD). Microdosing study appears to be feasible to roughly estimate the pharmacokinetic and pharmacogenetic profiles of atorvastatin following the oral therapeutic dose in hypercholesterolemic patients.

[22] *Rafey MF, Butt A, Coffey B et al.* **Prolonged acidosis is a feature of SGLT2i-induced euglycaemic diabetic ketoacidosis**. Endocrinology, diabetes & metabolism case reports 2019; 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31600728
ABSTRACT
Summary: We describe two cases of SGLT2i-induced euglycaemic diabetic ketoacidosis, which took longer than we anticipated to treat despite initiation of our DKA protocol. Both patients had an unequivocal diagnosis of type 2 diabetes, had poor glycaemic control with a history of metformin intolerance and presented with relatively vague symptoms post-operatively. Neither patient had stopped their SGLT2i pre-operatively, but ought to have by current treatment guidelines. Learning points: SGLT2i-induced EDKA is a more protracted and prolonged metabolic derangement and takes approximately twice as long to treat as hyperglycaemic ketoacidosis. Surgical patients ought to stop SGLT2i medications routinely pre-operatively and only resume them after they have made a full recovery from the operation. While the mechanistic basis for EDKA remains unclear, our observation of marked ketonuria in both patients suggests that impaired ketone excretion may not be the predominant metabolic lesion in every case. Measurement of insulin, C-Peptide, blood and urine ketones as well as glucagon and renal function at the time of initial presentation with EDKA may help to establish why this problem occurs in specific patients.

[23] *Berkan O, Arslan S, Lalem T et al.* **Regulation of microRNAs in coronary atherosclerotic plaque**. Epigenomics 2019; 11:1387-1397.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31596136
ABSTRACT
Aim: Identification of microRNAs (miRNAs) associated with atherosclerosis may unravel novel therapeutic targets and biomarkers. We studied miRNAs differentially expressed between coronary atherosclerotic plaques (CAP) and healthy arteries. Materials & methods: Paired CAP and internal mammary arteries (IMA) were collected from 14 coronary artery disease patients. The miRNA profiles between diseased (CAP) and healthy (IMA) tissues were compared using microarrays and quantitative PCR. Results: Thirty-one miRNAs were differentially expressed between CAP and IMA. Among these, miR-486-5p showed a high level of regulation (12-fold), had predicted interactions with atherosclerosis-associated genes and correlated with triglyceride levels and arterial stenosis. Regulation of miR-486-5p was validated by PCR ($p = 0.004$). Conclusion: The miRNAs are regulated in the atherosclerotic plaque. We highlight miR-486-5p whose role in atherosclerosis requires further investigation.

[24] *Cao YX, Liu HH, Jin JL et al.* **Plasma proprotein convertase subtilisin/kexin type 9 concentration and recurrent cardiovascular events in patients with familial hypercholesterolemia**. European journal of preventive cardiology 2019:2047487319880985.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31604401
ABSTRACT
AIMS: Familial hypercholesterolemia patients are characterized by early onset of coronary artery calcification and atherosclerosis, and high incidence of cardiovascular events. Plasma proprotein convertase subtilisin/kexin type 9 was reported to be a predictor for cardiovascular

risk in the general population. However, its prognostic value for predicting recurrent cardiovascular events in familial hypercholesterolemia patients remains undetermined. METHODS: A total of 249 patients with molecularly and/or clinically (Dutch Lipid Clinic Network score > 6) defined familial hypercholesterolemia who had experienced a first cardiovascular event were consecutively included and plasma proprotein convertase subtilisin/kexin type 9 concentrations were measured by enzyme-linked immunosorbent assay. Coronary artery calcification was measured using Agatston method and coronary severity was assessed by Gensini score, respectively. All patients received standard lipid-lowering therapy and were followed-up for recurrent cardiovascular events. Univariate and multivariate regression and Cox analyses was used to calculate hazard ratios with 95% confidence interval. RESULTS: Circulating proprotein convertase subtilisin/kexin type 9 concentrations were positively associated with coronary artery calcification scores and Gensini score by both univariate and multivariate analyses. During a mean follow-up of 43 +/- 19 months, 29 (11.51%) recurrent cardiovascular events occurred. Kaplan-Meier analysis showed that patients with the highest proprotein convertase subtilisin/kexin type 9 levels had the lowest event-free survival time. Multivariable Cox regression analysis revealed that proprotein convertase subtilisin/kexin type 9 was independently associated with recurrent cardiovascular events (hazard ratio: 1.45, 95% confidence interval: 1.11-1.88). The combination of proprotein convertase subtilisin/kexin type 9 to Cox prediction model led to an enhanced predictive value for recurrent cardiovascular events. CONCLUSIONS: Increased level of proprotein convertase subtilisin/kexin type 9 was a significant risk factor of atherosclerosis and independently predicted future recurrent cardiovascular events in familial hypercholesterolemia patients receiving standard lipid-lowering treatment.

[25] *Steffens D, Bramlage P, Scheeff C et al.* **PCSK9 inhibitors and cardiovascular outcomes**. Expert opinion on biological therapy 2019:1-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31593483
ABSTRACT
Introduction: Dyslipidemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a key risk factor for atherosclerotic cardiovascular disease (ASCVD), and lipid-lowering drugs are beneficial for the primary and secondary prevention of cardiovascular (CV) disease. While statins are clear first-line drugs, new drug developments such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to improve cardiovascular outcomes when added to statins. Evolocumab reduced the risk of cardiovascular events in patients with ASCVD when added to maximally tolerated statin therapy (+/- ezetimibe), and recent data from the ODYSSEY OUTCOMES trial indicate that alirocumab added to maximally tolerated statin therapy (+/- other lipid-lowering drugs) reduces the risk of cardiovascular events in patients with a recent acute coronary syndrome. In this article the authors review the available data on the effect of PCSK9 inhibitors on cardiovascular outcomes. Areas covered: This article reviews the available data on the effect of PCSK9 inhibitors on CV outcomes. Relevant papers were identified from a search of PubMed/Medline and the Cochrane Central Register of Controlled Trials (CENTRAL). Expert opinion: The authors conclude that PCSK9 inhibitors provide substantial and durable reductions in LDL-C levels and improve cardiovascular outcomes.

[26] *Mattesini A, Masiero G, Barbieri L et al.* **[Dyslipidemia management for secondary prevention in cardiovascular disease: from guidelines to clinical practice]**. Giornale italiano di cardiologia (2006) 2019; 20:44-49.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31593190
ABSTRACT
Despite improvements in the treatment and prevention of risk factors (i.e. dyslipidemia), cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality in countries with a high degree of socio-economic development. As a matter of fact, in the last decades, several trials and meta-analysis highlighted the impact of treatments targeted to lowering cholesterol levels (particularly LDL-cholesterol) on outcomes of patients affected by CVD, both in terms of primary and secondary prevention. The main international CVD guidelines recommend lifestyle modifications and optimal lipid-lowering therapy in individuals with established CVD. The aim of the present document is to describe the dimension of the problem and the available therapies, offering a practical pharmacological flow-chart useful for accurate monitoring and intensive treatment of dyslipidemias in this patient population.

[27] *von Schacky C*. **[Confusion about the effects of omega-3 fatty acids : Contemplation of study data taking the omega-3 index into consideration]**. Internist (Berl) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31591673
ABSTRACT
BACKGROUND: Confusion reigns about omega3 fatty acids and their effects. Scientific investigations did not appear to clarify the issue. Guidelines and regulatory authorities contradict each other. OBJECTIVE: This article provides clarity by considering not intake but levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in erythrocytes as a percentage of all fatty acids measured (omega3 index). CURRENT DATA: The largest database of all methods of fatty acid analyses has been generated with the standardized HS-Omega3 Index(R) (Omegametrix, Martinsried, Deutschland). The omega3 index assesses the in EPA+DHA status of a person, has a minimum of 2%, a maximum of 20%, and is optimal between 8% and 11%. In many western countries but not in Japan or South Korea, mean levels are suboptimal. Suboptimal levels correlate with increased total mortality, sudden cardiac death, fatal and non-fatal myocardial infarction, other cardiovascular diseases, cognitive impairment, major depression, premature birth and other health issues. Interventional studies on surrogate and intermediary parameters demonstrated many positive effects, correlating with the omega3 index when measured. Due to issues in methodology that became apparent from the perspective of the omega3 index many, even large interventional trials with clinical endpoints were not positive, which is reflected in pertinent meta-analyses. In contrast, interventional trials without issues in methodology the clinical endpoints mentioned were reduced. CONCLUSION: All humans have levels of EPA+DHA that if methodologically correctly assessed in erythrocytes, are optimal between 8% and 11%. Deficits can cause serious health issues that can be prevented by optimal levels.

[28] *Labos C, Brophy JM, Sniderman A, Thanassoulis G*. **Mortality Benefit of Alirocumab: A Bayesian Perspective**. Journal of the American Heart Association 2019; 8:e013170.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31599200

ABSTRACT
Background The ODYSSEY OUTCOMES (Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome) trial demonstrated that alirocumab reduced major cardiovascular events. However, because of the hierarchical testing strategy used for the multiple outcomes examined, the observed reduction in all-cause mortality was labeled "nominally significant" which has clouded its interpretation. Methods and Results We re-analyzed data from ODYSSEY OUTCOMES using Bayesian methods and generated various prior probabilities by incorporating mortality data from previous similar PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor trials. We first used data from the ODYSSEY OUTCOMES trial with a non-informative prior, then sequentially added data from ODYSSEY LONG TERM and the FOURIER trial, giving FOURIER full weight, 50% weight and 10%. The posterior probability of a mortality reduction using only the ODYSSEY OUTCOMES data was hazard ratio 0.85 (95% CI 0.74-0.99) which corresponded to a 98.4% probability of a mortality benefit. When the ODYSSEY LONG TERM data were added to the analysis, the posterior probability was hazard ratio 0.84 (95% CI 0.72-0.97) with a 99.9% probability of mortality reduction, and when the FOURIER data were added to the analysis the posterior probability was hazard ratio 0.94 (95% CI 0.85-1.04) with an 89.1% probability of a mortality reduction. When the FOURIER trial was given only 50% or 10% weight, the probability of a mortality reduction rose 95.4% and 98.7%, respectively. We estimate that the probability of >1% absolute risk reduction ranges from 8% to 24%, while the probability of >0.5% absolute risk reduction ranges from 66% to 89%. Conclusions Our analysis demonstrates a high likelihood that alirocumab confers a reduction in all-cause mortality, despite the equivocal interpretation of the data in the original ODYSSEY OUTCOMES publication.

[29] *Ipema J, Roozendaal NC, Bax WA et al.* **Medical adjunctive therapy for patients with chronic limb-threatening ischemia: a systematic review**. J Cardiovasc Surg (Torino) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31603294

ABSTRACT
INTRODUCTION: To systematically review the literature on medical adjunctive therapy for patients with chronic limb-threatening ischemia (CLTI). EVIDENCE ACQUISITION: MEDLINE, Embase, and Cochrane Database of Systematic Reviews were searched for studies published between January 1, 2009, and June 1, 2019. Articles that studied medical treatment of CLTI patients and reported clinical outcomes were eligible. Main exclusion criteria were case reports <20 patients, incorrect publication type, and CLTI caused by Buerger disease. The primary end point was major amputation (above the ankle) in studies with a follow-up of >/=6 months. Secondary end points were other clinical end points such as death and wound healing. Study quality was assessed according to the Downs and Black checklist. EVIDENCE SYNTHESIS: Included were 42 articles; 4 focused on antiplatelet therapy, 5 on antihypertensive medication, 6 on lipid-lowering therapy, 16 on stem cell therapy, 3 on growth factors, 5 on prostanoids, and 1 study each on cilostazol, glucose-lowering therapy, spinal cord stimulation, sulodexide, and hemodilution. Calcium channel blockers, iloprost, cilostazol, and hemodilution showed significant improvement of limb salvage, but data are limited. Stem cell therapy showed no significant improvement of limb salvage but could potentially improve wound healing. Antiplatelets, antihypertensives, and statins showed significantly lower cardiovascular events rates but not evident lower major amputation rates. The quality of the studies was fair to good.

CONCLUSIONS: Certain medical therapies serve to improve limb salvage next to revascularization in CLTI patients, whereas others are important in secondary prevention. Because high quality evidence is limited, further research is needed.

[30] *Palleria C, Roberti R, Iannone LF et al.* **Clinically relevant drug interactions between statins and antidepressants**. Journal of clinical pharmacy and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31587356
ABSTRACT
WHAT IS KNOWN AND OBJECTIVE: Statins, also known as 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, and antidepressant drugs are frequently used in combination due to the high and growing incidence of cardiovascular diseases and psychiatric disorders worldwide. Several aspects on management, the risk of adverse events (AEs) occurrence and the potential clinically relevant pharmacokinetic (PK) and pharmacodynamic (PD) drug-drug interactions (DDIs) between these two classes have not been well investigated. The aim of the present review was to describe the PK and PD interactions, of clinical relevance, between statins and antidepressant drugs and provide a comprehensive overview of their pharmacological features for appropriate multiple drug regimens. METHODS: Relevant studies were identified through a literature search of PubMed and the Cochrane databases focusing on clinically relevant DDIs between statins and antidepressants. Only papers in English were included in the search. RESULTS AND DISCUSSION: Pharmacodynamic (PD) drug-drug interactions (DDIs) are unlikely to occur as statins are highly selective inhibitors of HMG-CoA reductase with no relevant effect on other enzymes or receptor systems. Despite the numerous PK studies on individual drugs belonging to statins and antidepressant agents, only a few case reports regarding specific DDIs are present in the literature and no clinical studies have been performed. PK data allow to speculate on potential DDIs, comparing the metabolic pathways, intestinal and liver transporters and elimination routes. Overall, second-generation antidepressants, in particular citalopram, escitalopram, mirtazapine, reboxetine and venlafaxine, have weak inhibitory effects on various cytochrome (CYP) isozymes and seem to have a more advantageous DDIs profile in vivo. Conversely, nefazodone, fluoxetine, paroxetine and fluvoxamine influence considerably CYPs activity with potential effects on statins plasma levels, although pravastatin, pitavastatin and rosuvastatin are not susceptible to inhibition by any CYP. Albeit no studies have been performed on P-glycoprotein (P-gp), interactions of clinical relevance are unlikely. WHAT IS NEW AND CONCLUSION: Although DDIs with antidepressants are potentially, but rarely clinically significant, the use of antidepressants with a more favourable drug interaction profile is advisable. An evaluation on DDIs between these drugs can be useful for future PK/PD studies on drug-drug interaction to provide clinicians with more data for appropriate multiple drug regimens.

[31] *Huang W, Xie P, Cai Z*. **Lipid metabolism disorders contribute to hepatotoxicity of triclosan in mice**. Journal of hazardous materials 2019; 384:121310.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31586915
ABSTRACT
Previous in vivo exposure studies focused mainly on nuclear receptors involved in hepatotoxicity of triclosan (TCS). As liver plays a vital role in metabolic processes,

dysregulations in lipid metabolism have been identified as potential drivers of pathogenesis. Investigation of changes in lipid metabolism might widen our understanding of toxicological effects as well as the underlying mechanism occurring in the liver. In this study, we comprehensively assessed the effect of TCS exposure on hepatic lipid metabolism in mice. Our results showed that TCS induced significant changes in hepatic free fatty acid pool by upregulation of fatty acid uptake and de novo fatty acid synthesis. Besides, hepatic levels of lipids, including acyl carnitine (AcCa), ceramide (Cer), triacylglycerols (TG), phosphatidylcholine (PC), lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE) were also increased, together with upreguation of genes associated to TG synthesis, fatty acid oxidation and inflammation in TCS exposure group. These changes in lipid homeostasis could contribute to membrane instability, lipid accumulation, oxidative stress and inflammation. Our results suggested that TCS exposure could induce hepatic lipid metabolism disorders in mice, which would further contribute to the liver damage effects of TCS.

[32] *Dutta NK, Bruiners N, Zimmerman MD et al.* **Adjunctive host-directed therapy with statins improves tuberculosis-related outcomes in mice**. The Journal of infectious diseases 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31605489
ABSTRACT
BACKGROUND: Tuberculosis (TB) treatment is lengthy and complicated and patients often develop chronic lung disease. Recent attention has focused on host-directed therapies aimed at optimizing immune responses to M. tuberculosis (Mtb), as adjunctive treatment given with anti-tubercular drugs. In addition to their cholesterol-lowering properties, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have broad anti-inflammatory and immunomodulatory activities. METHODS: In the current study, we screened 8 commercially available statins for cytotoxic effect, anti-tubercular activity, synergy with first-line drugs in macrophages, pharmacokinetics and adjunctive bactericidal activity, and, in two different mouse models, as adjunctive therapy to first-line TB drugs. RESULTS: Pravastatin showed the least toxicity in THP-1 and Vero cells. At non-toxic doses, atorvastatin and mevastatin were unable to inhibit Mtb growth in THP-1 cells. Simvastatin, fluvastatin and pravastatin showed the most favorable therapeutic index, and enhanced the anti-tubercular activity of the first-line drugs isoniazid, rifampin and pyrazinamide in THP-1 cells. Pravastatin modulated phagosomal maturation characteristics in macrophages, phenocopying macrophage activation, and exhibited potent adjunctive activity in the standard mouse model of TB chemotherapy and in a mouse model of human-like necrotic TB lung granulomas. CONCLUSION: These data provide compelling evidence for clinical evaluation of pravastatin as adjunctive, host-directed therapy for TB.

[33] *Al-Kuraishy HM, Al-Gareeb AI, Hussien NR et al.* **Statins an oft-prescribed drug is implicated in peripheral neuropathy: The time to know more**. JPMA. The Journal of the Pakistan Medical Association 2019; 69(Suppl 3):S108-s112.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31603889
ABSTRACT
Statins are hydroxymethylglutaryl-coenzyme A reductase inhibitors inhibit denovo cholesterol synthesis leading to reduction of serum cholesterol and low density lipoprotein as well as

elevation of high density lipoprotein level. Statins are used in the treatment of dyslipidaemia, prevention of major cardiovascular events and complications. The potential role of statins in the induction of peripheral neuropathy has not been verified as most of statins induced-peripheral neuropathy had been reported as case reports. Also, statins therapy leads to noteworthy reduction of Coenzyme Q10, causing impairment of neuronal energy. The incidence of polyneuropathy was high with atorvastatin (65%) which is lipophilic, and relatively less with fluvastatin (54%) which is hydrophilic. Long-term statins therapy, mainly with atorvastatin and simvastatin, is linked with thedevelopment of peripheral neuropathy.

[34] *Rasheed HA, Al-Kuraishy HM, Al-Gareeb AI*. **Rosuvastatin Attenuates acute nephrotoxicity through modulation of oxidative stress in Sprague Dawley rats**. JPMA. The Journal of the Pakistan Medical Association 2019; 69(Suppl 3):S98-s102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31603887
ABSTRACT
Objective: To assess the reno-protective effect of rosuvastatin on gentamicin-induced nephrotoxicity in rats. Methods: The prospective experimental study was conducted at the College of Medicine, Mustansiriya University, Baghdad, Iraq, from March to July, 2018, and comprised Sprague Dawley male rats aged 3-4 months and weighing 200-400g each. The rats were divided into 3 equal groups which were treated for 14 days. Group1 was treated with distilled water plus normal saline, Group2 with distilled water plus gentamicin, and Group3 with rosuvastatin plus gentamicin. Parameters measured were blood urea, serum creatinine, serum malondialdehyde, superoxide dismutase, glutathione reductase, neutrophil gelatinase associated lipocalin, kidney injury molecule-1, interleukin- 18 and Cystatin-c. SPSS 20 was used for data analysis. Results: Of the 30 rats, there were 10(33.3%) in each of the three groups. Rosuvastatin produced significant renoprotective effect through reduction of blood urea, kidney injury molecule-1 and interleukin-18 ($p<0.01$) compared to the gentamicin group. Conclusions: Rosuvastatin was found to be a reno-protective against gentamicin-induced nephrotoxicity through modulation of pro-inflammatory and oxidative/anti-oxidant pathways.

[35] *Schilperoort M, van den Berg R, Bosmans LA et al.* **Disruption of circadian rhythm by alternating light-dark cycles aggravates atherosclerosis development in APOE*3-Leiden.CETP mice**. Journal of pineal research 2019:e12614.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31599473
ABSTRACT
Disruption of circadian rhythm by means of shift work has been associated with cardiovascular disease in humans. However, causality and underlying mechanisms have not yet been established. In this study, we exposed hyperlipidemic APOE*3-Leiden.CETP mice to either regular light-dark cycles, weekly 6 h phase advances or delays, or weekly alternating-light dark cycles (12 h shifts), as a well-established model for shift work. We found that mice exposed to 15 weeks of alternating light-dark cycles displayed a striking increase in atherosclerosis, with an approximately two-fold increase in lesion size and severity, while mice exposed to phase advances and delays showed a milder circadian disruption and no significant effect on atherosclerosis development. We observed a higher lesion macrophage content in mice exposed to alternating light-dark cycles without obvious changes in plasma lipids, suggesting

involvement of the immune system. Moreover, while no changes in the number or activation status of circulating monocytes and other immune cells were observed, we identified increased markers for inflammation, oxidative stress and chemoattraction in the vessel wall. Altogether, this is the first study to show that circadian disruption by shifting light-dark cycles directly aggravates atherosclerosis development.

[36] *Wu WQ, Peng S, Wan XQ et al.* **Physical exercise inhibits atherosclerosis development by regulating the expression of neuropeptide Y in apolipoprotein E-deficient mice**. Life sciences 2019; 237:116896.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31605707
ABSTRACT
AIMS: Population-based studies have shown that exercise has anti-atherosclerotic effects, but the mechanisms underlying this cardiac protection are poorly understood. The aim of this study was to investigate if the anti-atherosclerotic effects of exercise are associated with changes in neuropeptide Y (NPY) expression in apolipoprotein E-deficient (ApoE(-/-)) mice. MAIN METHODS: Thirty-one male ApoE(-/-) mice were randomly divided into regular exercise (5 days/week), occasional exercise (1-2 days/week), and sedentary groups. After 8 weeks, atherosclerotic burden and plaque stability were measured by histological and morphological analysis. Quantitative real-time PCR and immunohistochemistry were used to measure the expression of NPY and its receptors in the aorta. KEY FINDINGS: Eight weeks of occasional exercise was equally effective as regular exercise at preventing atherosclerotic plaque formation and enhancing atherosclerotic plaque stability. This was shown by increased plaque collagen and smooth muscle cell content and decreased plaque lipid and macrophage content. The expression of NPY and its receptors in the vasculature was decreased in the regular exercise and occasional exercise groups, and this expression was significantly correlated with the progress of atherosclerosis. Moreover, exercise may reduce the activity of macrophages by down-regulating the expression of NPY Y1 receptors, thereby reducing the release of inflammatory cytokines. SIGNIFICANCE: These results suggest that exercise training can attenuate plaque burden and enhance atherosclerotic plaque stability. The anti-atherosclerotic effect of exercise appears to be, at least in part, dependent on down-regulation of the expression of NPY and its receptors (especially Y1 receptors) in the aorta.

[37] **Expanded table: statins**. The Medical letter on drugs and therapeutics 2019; 61:e152.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31599870
ABSTRACT

[38] *Kraczkowska W, Jagodzinski PP*. **The Long Non-Coding RNA Landscape of Atherosclerotic Plaques**. Molecular diagnosis & therapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31602567
ABSTRACT
Currently, cardiovascular diseases continue to be the leading cause of death worldwide; therefore, atherosclerosis remains one of the most crucial public health problems. This chronic and complex disease is considered to be a result of aberrant lipid homeostasis and inflammation of the inner wall of arteries that leads to plaque development. In recent years, a

specific class of non-coding RNAs that are characterised by transcript lengths longer than 200 nucleotides, called long non-coding RNAs (lncRNAs), has emerged. Moreover, a growing body of evidence indicates that deregulation of lncRNA expression may contribute to the development of many diseases. Despite continuous efforts in deciphering the molecular basis of atherosclerotic plaque (AP) formation, many aspects of this process remain elusive. Therefore, continuing efforts in this area should remain the highest priority in the coming years. Establishment of a standardised experimental pipeline and validation of lncRNAs as possible relevant biomarkers for cardiovascular disease would enable the translation of gathered findings into clinical practice.

[39] *Bornstein SR, Voit-Bak K, Rosenthal P et al.* **Extracorporeal apheresis therapy for Alzheimer disease-targeting lipids, stress, and inflammation**. Molecular psychiatry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31595035
ABSTRACT
Current therapeutic approaches to Alzheimer disease (AD) remain disappointing and, hence, there is an urgent need for effective treatments. Here, we provide a perspective review on the emerging role of "metabolic inflammation" and stress as a key factor in the pathogenesis of AD and propose a novel rationale for correction of metabolic inflammation, increase resilience and potentially slow-down or halt the progression of the neurodegenerative process. Based on recent evidence and observations of an early pilot trial, we posit a potential use of extracorporeal apheresis in the prevention and treatment of AD. Apolipoprotein E, lipoprotein(a), oxidized LDL (low density lipoprotein)'s and large LDL particles, as well as other proinflammatory lipids and stress hormones such as cortisol, have been recognized as key factors in amyloid plaque formation and aggravation of AD. Extracorporeal lipoprotein apheresis systems employ well-established, powerful methods to provide an acute, reliable 60-80% reduction in the circulating concentration of these lipid classes and reduce acute cortisol levels. Following a double-membrane extracorporeal apheresis in patients with AD, there was a significant reduction of proinflammatory lipids, circulating cytokines, immune complexes, proinflammatory metals and toxic chaperones in patients with AD. On the basis of the above, we suggest designing clinical trials to assess the promising potential of such "cerebropheresis" treatment in patients with AD and, possibly, other neurodegenerative diseases.

[40] *Nakayama S, Taguchi N, Isaka Y et al.* **Combined Treatment with Hydrophilic and Lipophilic Statins Improves Neurological Outcomes Following Experimental Cardiac Arrest in Mice**. Neurocritical care 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31591692
ABSTRACT
BACKGROUND: Global ischemia due to cardiac arrest (CA) followed by cardiopulmonary resuscitation (CPR) causes significant neuronal damage in vulnerable areas in the brain. Currently, a majority of patients eventually die after successful CPR due to neurological injury. Statins have pleiotropic effects including anti-inflammatory and/or antioxidant responses. These pleiotropic effects can have a beneficial role in the post-CPR phase. We tested whether two different types of statins, hydrophilic pravastatin and lipophilic simvastatin, attenuated neurological injury following CA/CPR. The efficacy of pravastatin and simvastatin combination

treatment was also assessed. METHODS: Isoflurane-anesthetized adult male wild-type C57Bl/6 mice subjected to 8-min CA/CPR were randomized into four groups: control, 2 mg/kg pravastatin, 20 mg/kg simvastatin, or a combination of 3 mg/kg pravastatin and 10 mg/kg simvastatin. Neurobehavioral assessment and histological analyses were performed to assess overall general health condition and neuronal injury, respectively. RESULTS: Combination treatment with pravastatin and simvastatin significantly reduced neuronal injury in the striatum and hippocampus, reduced cerebral edema, and improved general health at 4 days after CA/CPR. Combination statin treatment upregulated endothelial nitric oxide synthase mRNA in the brain. Pravastatin alone, but not simvastatin alone, improved general health after CA/CPR. Pravastatin was less potent than simvastatin at reducing neuronal injury in the brain. CONCLUSION: Combination treatment with two different types of statins at the correct dose may be a promising approach to neuroprotection following CA/CPR.

[41] *Mudgil P*. **Evaluation of use of essential fatty acids in topical ophthalmic preparations for dry eye**. The ocular surface 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31589924
ABSTRACT
PURPOSE: Essential fatty acids (EFAs) as dietary supplements are used in treating dry-eye for reducing inflammation at the ocular surface. Their topical application in eye drops to deliver fatty acid (FA) directly to the ocular surface requires thorough investigation. Being lipids in nature EFAs can interact with tear lipids and affect tear stability. This study aimed at investigating the biophysical interactions of EFAs with Meibomian lipids. METHODS: Rheology of mixtures of Human Meibomian lipids with EFAs (LA-linoleic acid, ALA-alpha-linolenic acid), OA (oleic acid), and GLA (gamma-linolenic acid) was studied using Langmuir trough technology on an artificial tear solution at the ocular surface temperature. Pressure-area profiles were used to determine compressibility and elasticity of the mixed films. RESULTS: LA enhanced spreading of Meibomian lipids and increased their compressibility and elasticity which can be beneficial for tear stability. ALA condensed Meibomian lipids film with less elasticity deemed unfavourable for tear stability. OA expanded Meibomian lipids but decreased elasticity at high compressions making films less stable. GLA had little or no favourable effect on tear stability. Higher concentrations of FAs made films less stable. CONCLUSIONS: EFAs or OA in topical ophthalmic preparations can affect spread and stability of the tear film lipid layer. Rheology of mixed films should be tested using Langmuir trough technology to determine suitable type and amount of a lipid additive for therapeutic eye drops. In topical applications, the omega-6 LA (not omega-3 FA) at low concentrations (20mol%) can be beneficial for enhancing tear stability in dry eye patients.

[42] *Khammas ASA, Hassan HA, Salih SQM et al.* **Prevalence and risk factors of sonographically detected non alcoholic fatty liver disease in a screening centre in Klang Valley, Malaysia: an observational cross-sectional study**. Porto biomedical journal 2019; 4:e31.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31595260
ABSTRACT
Objectives: Nonalcoholic fatty liver disease (NAFLD) is a very common liver disorder in Western countries. As of late, it has been found to be prevalent in Asia as well. It is a benign disease

unless it develops into necroinflammation and fibrosis. This study was proposed to determine the prevalence and risk factors of sonography-detected NAFLD among Malaysian adults in Klang Valley, West Malaysia. Study design: An observational cross-sectional study. Methods: The participants were aged between 45 and 75 years who participated in a screening program at the Golden Horses Health Sanctuary in Klang Valley. Lipid profile and anthropometric measurements were collected from the subjects' medical records. Ultrasound machine and a structured self-administered questionnaire were used as instruments for recruiting data from the subjects. The subjects who consumed alcohol (>140 g/wk for men and >70 g/wk for females), had hepatitis B or C viruses, liver insults, and surgery, and taken lipid-lowering medications were excluded from the study. Results: A total of 628 subjects were analyzed, and 235 (37.4%) subjects were diagnosed with definite NAFLD. They comprised 518 (82.5%) Chinese, 92 (14.6%) Malays, and 18 (2.9%) Indians. Peak prevalence of NAFLD was found in 53 to 60 years age group. The higher prevalence of NAFLD was among men (48.3%) than women (27.3%) and among Indians (61.1%) and Malays (51.1%) than among Chinese (34.2%). NAFLD has been found to be strongly correlated with male sex, high body mass index (>/=23.0 kg/m(2)), hypertriglyceridemia, low high-density lipoprotein cholesterol, diabetes mellitus, and hypertension. Conclusion: NAFLD is quite common among adults in Malaysian urban population. The prevalence of NAFLD was inordinately high among the 53 to 60 years age group, male sex, Indians, and Malays (as compared with Chinese). Age >60 years, male sex, high body mass index (>/=23.0 kg/m(2)), hypertriglyceridemia, and diabetes mellitus were proven to be risk predictors for NAFLD.

[43] *Puschel GP, Henkel J*. **Dietary cholesterol does not break your heart but kills your liver**. Porto biomedical journal 2018; 3:e12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31595236
ABSTRACT
It is increasingly accepted that dietary cholesterol has a much lower impact on the progression of cardiovascular disease than previously assumed. However, both animal experiments and human studies seem to support the view that dietary cholesterol may contribute to the transition from benign steatosis to the potentially fatal non-alcoholic steatohepatitis. Cholesterol esters and cholesterol accumulate in the hepatocyte and impair its function. This leads to oxidative stress and endoplasmic reticulum stress triggering the release of pro-inflammatory cytokines and rendering the hepatocyte more susceptible to apoptotic or necrotic cell death. Kupffer cells group around dying hepatocytes and phagocytose the hepatocyte debris and lipids. In addition, they are exposed to lipid peroxidation products released from hepatocytes. Kupffer cells, thus activated, release pro-inflammatory, chemotactic and profibrotic cytokines that promote inflammation and fibrosis. Therefore, dietary cholesterol may be harmful to the liver, in particular when administered in combination with polyunsaturated fatty acids that favor lipid peroxidation.

[44] *Labudovic D, Kostovska I, Tosheska Trajkovska K et al.* **Lipoprotein(a) - Link between Atherogenesis and Thrombosis**. Prague medical report 2019; 120:39-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31586503
ABSTRACT

Lipoprotein(a) - Lp(a) - is an independent risk factor for cardiovascular disease (CVD). Indeed, individuals with plasma concentrations of Lp(a) > 200 mg/l carry an increased risk of developing CVD. Circulating levels of Lp(a) are remarkably resistant to common lipid lowering therapies, currently available treatment for reduction of Lp(a) is plasma apheresis, which is costly and labour intensive. The Lp(a) molecule is composed of two parts: LDL/apoB-100 core and glycoprotein, apolipoprotein(a) - Apo(a), both of them can interact with components of the coagulation cascade, inflammatory pathways and blood vessel cells (smooth muscle cells and endothelial cells). Therefore, it is very important to determine the molecular pathways by which Lp(a) affect the vascular system in order to design therapeutics for targeting the Lp(a) cellular effects. This paper summarises the cellular effects and molecular mechanisms by which Lp(a) participate in atherogenesis, thrombogenesis, inflammation and development of cardiovascular diseases.

[45] *Wei XY, Yang YJ, Zhu XH*. **The effect of bezafibrate in preventing glucolipid abnormalities induced by the antipsychotic risperidone**. Psychiatry research 2019; 281:112584.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31586837
ABSTRACT
The present study aimed to investigate the effect of bezafibrate on glucolipid abnormalities induced by antipsychotics in schizophrenia. Patients in the treatment group (group A) were treated with antipsychotics and a daily dose of 200mg bezafibrate for 12 weeks, and patients in the control group (group B) were treated with antipsychotics; sugar, fat and weight changes before and after the treatment were compared between the two groups. Before treatment the differences in TG, TC, LDL-C, HDL-C, body weight and blood glucose between groups A and B were not statistically significant. However, in group B, levels of TG, TC, LDL-C, body weight and blood glucose after treatment showed statistically significant increases, although levels of HDL-C did not register any statistically significant change. By contract, in group A, there were no statistically significant changes in any of the variables measured. Bezafibrate can prevent an increase in sugar, fat and weight gain in treating schizophrenia patients with antipsychotics, and low doses of bezafibrate are safe in the antipsychotic treatment for schizophrenia.

[46] *Arca M*. **[PCSK9 inhibitors (PCSK9i), a new opportunity for cardiovascular prevention: clinical and regulatory aspects and access to therapy.]**. Recenti progressi in medicina 2019; 110:401-411.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31593176
ABSTRACT
Elevated levels of LDL-C represent a major risk factor for cardiovascular (CV) disease and recent guidelines recommended early and appropriate interventions in hypercholesterolemic patients in order to reduce the risk of CV events. The current lipid lowering therapies (mainly statins and ezetimibe) not always allow patients to reach their appropriate LDL-C goals. This is particularly true in patients affected by genetic forms of hypercholesterolemia as well as in those who need to attain low LDL-C due to their high cardiovascular risk. In this context, the recent availability of monoclonal antibodies directed against the PCSK9 protein (PCSK9i) represent a novel therapeutic strategy to control resistant forms of hypercholesterolemia. In this review, we will examine the clinical pharmacology of PCSK9i and we will dedicated particular attention to

review the results of the two pivotal cardiovascular prevention trials, FOURIER and ODISSEY OUTCOMES that demonstrated the benefit of PCSK9i in prevention of cardiovascular events in patients at very high risk not at LDL-C goal with conventional LDL-lowering therapies. The PCSK9i has been approved for use in Italy under specific criteria and following a strict prescription procedures. We will examine the epidemiology of use of PCSK9i in Italy and will underlying the potential factors influencing the access and availability to this therapy.

[47] *Yadav D, Singh AK, Kumar B et al.* **Effect of n-3 PUFA rich fish oil supplementation during late gestation on kidding, uterine involution and resumption offollicular activityin goat**. Reproduction in domestic animals = Zuchthygiene 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31595997
ABSTRACT
We have shown that dietary supplementation of n-3 polyunsaturated fatty acid (n-3 PUFA) rich fish oil (FO) around the breeding time improved the utero-ovarian functions in the goat.Here, we investigated the effect of FO supplementation during the periparturient period on serum n-3 PUFA, prostaglandin F2alpha metabolite (PGFM), placental expulsion, uterine involution, resumption of estrus and neonatal vigour.Rohilkhandi goat in advanced gestation (n=16) were divided into two equal groups. Onegroup wassupplemented with FO containing 26% n-3 long chain PUFA at the rate of 156 mg per kgbody weight,while the control group wasfed isocaloric palm oil (PO) from -3 to +3 week of kidding.Dietary FO increased serum concentration of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by 7.3and 6.6 fold, respectively after 6 weeks of supplementation. Goats in FO groupexpelled the fetal membranes 99.1 min earlier ($P<0.01$) than those of PO group. Further, dietary FO significantly decreased the serum PGFM on day 7 postpartum. However, no difference was found on uterine involution, which was completeby day 20 postpartum in either group. Resumption of follicular activity by day 5 postpartum was 87.5% in the FO as compared to 25% in the PO group ($P<0.05$). Similarly, occurrence of behavioral estrus by day 90 postpartum was 57.1% in goats of the FO group while none of does wasin the PO group ($P<0.01$) expressed estrus. It was concluded that feeding FO rich diet during -3 to +3 weeks of kidding decreased the PGFM till day 7 postpartum, hastened the expulsion of fetal membranes and reduced the time from kidding to first postpartum estrus in Rohilkhandi does.

[48] *Jiang W, Wang M*. **New insights into the immunomodulatory role of exosomes in cardiovascular disease**. Reviews in cardiovascular medicine 2019; 20:153-160.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31601089
ABSTRACT
Exosomes, nanosized lipid bilayer membranous vesicles, are secreted by a variety of cells and contain protein, lipids, mRNA, miRNA, and signaling molecules that participate in intercellular material transfer and information exchange through binding, fusion or endocytosis. Exosomes mediate the gene expression of target cells and regulate pathological and physiological processes, thereby playing a key role in the occurrence and development of various diseases. Accumulated studies has shown that exosomes hold therapeutic potential though their anti-apoptotic and anti-fibrotic roles. They also have been shown to promote angiogenesis, inhibit ventricular remodeling and improve cardiac function, as well as inhibiting local inflammation

and regulating the immune response. As such, exosomes represent a new target for the treatment of cardiovascular diseases. This review summarizes the literature in this field to date, including the basic biological characteristics of exosomes, and new progress in the understanding of the mechanisms of their involvement in immune regulation in cardiovascular diseases. In this way, it servrs as a basis for future research and the development of therapeutic exosomes.

[49] *Yebyo HG, Aschmann HE, Menges D et al.* **Net benefit of statins for primary prevention of cardiovascular disease in people 75 years or older: a benefit-harm balance modeling study**. Therapeutic advances in chronic disease 2019; 10:2040622319877745.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31598209
ABSTRACT
Background: We determined the risk thresholds above which statin use would be more likely to provide a net benefit for people over the age of 75 years without history of cardiovascular disease (CVD). Methods: An exponential model was used to estimate the differences in expected benefit and harms in people treated with statins over a 10-year horizon versus not treated. The analysis was repeated 100,000 times to consider the statistical uncertainty and produce a distribution of the benefit-harm balance index from which we determined the 10-year CVD risk threshold where benefits outweighed the harms. We considered treatment estimates from trials and observational studies, baseline risks, patient preferences, and competing risks of non-CVD death, and statistical uncertainty. Results: Based on average preferences, statins were more likely to provide a net benefit at a 10-year CVD risk of 24% and 25% for men aged 75-79 years and 80-84 years, respectively, and 21% for women in both age groups. However, these thresholds varied significantly depending on differences in individual patient preferences for the statin-related outcomes, with interquartile ranges of 21-33% and 23-36% for men aged 75-79 years and 80-84 years, respectively, as well as 20-32% and 21-32% for women aged 75-79 years and 80-84 years, respectively. Conclusions: Statins would more likely provide a net benefit for primary prevention in older people taking the average preferences if their CVD risk is well above 20%. However, the thresholds could be much higher or lower depending on preferences of individual patients, which suggests more emphasis should be placed on individual-based decision-making, instead of recommending statins for everyone based on a single or a small number of thresholds.

[50] *Dou L, Jourde-Chiche N*. **Endothelial Toxicity of High Glucose and its by-Products in Diabetic Kidney Disease**. Toxins 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31590361
ABSTRACT
Alterations of renal endothelial cells play a crucial role in the initiation and progression of diabetic kidney disease. High glucose per se, as well as glucose by-products, induce endothelial dysfunction in both large vessels and the microvasculature. Toxic glucose by-products include advanced glycation end products (AGEs), a group of modified proteins and/or lipids that become glycated after exposure to sugars, and glucose metabolites produced via the polyol pathway. These glucose-related endothelio-toxins notably induce an alteration of the glomerular filtration barrier by increasing the permeability of glomerular endothelial cells,

altering endothelial glycocalyx, and finally, inducing endothelial cell apoptosis. The glomerular endothelial dysfunction results in albuminuria. In addition, high glucose and by-products impair the endothelial repair capacities by reducing the number and function of endothelial progenitor cells. In this review, we summarize the mechanisms of renal endothelial toxicity of high glucose/glucose by-products, which encompass changes in synthesis of growth factors like TGF-beta and VEGF, induction of oxidative stress and inflammation, and reduction of NO bioavailability. We finally present potential therapies to reduce endothelial dysfunction in diabetic kidney disease.