Literature update week 09 (2019)

[1] *Janse Van Rensburg WJ*. **Lifestyle Change Alone Sufficient to Lower Cholesterol in Male Patient With Moderately Elevated Cholesterol: A Case Report**. American journal of lifestyle medicine 2019; 13:148-155.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30800020
ABSTRACT
Background. Cardiovascular disease is a major cause of deaths. Elevated cholesterol levels to above the normal reference range is a major risk factor for developing cardiovascular disease. Current guidelines recommend the use of cholesterol-lowering drugs to lower cholesterol levels to within the normal reference range. However, the American Heart Association further recommends a change in lifestyle in managing cholesterol levels. Thus, cholesterol-lowering drugs may not be needed if a lifestyle-change alone is sufficient in lowering cholesterol levels to within normal ranges. Unfortunately, limited examples exist in academic literature to illustrate the effectiveness of lifestyle change alone in lowering of cholesterol levels. Case report. We report a case of a 33-year-old man, with moderately elevated cholesterol levels and a family history of cardiovascular disease. Method. The man followed an altered healthy fat diet accompanied with moderate exercise for 6 weeks, without the addition of cholesterol-lowering agents. Results. At the 6-week follow-up, he was able to decrease his total cholesterol by 40.25% and low-density lipid cholesterol by 52.8%, to within normal ranges. The cholesterol levels remained within normal ranges after 6 months. Conclusion. This case illustrates that in some individuals, lifestyle change alone is sufficient to lower moderately elevated cholesterol levels.

[2] *Ma X, Wang Z, Wang J et al.* **Admission Heart Rate Is Associated With Coronary Artery Disease Severity and Complexity in Patients With Acute Coronary Syndrome**. Angiology 2019:3319719832376.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30813736
ABSTRACT
We evaluated the relationship between admission heart rate (HR) and coronary artery disease severity and complexity in patients with acute coronary syndrome (ACS). A total of 884 patients (mean age 59 [11] years, 24.7% female) who underwent coronary angiography for ACS and were treated with primary or selective percutaneous coronary intervention were included in this cross-sectional study. The measurement of admission HR was based on the first available resting electrocardiogram after admission. The SYNTAX score (SS) was calculated. Patients with an SS </= 22 (n = 538) were classified as the low SS group and those with an SS > 22 (n = 346) were classified as the intermediate-to-high SS group. Admission HR was greater in the intermediate-to-high SS group compared with the low SS group (75 [10] bpm vs 67 [8] bpm, P < .001). Admission HR was positively and significantly correlated with the SS (r = 0.475, P < .001). After multivariate analysis, admission HR (per 1 standard deviation, ie, 10 bpm) remained an independent predictor of intermediate-to-high SS (odds ratio: 3.135, 95% confidence interval: 2.538-3.873, P < .001). Admission HR is independently and positively associated with the SS. Thus, elevated admission HR may be useful to identify patients with ACS with a high coronary atherosclerotic plaque burden.

[3] *Liang CL, Chen HJ, Liliang PC et al.* **Simvastatin and Simvastatin-Ezetimibe Improve the Neurological Function and Attenuate the Endothelial Inflammatory Response after Spinal Cord Injury in Rat**. Annals of clinical and laboratory science 2019; 49:105-111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30814085

ABSTRACT

During a spinal cord injury (SCI), mechanical trauma rapidly leads to a blood-spinal cord barrier (BSB) disruption, neural cell damage, axonal damage, and demyelination, followed by a cascade of secondary inflammatory reactions. These inflammatory responses spread the damage to the neural cells and impair the recovery of neurological functions. In the present study, we evaluated the efficacy of simvastatin and a simvastatin-ezetimibe combination therapy in managing the endothelial inflammatory response in an SCI rat model. Adult male Sprague-Dawley rats were group-housed and SCI was induced by using the modified weight-drop method. The animals were divided into 4 groups: (1) sham group, laminectomy only (n=6); (2) no-treatment group, SCI without therapy (n=8); (3) simvastatin group (n=8), and (4) ezetimibe and simvastatin combination therapy group (n=8). A high dose (15 mg/kg) of simvastatin was given to the simvastatin group, and 10 mg/kg simvastatin and 10 mg/kg ezetimibe were given to the combination group. Neurological function was assessed using the Basso, Beattie, and Bresnahan locomotor scale score. Intercellular adhesion molecule-1 (ICAM-1) level was used as an SCI biomarker. ICAM-1 level was the highest at 72 hours after SCI in the no-treament group. The treatment groups showed significant reduction in ICAM-1 levels at 72 hours. The treatment groups, especially the combination treatment group, showed better neurological function scores. Simvastatin and simvastatin- ezetimibe all could improve the neurological function and attenuate the endothelial inflammatory response after spinal cord injury in rat.

[4] *Libby P, Everett B*. **Novel Antiatherosclerotic Therapies**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118310958.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30816799

ABSTRACT

Many measures can control lipid risk factors for atherosclerosis. Yet, even with excellent control of dyslipidemia, other sources of risk remain. Hence, we must look beyond lipids to address residual risk. Lifestyle measures should form the foundation of cardiovascular risk control. Many pharmacological interventions targeting oxidation have proven disappointing. A large program tested inhibition of a LpPLA2 (lipoprotein-associated phospholipase A2), culminating in 2 large-scale clinical trials that did not meet their primary end points. A variety of antioxidants have not shown benefit in clinical trials. Numerous laboratory and clinical studies have inculpated inflammatory pathways in the pathogenesis of atherosclerotic events. The p38 MAPK (mitogen-activated protein kinase) inhibitor losmapimod and an inhibitor of a leukocyte adhesion molecule, P-selectin, did not alter adverse events in trials. Low-dose methotrexate, despite the promising observational studies, did not lower biomarkers of inflammation or alter cardiovascular outcomes in the CIRT (cardiovascular inflammation reduction trial). Four large-scale investigations underway will determine colchicine's ability to reduce recurrent events in secondary prevention. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) showed that an antibody that neutralizes IL (interleukin)-1beta can reduce recurrent cardiovascular events in secondary prevention. The success of CANTOS points to the pathway

that leads from the NLRP3 (NOD-like receptor family, pyrin domain-containing protein 3) inflammasome through IL-1beta to IL-6 as an attractive target for further study and clinical development beyond lipid therapies to address the unacceptable burden of risk that remains despite our best current care in secondary prevention.

[5] *Momtazi-Borojeni AA, Jaafari MR, Badiee A, Sahebkar A*. **Long-term generation of antiPCSK9 antibody using a nanoliposome-based vaccine delivery system**. Atherosclerosis 2019; 283:69-78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30797988

ABSTRACT
BACKGROUND AND AIMS: Proprotein convertase subtilisin kexin type 9 (PCSK9) is a liver secretory enzyme that controls plasma low-density lipoprotein cholesterol (LDL-C) levels through modulation of LDL receptor (LDLR). Inhibition of PCSK9 using monoclonal antibodies (mAbs) can efficiently lower plasma LDL-C. However, the relatively short half-life of mAbs necessitates frequent passive immunization, which is costly. These limitations can be circumvented by active immunization. Here, we evaluated the long-term antiPCSK9 antibody generation in BALB/c mice vaccinated with a nanoliposomal PCSK9-specific active vaccine. METHODS: Negatively charged nanoliposomes were used as a vaccine delivery system and prepared via lipid-film hydration method. We constructed a peptide vaccine termed Immunogenic Fused PCSK9-Tetanus (IFPT) by linking a short PCSK9 peptide (as B cell epitope) to a tetanus peptide (as T cell epitope). The IFPT peptide was conjugated to the surface of nanoliposome carriers using a DSPE-PEG- Maleimide (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(PEG)-2000]) linker. Nanoliposomal IFPT (L-IFPT) construct was formulated with alum vaccine adjuvant (L-IFPTA(+)). To evaluate induction of antiPCSK9 antibody in vivo, BALB/c mice were subcutaneously inoculated four times in bi-weekly intervals with prepared vaccine formulations, including L-IFPT, L-IFPTA(+), IFPTA(+), IFPT, and empty liposomes as negative control. The long-term efficacy of antiPCSK9 antibodies was evaluated over 48 weeks after prime inoculation. Specificity of generated antiPCSK9 antibodies was assessed using ELISA method. To evaluate immunogenic safety, production of IL-4 and IFN-gamma, and population of CD8(+) and CD4(+) T cells in splenic cells isolated from the vaccinated mice were analyzed. RESULTS: The L-IFPTA(+) vaccine was found to elicit the highest IgG antibody response against PCSK9 peptide in the vaccinated mice, when compared with the other vaccine formulations. Antibody titer analyses over 48 weeks post-prime vaccination revealed that the L-IFPTA(+) vaccine was able to stimulate a long-lasting humoral immune response against PCSK9 peptide, and thereby decrease plasma PCSK9. Generated antibodies could specifically target PCSK9 and thereby inhibit PCSK9-LDLR interaction. Analysis of splenic cells showed that the population of anti-inflammatory CD4(+) Th2 cells and production and secretion of IL-4 cytokine were increased in mice vaccinated with the L-IFPTA(+) vaccine, while population of inflammatory CD4(+) Th1 cell and cytotoxic CD8(+) T cells as well as production and secretion of IFN-gamma were not altered. CONCLUSIONS: The results indicate efficient activity of the tested nanoliposomal construct (L-IFPTA(+)) to induce humoral immune response against PCSK9 in BALB/c mice. L-IFPTA(+) vaccine can induce immunogenic-safe and long-term generation of antiPCSK9 antibodies in BALB/c mice.

[6] *Hu K, Wan Q*. **Biphasic influence of pravastatin on human cardiac microvascular endothelial cell functions under pathological and physiological conditions**. Biochem Biophys Res Commun 2019; 511:476-481.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30803760
ABSTRACT
HMG-CoA reductase inhibitor statins are used to treat patients with hypercholesterolemia. The pleiotropic effects of statins have been recently extended to the regulation of angiogenesis. However, the observations on the effects of statins on endothelial cells seem to be contradictory. In this work, we systematically analysed the effects of pravastatin at concentrations covering 10,000-fold range on the functions of human cardiac microvascular endothelial cells (HMVEC-C) under H2O2-induced oxidative stress and normal physiological conditions. We observed the biphasic effects of pravastatin in protecting HMVEC-C dysfunctions induced by H2O2: pravastatin at low concentrations significantly enhanced vascular network formation, growth, migration and survival under H2O2-induced oxidative stress condition whereas this effect disappeared at higher concentrations. Interestingly, pravastatin at low concentrations did not affect HMVEC-C functions but at high concentrations significantly inhibited HMVEC-C vascular network formation, growth, migration and survival in a dose-dependent manner. We further demonstrated the different molecular mechanisms of the action of pravastatin at low and high concentrations on HMVEC-C: pravastatin at low concentrations alleviates H2O2-induced oxidative stress and damage and at high concentrations inhibits prenylation. Our work provides better understanding on the multiple differential effects and the underlying mechanisms of pravastatin on HMVEC-C, which may be of relevance to the influence of statins in cardiovascular system.

[7] *Choudhary MK, Eraranta A, Koskela J et al.* **Atherogenic index of plasma is related to arterial stiffness but not to blood pressure in normotensive and never-treated hypertensive subjects**. Blood pressure 2019:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30821503
ABSTRACT
BACKGROUND AND AIMS: Atherogenic index of plasma (AIP), defined as the logarithm of triglycerides to high-density lipoprotein cholesterol (HDL-C) ratio, is a strong predictor of future cardiovascular disease. Our aim was to examine the association of AIP with haemodynamic variables in normotensive and never-treated hypertensive subjects in a cross-sectional study. METHODS: Supine haemodynamics in 615 subjects without antihypertensive and lipid-lowering medications were examined using whole-body impedance cardiography and radial pulse wave analysis. Linear regression analysis was applied to investigate the association of AIP with haemodynamic variables and age, sex, body mass index (BMI), smoking status, alcohol consumption, plasma C-reactive protein, electrolytes, uric acid, low density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate, and quantitative insulin sensitivity check index. RESULTS: The demographics and laboratory values of the study population were (mean +/- 95% confidence interval): age 44.9 +/- 1.0 years, BMI 26.8 +/- 0.4 kg/m(2), office blood pressure 140.6 +/- 1.6/89.4 +/- 1.0 mmHg, total cholesterol 5.2 +/- 0.08, LDL-C 3.1 +/- 0.08, triglycerides 1.2 +/- 0.08, HDL-C 1.6 +/- 0.04 mmol/l, and AIP -0.15 +/- 0.02. Age (standardized coefficient Beta 0.508, p < .001) and aortic systolic blood pressure (Beta 0.239, p

< .001) presented with the strongest associations with pulse wave velocity. However, AIP was also associated with pulse wave velocity (Beta 0.145, p < .001). AIP was not related with aortic or radial blood pressure, cardiac output, systemic vascular resistance, or augmentation index. CONCLUSIONS: AIP is directly and independently associated with arterial stiffness, a variable strongly related to cardiovascular risk. This supports more widespread use of AIP in standard clinical cardiovascular disease risk evaluation.

[8] *Raina R, Young C, Krishnappa V, Chanchlani R*. **Role of Lipoprotein Apheresis in Cardiovascular Disease Risk Reduction**. Blood purification 2019:1-16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30799420
ABSTRACT
BACKGROUND AND AIM: Elevated low-density lipoprotein cholesterol and/or lipoprotein(a) are established risk factors for cardiovascular disease (CVD). Management of hypercholesterolemia consists of drug therapies, including statins and proprotein convertase subtilisin/kexin type 9 inhibitors. In patients with familial hypercholesterolemia (FH), lipoprotein apheresis (LA) is utilized to control lipid levels. However, LA is not currently a standard therapy for non-FH. This review summarizes the literature regarding LA therapy in CVD prevention. METHODS: PubMed/MEDLINE databases were searched using the keywords "LA" and "CVD". Citations were individually reviewed for relevance. RESULTS: The efficacy of LA was clearly demonstrated, largely based on evidence from observational studies. In patients who are unresponsive to traditional lipid-lowering medications, LA effectively reduced serum lipoprotein levels and adverse cardiovascular events. CONCLUSION: It was concluded that LA is a safe and effective technique that could be considered in the management of hypercholesterolemia and future risk. Randomized control trials would further support a role for LA as a therapeutic option.

[9] *Shrestha A, Tamrakar D, Karmacharya BM et al.* **Nepal Pioneer Worksite Intervention Study to lower cardio-metabolic risk factors: design and protocol**. BMC cardiovascular disorders 2019; 19:48.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30819098
ABSTRACT
BACKGROUND: To increase cardiovascular disease prevention efforts, worksite interventions can promote healthy food choices, facilitate health education, increase physical activity and provide social support. This pioneer study will measure the effectiveness of a cafeteria and a behavioral intervention on cardio-metabolic risk in a worksite in Nepal. METHODS: The Nepal Pioneer Worksite Intervention Study is a two-step intervention study conducted in Dhulikhel Hospital in eastern Nepal. In the first step, we will assess the effectiveness of a 6-month cafeteria intervention on cardio-metabolic risk using a pre-post design. In the second step, we will conduct a 6-month, open-masked, two-arm randomized trial by allocating half of the participants to an individual behavioral intervention based on the 'diabetes prevention program' for the prevention of cardio-metabolic risk. We will recruit 366 full time employees with elevated blood pressure, fasting blood sugar, or glycosylated haemoglobin (HbA1c). At baseline, we will measure their demographic variables, lifestyle factors, anthropometry, fasting blood sugar, HbA1c,and lipid profiles. We will measure cardio-metabolic outcomes at 6 months,

12 months, and 18 months. At 12 months, we will compare the proportion of participants who have attained two or more cardio-metabolic risk factor reduction goals (HbA1c decrease >/=0.5%; systolic blood pressure decrease >/=5 mmHg; or triglycerides decrease >/=10 mg/dL) during the cafeteria intervention period and the control period using generalized estimating equations. At 18 months, we will compare the proportion from the 'cafeteria only arm' to the 'cafeteria and behavior arm' for the same outcome using a chi-square test. DISCUSSION: This pioneer study will estimate the effect of environmental-level changes on lowering cardio-metabolic risks; and added benefit of an individual-level dietary intervention. If the study demonstrates a significant effect, a scaled up approach could produce an important reduction in cardiovascular disease burden through environmental and individual level prevention programs in Nepal and similar worksites worldwide. TRIAL REGISTRATION: The trial was retrospectively registered on clincaltrials.gov (Identification Member: NCT03447340 ; Date of Registration: February 27, 2018).

[10] *Godinho R, Bugnon S, Gracin T, Tataw J*. **Severe rhabdomyolysis-induced acute kidney injury following concomitant use of Genvoya(R) (EVG/COBI/FTC/TAF) and simvastatin; a case report**. BMC Nephrol 2019; 20:69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30808332
ABSTRACT
BACKGROUND: Genvoya(R) (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) is a recent single regimen for the treatment of Human Immunodeficiency Virus (HIV). However, because of its complexity, it is difficult to predict drug interactions, especially when associated with HMG-CoA reductase inhibitors and/or in the setting of other comorbidities. We discuss the mechanisms of these potential drug interactions as the cause of rhabdomyolysis and acute kidney injury in the context of prior and current medication therapy with possible underlying liver and kidney dysfunction. CASE PRESENTATION: We describe the case of a 54-year-old man diagnosed with HIV who developed severe rhabdomyolysis-induced anuric acute kidney injury (AKI) requiring renal replacement therapy following introduction of Genvoya(R) concomitantly with simvastatin, in the context of recently diagnosed hepatitis C and hepatitis A. Haemodialysis was continued over 5 weeks followed by progressive clinical and biological improvements. Five months later, a new antiretroviral regimen was started and has been well tolerated. CONCLUSION: Simvastatin, as well as lovastatin, because of their CYP3A4 metabolism, and to a lesser extent atorvastatin, which is only partially metabolized by CYP3A4, are the HMG-CoA reductase inhibitors with the greatest risk of drug interactions and should not be used in patients under HIV-therapy. Patients receiving HMG-CoA reductase inhibitors should be monitored regularly for the occurrence of muscular adverse effects and drug interactions should be considered with each new prescription or change in clinical status. There are many online tools that enable clinicians to rapidly check for drug interactions. We recommend the one from the University of Liverpool for patients under HIV-therapy (https://www.hiv-druginteractions.org/checker), while for patients under hepatitis C-therapy, we advise to consult http://www.hep-druginteractions.org/ . This case illustrates the importance of multidisciplinary collaboration in the treatment of HIV-positive patients because of their complexity, associated comorbidities and the potential of multiple drug-drug interactions potentially exacerbated by underlying liver and/or kidney dysfunction.

[11] *Nash M, McGrath JP, Cartland SP et al.* **TNF superfamily members in ischemic vascular diseases**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30816914
ABSTRACT
Current treatment of ischemic vascular diseases such as coronary and peripheral artery disease includes angioplasty and bypass grafting, as well as lipid lowering therapies and control of other cardiovascular risk factors. Numerous members of the tumour necrosis factor (TNF) superfamily (TNFSF) have recently shown emerging roles in both the protection and progression of such diseases. Understanding the role TNFSF members play in ischemic vascular disease may provide insight into the development of novel therapeutics to prevent or treat diseases relating to atherosclerosis and ischemia. This review summarises the most recent findings relating to TNF superfamily members and the mechanisms that precede ischemic vascular disease progression, particularly endothelial dysfunction, chronic inflammation, and atherosclerotic plaque development. This review also explores recent translational research on the role of TNFSF therapies in cardiovascular disease.

[12] *Ino Y, Kubo T, Shimamura K et al.* **Stabilization of High Risk Coronary Plaque on Optical Coherence Tomography and Near-Infrared Spectroscopy by Intensive Lipid-Lowering Therapy With Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor**. Circulation journal : official journal of the Japanese Circulation Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30799312
ABSTRACT

[13] *Ndrepepa G*. **Myeloperoxidase - A bridge linking inflammation and oxidative stress with cardiovascular disease**. Clinica chimica acta; international journal of clinical chemistry 2019; 493:36-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30797769
ABSTRACT
Myeloperoxidase (MPO) is a member of the superfamily of heme peroxidases that is mainly expressed in neutrophils and monocytes. MPO-derived reactive species play a key role in neutrophil antimicrobial activity and human defense against various pathogens primarily by participating in phagocytosis. Elevated MPO levels in circulation are associated with inflammation and increased oxidative stress. Multiple lines of evidence suggest an association between MPO and cardiovascular disease (CVD) including coronary artery disease, congestive heart failure, arterial hypertension, pulmonary arterial hypertension, peripheral arterial disease, myocardial ischemia/reperfusion-related injury, stroke, cardiac arrhythmia and venous thrombosis. Elevated MPO levels are associated with a poor prognosis including increased risk for overall and CVD-related mortality. Elevated MPO may signify an increased risk for CVD for at least 2 reasons. First, low-grade inflammation and increased oxidative stress coexist with many metabolic abnormalities and comorbidities and consequently an elevated MPO level may represent an increased cardiometabolic risk in general. Second, MPO produces a large number of highly reactive species which can attack, destroy or modify the function of every known cellular component. The most common MPO actions relevant to CVD are generation of

dysfunctional lipoproteins with an increased atherogenicity potential, reduced NO availability, endothelial dysfunction, impaired vasoreactivity and atherosclerotic plaque instability. These actions strongly suggest that MPO is directly involved in the pathophysiology of CVD. In this regard MPO may be seen as a mediator or an instrument through which inflammation promotes CVD at molecular and cellular level. Clinical value of MPO therapeutic inhibition remains to be tested.

[14] *Beg S, Alam MN, Ahmad FJ, Singh B*. **Chylomicron mimicking nanocolloidal carriers of rosuvastatin calcium for lymphatic drug targeting and management of hyperlipidemia**. Colloids and surfaces. B, Biointerfaces 2019; 177:541-549.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30825846
ABSTRACT
The present work entails development of novel phospholipid-based self-nanoemulsifying systems (SNES) of rosuvastatin calcium for improving the oral biopharmaceutical performance via intestinal lymphatic pathways. The phospholipid complex-loaded SNES exhibited emulsification time of 142 s, particle size of 182.5 nm, polydispersity index of 0.35, zeta potential of -22.5 mV and complete in vitro drug release within 3 h. Cell line study on Caco-2 indicated absence of cytotoxicity and excellent cellular uptake of PL-SNES vis-a-vis plain SNES. Permeability study revealed >85% enhancement in the permeation, while intestinal perfusion study showed 2.9 and 3.5-fold increase in the permeation and absorption of the drug from the optimized PL-SNES over the pure drug suspension. Nearly 2.2 and 7.2-folds improvement in AUC0-t and Cmax, and 0.33-fold reduction in the Tmax of drug was observed for PL-SNES vis-a-vis the pure drug suspension during pharmacokinetic study. Moreover, PL-SNES also showed superior antihyperlipidemic activity over the pure drug suspension during pharmacodynamic study. Overall, the developed nanoformulation yielded significant improvement in the oral deliverability of the explored drug candidate.

[15] *Rhoads JP, Major AS*. **How Oxidized Low-Density Lipoprotein Activates Inflammatory Responses**. Critical reviews in immunology 2018; 38:333-342.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30806246
ABSTRACT
Cardiovascular disease (CVD) is the number one cause of death in the United States and worldwide. The most common cause of cardiovascular disease is atherosclerosis, or formation of fatty plaques in the arteries. Low-density lipoprotein (LDL), termed "bad cholesterol", is a large molecule comprised of many proteins as well as lipids including cholesterol, phospholipids, and triglycerides. Circulating levels of LDL are directly associated with atherosclerosis disease severity. Once thought to simply be caused by passive retention of LDL in the vasculature, atherosclerosis studies over the past 40-50 years have uncovered a much more complex mechanism. It has now become well established that within the vasculature, LDL can undergo many different types of oxidative modifications such as esterification and lipid peroxidation. The resulting oxidized LDL (oxLDL) has been found to have antigenic potential and contribute heavily to atherosclerosis associated inflammation, activating both innate and adaptive immunity. This review discusses the many proposed mechanisms by which oxidized LDL modulates inflammatory responses and how this might modulate atherosclerosis.

[16] *Narayanankutty A*. **Toll like receptors as a novel therapeutic target for natural products against chronic diseases**. Current drug targets 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30806312
ABSTRACT
Toll-like receptors (TLR) are one among the initial responders of the immune system which participate in the activation inflammatory processes. Several different types of TLR such as TLR2, TLR4, TLR7 and TLR9 have been identified in various cell types, each having distinct ligands like lipids, lipoproteins, nucleic acids and proteins. Thought its prime concern is xenobiotic defences, TLR signalling has also recognized as an activator of inflammation and associated development of chronic degenerative disorders (CDDs) including obesity, type 2 diabetes mellitus (T2DM), fatty liver disease, cardiovascular and neurodegenerative disorders as well as various types of cancers. Numerous drugs are in use to prevent these disorders, which specifically inhibit different pathways associated with the development of CDDs. Compared to these drug targets, inhibition of TLR, which specifically responsible for the inflammatory insults have proven to be a better drug target. Several natural products have emerged as inhibitors of CDDs, which specifically targets TLR signalling, among these many, are in the clinical trials. This review is intended to summarize the recent progress on TLR association with CDDs and to list possible use of natural products, their combinations and their synthetic derivative in the prevention of TLR-driven CDD development.

[17] *Kim DD, Barr AM, Fredrikson DH et al.* **Association between serum lipids and antipsychotic response in schizophrenia**. Curr Neuropharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30819084
ABSTRACT
Metabolic abnormalities are serious health problems in individuals with schizophrenia. Paradoxically, studies have noted an association where individuals who gained body weight or who have increases in their serum lipids demonstrated better antipsychotic response. As serum lipids serve as more specific physiological markers than body weight, the objective of this study was to review studies that examined the association between changes in serum lipids and changes in symptoms during antipsychotic treatment in individuals with schizophrenia. A Medline(R) literature search was performed. Fourteen studies were included and analyzed. Evidence suggests that increases in serum lipids may be associated with decreases in symptoms during antipsychotic treatment. This inverse association may be independent of confounding variables, such as weight gain, and may be most evident during treatment with clozapine. Also, according to recent randomized controlled trials, lipid-lowering agents do not appear to worsen symptoms although this needs to be further investigated in clozapine-treated patients. Future studies should investigate the association in question in a larger population and identify underlying mechanisms.

[18] *Yaribeygi H, Bo S, Ruscica M, Sahebkar A*. **Ceramides and diabetes mellitus: an update on the potential molecular relationships**. Diabetic medicine : a journal of the British Diabetic Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30803019

ABSTRACT
Recent evidence suggests that ceramides can play an important pathophysiological role in the development of diabetes. Ceramides are primarily recognized as lipid bilayer building blocks, but recent work has shown that these endogenous molecules are important intracellular signalling mediators and may exert some diabetogenic effects via molecular pathways involved in insulin resistance, beta-cell apoptosis and inflammation. In the present review, we consider the available evidence on the possible roles of ceramides in diabetes mellitus and introduce eight different molecular mechanisms mediating the diabetogenic action of ceramides, categorized into those predominantly related to insulin resistance vs those mainly implicated in beta-cell dysfunction. Specifically, the mechanistic evidence involves beta-cell apoptosis, pancreatic inflammation, mitochondrial stress, endoplasmic reticulum stress, adipokine release, insulin receptor substrate 1 phosphorylation, oxidative stress and insulin synthesis. Collectively, the evidence suggests that therapeutic agents aimed at reducing ceramide synthesis and lowering circulating levels may be beneficial in the prevention and/or treatment of diabetes and its related complications. This article is protected by copyright. All rights reserved.

[19] *Lorenzatti AJ, Eliaschewitz FG, Chen Y et al.* **Randomised Study of Evolocumab in Patients With Type 2 Diabetes and Dyslipidaemia on Background Statin: Primary Results of the BERSON Clinical Trial**. Diabetes Obes Metab 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30821053

ABSTRACT
AIM: To evaluate the lipid-lowering efficacy and safety of evolocumab combined with background atorvastatin in patients with type 2 diabetes mellitus (T2DM) and hyperlipidaemia or mixed dyslipidaemia. MATERIALS AND METHODS: BERSON was a double-blind, 12-week, phase 3 study (NCT02662569) conducted in 10 countries. Patients >/=18 to </=80 years with type T2DM received atorvastatin 20 mg/day and were randomised 2:2:1:1 to evolocumab 140mg every 2 weeks (Q2W) or 420mg monthly (QM) or placebo Q2W or QM. Co-primary endpoints were the percentage change in LDL-C from baseline to week 12 and from baseline to the mean of weeks 10 and 12. Additional endpoints included atherogenic lipids, glycaemic measures, and adverse events (AEs). RESULTS: Overall, 981 patients were randomised and received >/=1 dose of study drug. Evolocumab significantly reduced LDL cholesterol (LDL-C) versus placebo at week 12 (Q2W, -71.8%; QM, -74.9%) and at the mean of weeks 10 and 12 (Q2W, -70.3%; QM, -70.0%; adjusted P<0.0001 for all) when administered with atorvastatin. Non-HDL-C, ApoB100, total cholesterol, Lp(a), triglycerides, HDL-C, and VLDL-C improved significantly with evolocumab versus placebo. The overall incidence of AEs was similar between evolocumab- and placebo-treated patients, and there were no clinically meaningful differences in changes over time in glycaemic parameters (fasting serum glucose and haemoglobin A1c) between the two groups. CONCLUSIONS: In patients with T2DM and hyperlipidaemia or mixed dyslipidaemia on statin, evolocumab significantly reduced LDL-C and other atherogenic lipids, was well tolerated, and had no notable impact on glycaemic measures. This article is protected by copyright. All rights reserved.

[20] *Kawasaki R, Kitano S, Sato Y et al.* **Factors associated with non-proliferative diabetic retinopathy in patients with type 1 and type 2 diabetes: the Japan Diabetes Complication and its Prevention prospective study (JDCP study 4)**. Diabetology international 2019; 10:3-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30800559

ABSTRACT

Aims: This study aims to identify associations of non-proliferative diabetic retinopathy (NPDR) in the Japan Diabetes Complication and its Prevention prospective (JDCP) study, a nation-wide study capturing real-world practice for diabetes in Japan. Methods: We recruited patients with type 1 and type 2 diabetes mellitus aged between 40 and 75 years from 464 hospitals and clinics. Seven thousand and seven hundred patients fulfilled the inclusion criteria, and 5852 patients were included for this specific analysis. Multiple logistic regression models were used to identify associated factors of NPDR. Results: Of the 363 patients with type 1 diabetes, 83 patients (22.8%) had NPDR; there were significant associations of duration of diabetes and high-density lipoprotein cholesterol with the presence of NPDR. Of the 5489 patients with type 2 diabetes, 1515 (27.6%) had NPDR. Female, duration of diabetes, lifetime maximum body weight, treatment types, systolic blood pressure, and the number of oral hypoglycemic agents (OHA) and antihypertensive drug were associated with increased odds of having NPDR. Diastolic BP, body mass index, alcohol intake, and the number of lipid-lowering drugs were associated with lower odds of having NPDR. Statin and fibrate use was associated with lower odds of having NPDR; this association was confirmed in the model adjusting for the propensity score for taking fibrate or statin (odds ratio 0.80, 95% confidence interval 0.70-0.92; p = 0.002). Conclusions: There was a potential protective association of lipid-lowering medication (statin or fibrate) and statin use and the presence of NPDR in patients with type 2 diabetes in the JDCP study.

[21] *Ruscica M, Banach M, Sahebkar A et al.* **ETC-1002 (Bempedoic acid) for the management of hyperlipidemia: from preclinical studies to phase 3 trials**. Expert opinion on pharmacotherapy 2019:1-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30810432

ABSTRACT

INTRODUCTION: Tolerability problems in treating hypercholesterolemic patients undergoing statin treatment are of growing concern to physicians and patients, thus underlining the need for an agent with a similar mechanism but minimal side effects. A drug with a somewhat similar mechanism to statins but free of muscular side effects is ETC-1002 (bempedoic acid). It inhibits cholesterol biosynthesis at a step preceding HMG-CoA reductase, i.e. ATP citrate lyase (ACLY). A prodrug, ETC-1002 is converted to the active agent only in liver, not in skeletal muscle, and this may prevent any myotoxic activity. Area covered: The mechanism of ETC-1002 activity is described in detail, considering that ACLY inhibition markedly attenuated atherosclerosis in animal models. Clinical studies are also reported. Expert opinion: Present day LDL-C lowering treatments lead to significant reductions of cardiovascular (CV) events but, at times, the need to interrupt statin treatment appears to be dangerous due to a rapid rise in CV risk. The excellent tolerability of ETC-1002 makes it a useful alternative, either alone or as an adjunct to ezetimibe, for patients with statin intolerance needing to achieve significant CV risk reduction. ETC-1002 is also associated with a marked fall in high-sensitivity C-reactive protein.

[22] *Caetano Dos Santos FL, Kolasa M, Terada M et al.* **VASIM: an automated tool for the quantification of carotid atherosclerosis by computed tomography angiography**. The international journal of cardiovascular imaging 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30820803
ABSTRACT
The diagnostic imaging techniques currently used to evaluate the arterial atherosclerosis hinge on the manual marking and calculation of the stenosis degree. However, the manual assessment is highly dependent on the operator and characterized by low replicability. The study aimed to develop a fully-automated tool for the segmentation and analysis of atherosclerosis in the extracranial carotid arteries. The dataset consisted of 59 randomly-chosen individuals who had undergone head-and-neck computed tomography angiography (CTA), at the Tampere University Hospital, Tampere, Finland. The analysis algorithm was mainly based on the detection of carotid arteries, delineation of the vascular wall, and extraction of the atherosclerotic plaque. To improve the vascular detection rate, the model-based and volume-wide analytical approaches were deployed. A new fully-automated vascular imaging (VASIM) software tool was developed. For stenosis over 50%, the success rate was 83% for the detection and segmentation. Specificity and sensitivity of the algorithm were 25% and 83%, respectively. The overall accuracy was 71%. The VASIM tool is the first published approach for the fully-automated analysis of atherosclerosis in extracranial carotid arteries. The tool provides new outputs, which may help with the quantitative and qualitative, clinical evaluation of the atherosclerosis burden and evolution. The findings from this study provide a basis for the further development of automated atherosclerosis diagnosis and plaque analysis with CTA.

[23] *Solati Z, Ravandi A*. **Lipidomics of Bioactive Lipids in Acute Coronary Syndromes**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30823404
ABSTRACT
Acute coronary syndrome (ACS) refers to ischemic conditions that occur as a result of atherosclerotic plaque rupture and thrombus formation. It has been shown that lipid peroxidation may cause plaque instability by inducing inflammation, apoptosis, and neovascularization. There is some evidence showing that these oxidized lipids may have a prognostic value in ACS. For instance, higher levels of oxidized phospholipids on apo B-100 lipoproteins (OxPL/apoB) predicted cardiovascular events independent of traditional risk factors, C-reactive protein (hsCRP), and the Framingham Risk Score (FRS). A recent cross-sectional study showed that levels of oxylipins, namely 8,9-DiHETrE and 16-HETE, were significantly associated with cardiovascular and cerebrovascular events, respectively. They found that with every 1 nmol/L increase in the concentrations of 8,9-DiHETrE, the odds of ACS increased by 454-fold. As lipid peroxidation makes heterogonous pools of secondary products, therefore, rapid multi-analyte quantification methods are needed for their assessment. Conventional lipid assessment methods such as chemical reagents or immunoassays lack specificity and sensitivity. Lipidomics may provide another layer of a detailed molecular level to lipid assessment, which may eventually lead to exploring novel biomarkers and/or new treatment options. Here, we will briefly review the lipidomics of bioactive lipids in ACS.

[24] *Al-Kuraishy HM, Al-Gareeb AI*. **Effects of rosuvastatin on metabolic profile: Versatility of dose-dependent effect**. Journal of advanced pharmaceutical technology & research 2019; 10:33-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30815386
ABSTRACT
Obesity refers to an excess of body fat content causing metabolic and inflammatory disorders. Therefore, the aim of the present study was to investigate dose-dependent effect of rosuvastatin on the metabolic profile of diet-induced obesity in mice model study. A total number of 40 male Albino Swiss mice were used which divided into Group I: Control group, fed normal diet for 8 weeks (n = 10); Group II: High-fat diet (HFD) group, fed on HFD for 8 weeks (n = 10); Group III: HFD + 20 mg/kg rosuvastatin for 8 weeks (n = 10); and Group IV: HFD +40 mg/kg rosuvastatin for 8 weeks (n = 10). Anthropometric and biochemical parameters were estimated, including fasting blood glucose, lipid profile, fasting insulin, and glucose tolerance test (GTT). Mice on HFD fed showed a significant increase in the insulin resistance, body weight, deterioration of lipid profile and significant reduction in the beta-cell function, and insulin sensitivity compared to the control $P < 0.05$. GTT and blood glucose level were significantly high in HFD fed group compared to the control group $P < 0.05$. Rosuvastatin in a dose of 40 mg/kg illustrated better effect than 20 mg/kg on the glucometabolic profile $P < 0.05$. Rosuvastatin may has a potential effect on reduction of glucometabolic changes induced by HFD with significant amelioration of pancreatic beta-cell function in dose-dependent manner.

[25] *Dudum R, Whelton SP*. **Non-statin lipid lowering and coronary plaque composition**. Journal of cardiovascular computed tomography 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30803836
ABSTRACT

[26] *Spitthover R, Roseler T, Julius U et al.* **Real-world study: Escalating targeted lipid-lowering treatment with PCSK9-inhibitors and lipoprotein apheresis**. Journal of clinical apheresis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30817043
ABSTRACT
INTRODUCTION: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition with monoclonal antibodies has complemented the armamentarium of lipid-lowering therapy (LLT) before the final step of commencing chronic lipoprotein apheresis (LA). Data are scarce on patients who, after escalation of LLT with PCSK9 antibodies, have commenced chronic LA or PCSK9 antibody treatment during ongoing long-term LA. PATIENTS AND METHODS: In this study, a cohort of 110 patients with established atherosclerotic cardiovascular disease (ASCVD) due to hypercholesterolemia or concomitant lipoprotein(a)-hyperlipoproteinemia, who received PCSK9 antibodies for the first time during routine care, were consecutively identified. RESULTS: Mean LDL-C concentration prior to initiation of LA or PCSK9 antibody treatment was 5.3 +/- 2.6 mmol/L (205 +/- 102 mg/dL). Due to established ASCVD, the risk-adjusted LDL-C target value was <1.8 mmol/L (<70 mg/dL) in all patients. Use of PCSK9 antibodies increased the proportion of patients attaining the LDL-C target concentration by 41.8% overall. Treatment emergent adverse events (TEAE) associated with PCSK9 antibody medication were reported in

35 patients (31.8%). Discontinuation of PCSK9 antibody therapy due to TEAEs occurred in 25 patients (22.7%). CONCLUSION: Finally, 55.5% of patients received a combination of PCSK9 antibody therapy and LA at individually optimized treatment frequencies resulting in an increase of target attainment in 54.1% of patients. About 18.1% of chronic LA patients terminated LA treatment in this real-world study. The termination of long-term LA therapy, which has hitherto prevented the progression of ASCVD, requires careful individual risk assessment and cannot be recommended by the general criteria of LDL-C reduction.

[27] *Yao BC, Meng LB, Hao ML et al.* **Chronic stress: a critical risk factor for atherosclerosis**. J Int Med Res 2019:300060519826820.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30799666
ABSTRACT
Chronic stress refers to the non-specific systemic reaction that occurs when the body is stimulated by various internal and external negative factors over a long time. The physiological response to chronic stress exposure has long been recognized as a potent modulator in the occurrence of atherosclerosis. Furthermore, research has confirmed the correlation between atherosclerosis and cardiovascular events. Chronic stress is pervasive during negative life events and may lead to the formation of plaque. Several epidemiological studies have shown that chronic stress is an independent risk factor for the development of vascular disease and for increased morbidity and mortality in patients with pre-existing coronary artery disease. One possible mechanism for this process is that chronic stress causes endothelial injury, directly activating macrophages, promoting foam cell formation and generating the formation of atherosclerotic plaque. This mechanism involves numerous variables, including inflammation, signal pathways, lipid metabolism and endothelial function. The mechanism of chronic stress in atherosclerosis should be further investigated to provide a theoretical basis for efforts to eliminate the effect of chronic stress on the cardiocerebral vascular system.

[28] *Zvizdic F, Godinjak A, Durak-Nalbantic A et al.* **Impact of Different Types of Statins on Clinical Outcomes in Patients Hospitalized for Ischemic Heart Failure**. Medical archives (Sarajevo, Bosnia and Herzegovina) 2018; 72:401-405.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30814769
ABSTRACT
Introduction: The effect of statins on risk of heart failure (HF) hospitalization and lethal outcome remains dubious. Aim: To investigate whether statin therapy improves clinical outcomes in patients hospitalized for ischemic heart failure (HF), to compare the efficacy of lipophilic and hydrophilic statins and to investigate which statin subtype provides better survival and other outcome benefits. Material and Methods: Total amount of 155 patients in the study were admitted to the Clinic for Cardiology, Rheumatology and Vascular diseases in Clinical Center University of Sarajevo in the period from January 2014- December 2017. Inclusion criteria was HF caused by ischemic coronary artery disease upon admission. For each patient the following data were obtained: gender, age, comorbidities and medications on discharge. New York Heart Association (NYHA) class for heart failure was determined by physician evaluation and left ventricle ejection fraction (LVEF) was determined by echocardiography. The patients were followed for a period of two years. Outcome points were:

rehospitalization, in-hospital death, mortality after 6 months, 1 year and 2 years. All-cause mortality included cardiovascular events or worsening heart failure. Results: Overall, 58.9% of HF patients received statin therapy, with 33.9% patients receiving atorvastatin and 25.0% rosuvastatin therapy. The most frequent rehospitalization was in patients without statin therapy (66.7%), followed by patients on rosuvastatin (64.1%), and atorvastatin (13.2%), with statistically significant difference p = 0.001 between the groups. Mortality after 6 months, 1 year and 2 years was the most frequent in patients without statin therapy with a statistically significant difference (p = 0.001). Progression of HF accounted for 31.7% of mortality in patients without statin therapy, 12.8% in patients on rosuvastatin therapy and 3.8% in patients on atorvastatin therapy (p = 0.004). Conclusion: Lipophilic statin therapy is associated with substantially better long-term outcomes in patients with HF.

[29] *Feng PF, Zhang B, Zhao L et al.* **Intracellular mechanism of rosuvastatin-induced decrease in mature hERG protein expression on membrane**. Molecular pharmaceutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30807184

ABSTRACT

The hERG potassium channel (IKr) encoded by human ether-a-go-go-related gene plays an important role in cardiac repolarization. Decreased IKr may lead to long QT syndrome, which subsequently causes torsade de pointes and sudden cardiac death. Previous studies have shown that statins inhibit IKr and are more potent in inhibiting hERG currents when combined with other drugs. Since chemical structure of rosuvastatin is similar to that of several IKr blockers (ibutilide and E-4031), the present study aimed to reveal the mechanism that underlies rosuvastatin-induced hERG current reduction and to evaluate the possibility of cardiac toxicity. The results showed that rosuvastatin reduced hERG currents by accelerating the inactivation and prolonged action potential duration (APD) in hiPSC-CMs. Meanwhile, it was observed that rosuvastatin reduced the expression of the mature hERG. Transcription factor Sp1 was involved in hERG protein downregulation induced by rosuvastatin, and the result was verified by Sp1 siRNA and Sp1 agonist epicatechin. These results indicated that rosuvastatin could potentially inhibit transcription and reduce hERG mRNA expression. The interaction between hERG and heat shock protein was evaluated to study the mechanism of trafficking inhibition through Co-Immunoprecipitation. We found that rosuvastatin reduces the interaction of heat shock protein 70 (Hsp70) with the hERG protein, thereby affecting the folding of the hERG channel. Additionally, rosuvastatin significantly activated ATF6, which plays a key role in the activation of the unfolded protein response (UPR) pathway. Increased expression of the molecular chaperone calnexin and calreticulin, which are activated by ATF6 to help channel folding, further confirmed UPR activation. Meanwhile, the degradation of the hERG channel was mediated by lysosomes and proteasomes. In conclusion, Rosuvastatin reduced the expression of hERG plasma membrane by two pathways, the first is to disrupt the transport of immature hERG channels to the membrane, and the second is to increase the degradation of mature hERG channels. In addition, Rosuvastatin potently blocked hERG current, delayed cardiac repolarization and thereby prolonged APDs and QTc intervals. Therefore, caution should be taken when rosuvastatin is used in the treatment of hyperlipidemia, especially when combined with drugs that can prolong the QT interval.

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[30] *Martin Navarro JA, Gutierrez Sanchez MJ, Petkov Stoyanov V, Jimenez Herrero MC*. **Acute renal failure secondary to rhabdomyolysis in a patient receiving treatment with ticagrelor and atorvastatin**. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30798999
ABSTRACT

[31] *Liu H, Yang J, Wang K et al.* **Moderate- and Low-Dose of Atorvastatin Alleviate Cognition Impairment Induced by High-Fat Diet via Sirt1 Activation**. Neurochemical research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30820818
ABSTRACT

Mounting evidences have demonstrated that diet-induced obesity is associated with cognition impairment via increasing oxidative stress and inflammation in the brain. Atorvastatin (Ator, a HMG-CoA reductase inhibitor) is a cholesterol lowering drug. Studies have reported that Ator can ameliorate the development and progression of cognition impairment. Additionally, silent information regulator 1 (SIRT1) has been demonstrated to be beneficial in cognition impairment. However, the interaction between Ator and SIRT1 activation for cognition impairment remains unclear. This study aimed to identify a relationship between the use of Ator and cognition impairment induced by high-fat diet via Sirt1 activation. A total of 60 healthy male C57BL/6J mice were purchased and then divided into 6 groups, including normal diet group (control), a high-fat diet group (40%HFD, 40% energy from fat), a model group (60%HFD, 60% energy from fat), and model group treated with different doses of Ator (high-dose (80 mg), moderate-dose (40 mg), and low-dose (20 mg) groups). All interventions took place for 7 months. Metabolic phenotypes were characterized for body weight and analysis of serum lipid level. The level of cognition development was examined by Morris water maze (MWM) approach and novel object recognition test (NORT); besides, the expression of Creb1, Gap-43, BDNF, CaMKII, and ERKs of frontal cortex and hippocampus was determined by reverse transcription polymerase chain reaction (RT-PCR). Then, the levels of factors related to inflammation (TNF-a, IL-1beta, HMGB1 and IL-6) and oxidation stress (SOD, MDA, CAT and GSH-Px) were assessed using commercially available kits. Finally, SIRT1 and its downstream molecules (Ac-FoxO1, Ac-p53, Ac-NF-kappaB, Bcl-2 and Bax) were evaluated by Western blot analysis. Compared with the 60% HFD group, body weight and serum lipid levels were significantly decreased in the Ator treated groups. The results of MWM and NORT, as well as the levels of Creb1, Gap-43, BDNF, CaMKII, and ERKs were markedly reversed in the moderate- and low-dose of Ator treated groups. Meanwhile, the expression of IL-1beta, TNF-a, IL-6, HMGB1, and MDA was notably decreased, whereas the activity of SOD, CAT, and GSH-Px was increased. It was also revealed that the expression of SIRT1 was remarkably unregulated, the level of Bcl-2 was upregulated, and the content of Ac-FoxO1, Ac-p53, Ac-NF-kappaB, and Bax was downregulated in the moderate- and low-dose of Ator. Furthermore, results showed that the effect of moderate-dose of Ator was significantly greater than the low-dose of Ator. However, these effects were not observed in the high-dose of Ator. Our results showed that moderate- and low-dose of Ator can significantly attenuate cognition impairment induced by HFD through its antioxidant and anti-inflammatory functions related to SIRT1 activation.

[32] *Bosch J, O'Donnell M, Swaminathan B et al.* **Effects of blood pressure and lipid lowering on cognition: Results from the HOPE-3 study**. Neurology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30814321
ABSTRACT
OBJECTIVE: To assess whether long-term treatment with candesartan/hydrochlorothiazide, rosuvastatin, or their combination can slow cognitive decline in older people at intermediate cardiovascular risk. METHODS: The Heart Outcomes Prevention Evaluation-3 (HOPE-3) study was a double-blind, randomized, placebo-controlled clinical trial using a 2 x 2 factorial design. Participants without known cardiovascular disease or need for treatment were randomized to candesartan (16 mg) plus hydrochlorothiazide (12.5 mg) or placebo and to rosuvastatin (10 mg) or placebo. Participants who were >/=70 years of age completed the Digit Symbol Substitution Test (DSST), the modified Montreal Cognitive Assessment, and the Trail Making Test Part B at baseline and study end. RESULTS: Cognitive assessments were completed by 2,361 participants from 228 centers in 21 countries. Compared with placebo, candesartan/hydrochlorothiazide reduced systolic blood pressure by 6.0 mm Hg, and rosuvastatin reduced low-density lipoprotein cholesterol by 24.8 mg/dL. Participants were followed up for 5.7 years (median), and 1,626 completed both baseline and study-end assessments. Mean participant age was 74 years (SD +/-3.5 years); 59% were women; 45% had hypertension; and 24% had >/=12 years of education. The mean difference in change in DSST scores was -0.91 (95% confidence interval [CI] -2.25 to 0.42) for candesartan/hydrochlorothiazide compared with placebo, -0.54 (95% CI -1.88 to 0.80) for rosuvastatin compared with placebo, and -1.43 (95% CI -3.37 to 0.50) for combination therapy vs double placebo. No significant differences were found for other measures. CONCLUSIONS: Long-term blood pressure lowering with candesartan plus hydrochlorothiazide, rosuvastatin, or their combination did not significantly affect cognitive decline in older people. CLINICALTRIALSGOV IDENTIFIER: NCT00468923. CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that for older people, candesartan plus hydrochlorothiazide, rosuvastatin, or their combination does not significantly affect cognitive decline.

[33] *Cho O, Jang YJ, Park KY, Heo TH*. **Beneficial anti-inflammatory effects of combined rosuvastatin and cilostazol in a TNF-driven inflammatory model**. Pharmacological reports : PR 2018; 71:266-271.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30822620
ABSTRACT
BACKGROUND: Due to anti-inflammatory and anti-thrombotic functions, statins and antiplatelets are widely used for patients with cardiovascular-related or coronary artery diseases. Patients with systemic or complex diseases are commonly prescribed multiple targeted medications; thus, a proper combination of two or more drugs for beneficial efficacy is considered in clinical therapy. Recent studies have suggested that combinational therapy with statins and other medications accelerates their single effect to suppress inflammatory responses. However, the therapeutic efficacy and underlying mechanism of combination treatment with rosuvastatin and cilostazol have been poorly studied. METHODS: Mice were administered rosuvastatin alone, cilostazol alone or rosuvastatin and cilostazol in combination, and then injected with LPS or TNF to induce acute inflammation. The serum TNF level,

macrophage infiltration of the lesioned aortas and mice mortality were observed in the acute inflammation model. The phosphorylation of MAPK was analyzed in TNF-stimulated HeLa cells. RESULTS: Compared to the treatment with cilostazol alone, the combination treatment with rosuvastatin and cilostazol significantly reduced not only the levels of TNF in the sera but also macrophage infiltration in aortic lesions. In addition, the combination therapy decreased TNF-mediated phosphorylation of the MAPK signaling pathway and improved the survival rate in the TNF-driven inflammatory mice model. CONCLUSION: Rosuvastatin combined with cilostazol therapy can greatly improve the anti-inflammatory effect of monotherapies, resulting in reduced mortality of mice; thus, we propose the potential of use of this combination therapy as anti-TNF agent.

[34] *Plat J, Baumgartner S, Vanmierlo T et al.* **Plant-based sterols and stanols in health & disease: "Consequences of human development in a plant-based environment?"**. Progress in lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30822462
ABSTRACT
Dietary plant sterols and stanols as present in our diet and in functional foods are well-known for their inhibitory effects on intestinal cholesterol absorption, which translates into lower low-density lipoprotein cholesterol concentrations. However, emerging evidence suggests that plant sterols and stanols have numerous additional health effects, which are largely unnoticed in the current scientific literature. Therefore, in this review we pose the intriguing question "What would have occurred if plant sterols and stanols had been discovered and embraced by disciplines such as immunology, hepatology, pulmonology or gastroenterology before being positioned as cholesterol-lowering molecules?" What would then have been the main benefits and fields of application of plant sterols and stanols today? We here discuss potential effects ranging from its presence and function intrauterine and in breast milk towards a potential role in the development of non-alcoholic steatohepatitis (NASH), cardiovascular disease (CVD), inflammatory bowel diseases (IBD) and allergic asthma. Interestingly, effects clearly depend on the route of entrance as observed in intestinal-failure associated liver disease (IFALD) during parenteral nutrition regimens. It is only until recently that effects beyond lowering of cholesterol concentrations are being explored systematically. Thus, there is a clear need to understand the full health effects of plant sterols and stanols.

[35] *Zhang Z, Wei TF, Zhao B et al.* **Sex Differences Associated With Circulating PCSK9 in Patients Presenting With Acute Myocardial Infarction**. Scientific reports 2019; 9:3113.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30816133
ABSTRACT
A limited number of studies have explored whether the role of circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) in the pathogenesis of acute myocardial infarction (AMI) is sex specific. The purpose of the present study was to examine sex differences in plasma PCSK9 in Chinese patients with AMI. In this study, a total of 281 records from patients presenting with AMI were analyzed.We compared hospital data and plasma PCSK9 levels by sex difference for inpatients presenting with AMI. After 1 year of follow-up, major adverse cardiac events(MACE) were recorded. A Cox proportional hazards model was used to calculate hazard

ratios with 95% confidence intervals. We found that, compared with male groups, PCSK9 levels were higher in female patients not only for overall patients with AMI but also for patients with ST-elevation myocardial infarction (STEMI) (median: 273.6 [215.6-366.8] vs. 325.1 [247.5-445.3] ng/ml, P = 0.0136; 273.4 [215.6-369.7] vs. 317.1 [249.6-450.1], P = 0.0275, respectively). The cumulative incidence of cardiac death and 1-year MACE were significantly higher in the female group compared with male group (10% vs. 2.74%, P = 0.025; 15% vs. 4.11%, P = 0.0054, respectively). On multivariate Cox regression analysis, female sex, total triglyceride, glycosylated hemoglobin A, and homocysteic acid were independent risk factors of 1-year MACE. There was no significant correlation between PCSK9 and 1-year MACE in total AMI patients. In conclusion, PCSK9 levels and 1-year MACE were higher in women with AMI than in men with AMI, however, female sex but not PCSK9 were significant correlated with the 1-year MACE. The clinical implications of this finding are worthy of further investigations and must be confirmed in larger cohorts.

[36] *Miedema MD, Nauffal VD, Singh A, Blankstein R*. **Statin therapy for young adults: A long-term investment worth considering**. Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30808553
ABSTRACT
HMG coenzyme A reductase inhibitors (statins) significantly decrease low-density lipoprotein-cholesterol, resulting in stabilization, and in some cases regression, of atherosclerotic plaque with subsequent reduction in atherosclerotic cardiovascular disease (ASCVD) events. To date, there remains a paucity of data to guide the use of statins in young adults (20-49 years old). We herein aim to summarize the potential benefits and risks for statin therapy in younger adults, outlining a possible approach to statin use in young adults. Early identification and treatment of young individuals at risk for ASCVD offers the potential to significantly reduce the lifetime risk of ASCVD. However, there is a paucity of data on the potential side effects of long-term statin use over many decades. Comprehensive risk assessment, including calculation of life-time ASCVD risk, as well as incorporating non-traditional risk factors including lipoprotein (a), strong family history of premature ASCVD, familial hypercholesterolemia, LDL-C level and presence of underlying systemic inflammatory disorders can be helpful in identifying young adults who stand to benefit the most from statin therapy. Selective use of coronary artery calcium (CAC) assessment, as well as potentially polygenic risk scores, can be considered in situations where there remains uncertainty regarding risk assessment. Importantly, the decision for statin treatment should occur in the context of a patient centered shared decision-making process.

[37] *Ma YY, Han YL*. **[New choice of lipid-lowering therapy:PCSK9 inhibitors]**. Zhonghua xin xue guan bing za zhi 2019; 47:164-167.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30818947
ABSTRACT