Literature update week 13 (2019)

[1] *Khambule L, George JA*. **The Role of Inflammation in the Development of GDM and the Use of Markers of Inflammation in GDM Screening**. Advances in experimental medicine and biology 2019; 1134:217-242.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30919340
ABSTRACT
Gestational diabetes mellitus is a hyperglycaemic state first recognised in pregnancy. GDM affects both mother and child. Women with GDM and their new-borns are at risk of developing type 2 diabetes in the future. The screening and diagnostic criteria for GDM are inconsistent and thus novel biomarkers of GDM are required to strengthen the screening and diagnostic processes in GDM. Chronic low-grade inflammation is linked to the majority of the well-established risk factors of GDM such as old age, obesity and PCOS. This review provides an overview of the present knowledge on the pathology of GDM, the screening criteria applied, the role of inflammation in the development of GDM and the use of markers of inflammation namely cytokines, oxidative stress markers, lipids, amino acids and iron markers in screening and diagnosis of GDM.

[2] *He M, Huang TS, Li S et al.* **Atheroprotective Flow Upregulates ITPR3 (Inositol 1,4,5-Trisphosphate Receptor 3) in Vascular Endothelium via KLF4 (Kruppel-Like Factor 4)-Mediated Histone Modifications**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118312301.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30917677
ABSTRACT
Objective- The topographical distribution of atherosclerosis in vasculature underscores the importance of shear stress in regulating endothelium. With a systems approach integrating sequencing data, the current study aims to explore the link between shear stress-regulated master transcription factor and its regulation of endothelial cell (EC) function via epigenetic modifications. Approach and Results- Acetylation of histone 3 lysine 27 (H3K27ac)-chromatin immunoprecipitation followed by high throughput sequencing, an assay for transposase-accessible chromatin-sequencing, and RNA-sequencing were performed to investigate the genome-wide epigenetic regulations in ECs in response to atheroprotective pulsatile shear stress (PS). In silico prediction revealed that KLF4 binding motifs were enriched in the PS-enhanced H3K27ac regions. By integrating PS- and KLF4-modulated H3K27ac, we identified 18 novel PS-upregulated genes. The promoter regions of these genes showed an overlap between the KLF4-enhanced assay for transposase-accessible chromatin signals and the PS-induced H3K27ac peaks. Experiments using ECs isolated from mouse aorta, lung ECs from EC-KLF4-TG versus EC-KLF4-KO mice, and atorvastatin-treated ECs showed that ITPR3 (inositol 1,4,5-trisphosphate receptor 3) was robustly activated by KLF4 and statins. KLF4 assay for transposase-accessible chromatin-quantitative polymerase chain reaction and chromatin immunoprecipitation followed by high throughput-quantitative polymerase chain reaction further demonstrated that a specific locus in the promoter region of the ITPR3 gene was essential for KLF4 binding, H3K27ac enrichment, chromatin accessibility, RNA polymerase II recruitment, and ITPR3 transcriptional activation. Deletion of this KLF4 binding locus in ECs by using CRISPR-Cas9 resulted in blunted calcium influx, reduced expression of endothelial nitric oxide synthase, and diminished nitric oxide bioavailability. Conclusions- These results from a

novel multiomics study suggest that KLF4 is crucial for PS-modulated H3K27ac that allow the transcriptional activation of ITPR3. This novel mechanism contributes to the Ca(2+)-dependent eNOS (endothelial nitric oxide synthase) activation and EC homeostasis.

[3] *Ouweneel AB, Verwilligen RAF, Van Eck M*. **Vulnerable plaque and vulnerable blood: Two critical factors for spontaneous atherothrombosis in mouse models**. Atherosclerosis 2019; 284:160-164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30913516
ABSTRACT
Atherothrombotic events such as myocardial infarction and ischemic stroke are a major cause of morbidity and mortality worldwide. Understanding the molecular and cellular mechanisms of atherosclerotic plaque destabilization or erosion, and developing new therapeutics to prevent acute cardiovascular events is important for vascular biology research and clinical cardiovascular medicine. However, basic research on plaque destabilization, rupture and erosion is hampered by the lack of appropriate animal models of atherothrombosis. Unprovoked atherothrombosis is very scarce in commonly used mouse models for atherosclerosis, the low-density lipoprotein receptor knockout and apolipoprotein E knockout mice. Therefore, specific interventions are required to induce atherothrombosis in these models. Two strategies can be employed to induce atherothrombosis: 1) plaque destabilization and 2) induction of blood hypercoagulability. Although the individual strategies yield atherothrombosis at low incidence, it appears that the combination of both plaque destabilization and an increase in blood coagulability is the most promising strategy to induce atherothrombosis on a larger scale. In this review, we summarize the recent developments on mouse models for the investigation of atherothrombosis.

[4] *Kim K, Kwak A, Choi CU et al.* **Differences in preventing new-onset cardiovascular events with statin therapy in seniors aged 75 years and over: a cohort study in the South Korean National Health Insurance Database**. Basic & clinical pharmacology & toxicology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30924261
ABSTRACT
The aim of this cohort study was to compare the effectiveness of statin regimens for primary prevention among seniors aged >/= 75 years. Seniors aged 75-100 years for whom statin therapies for primary prevention was newly initiated between 1 January 2009 and 31 December 2011, and who continued the same statin regimen during the first year after the index date were identified using the claims data from the South Korean National Health Insurance Database. A propensity score matching and multivariable Cox proportional hazards model was developed to evaluate adjusted ischaemic cardiovascular-cerebrovascular event (CCE) risk and all-cause mortality risk for all patients, as well as for subgroups. A total of 5,629 older patients aged 75-100 years were included in the study population. Compared to moderate-intensity statin therapy, low-intensity statin therapy was significantly associated with increased risk of ischaemic CCEs, while high-intensity statin therapy was associated with reduced risk of ischaemic CCEs; however, compared to moderate-intensity statin therapy, both low-intensity and high-intensity statin therapies were associated with increased risk of all-cause mortality. For the 4,689 older patients who regularly received moderate-intensity statin therapy including

10 mg atorvastatin, 20 mg atorvastatin, 10 mg rosuvastatin, or 20 mg simvastatin for primary prevention, multivariable regression adjusting for potential covariates revealed no significant difference in ischaemic CCEs or all-cause mortality between the moderate-intensity statin users and 10 mg atorvastatin users both before and after propensity scoring matching. No significant heterogeneity was detected in the patient subgroups. The results of this study based on real-world data can supply evidence-based reasons for choice of statin regimen for the primary prevention of CCEs in older people aged >/= 75 years.

[5] *Dore E, Boilard E*. **Roles of secreted phospholipase A2 group IIA in inflammation and host defense**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019; 1864:789-802.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30905346
ABSTRACT
Among all members of the secreted phospholipase A2 (sPLA2) family, group IIA sPLA2 (sPLA2-IIA) is possibly the most studied enzyme. Since its discovery, many names have been associated with sPLA2-IIA, such as "non-pancreatic", "synovial", "platelet-type", "inflammatory", and "bactericidal" sPLA2. Whereas the different designations indicate comprehensive functions or sources proposed for this enzyme, the identification of the precise roles of sPLA2-IIA has remained a challenge. This can be attributed to: the expression of the enzyme by various cells of different lineages, its limited activity towards the membranes of immune cells despite its expression following common inflammatory stimuli, its ability to interact with certain proteins independently of its catalytic activity, and its absence from multiple commonly used mouse models. Nevertheless, elevated levels of the enzyme during inflammatory processes and associated consistent release of arachidonic acid from the membrane of extracellular vesicles suggest that sPLA2-IIA may contribute to inflammation by using endogenous substrates in the extracellular milieu. Moreover, the remarkable potency of sPLA2-IIA towards bacterial membranes and its induced expression during the course of infections point to a role for this enzyme in the defense of the host against invading pathogens. In this review, we present current knowledge related to mammalian sPLA2-IIA and its roles in sterile inflammation and host defense.

[6] *Mouchlis VD, Dennis EA*. **Phospholipase A2 catalysis and lipid mediator lipidomics**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019; 1864:766-771.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30905345
ABSTRACT
Phospholipase A2 (PLA2) enzymes are the upstream regulators of the eicosanoid pathway liberating free arachidonic acid from the sn-2 position of membrane phospholipids. Free intracellular arachidonic acid serves as a substrate for the eicosanoid biosynthetic enzymes including cyclooxygenases, lipoxygenases, and cytochrome P450s that lead to inflammation. The Group IVA cytosolic (cPLA2), Group VIA calcium-independent (iPLA2), and Group V secreted (sPLA2) are three well-characterized human enzymes that have been implicated in eicosanoid formation. In this review, we will introduce and summarize the regulation of catalytic activity and cellular localization, structural characteristics, interfacial activation and kinetics, substrate

specificity, inhibitor binding and interactions, and the downstream implications for eicosanoid biosynthesis of these three important PLA2 enzymes.

[7] *Nikolaou A, Kokotou MG, Vasilakaki S, Kokotos G*. **Small-molecule inhibitors as potential therapeutics and as tools to understand the role of phospholipases A2**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019; 1864:941-956.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30905350
ABSTRACT
Phospholipase A2 (PLA2) enzymes are involved in various inflammatory pathological conditions including arthritis, cardiovascular and autoimmune diseases. The regulation of their catalytic activity is of high importance and a great effort has been devoted in developing synthetic inhibitors. We summarize the most important small-molecule synthetic PLA2 inhibitors developed to target each one of the four major types of human PLA2 (cytosolic cPLA2, calcium-independent iPLA2, secreted sPLA2, and lipoprotein-associated LpPLA2). We discuss recent applications of inhibitors to understand the role of each PLA2 type and their therapeutic potential. Potent and selective PLA2 inhibitors have been developed. Although some of them have been evaluated in clinical trials, none reached the market yet. Apart from their importance as potential medicinal agents, PLA2 inhibitors are excellent tools to unveil the role that each PLA2 type plays in cells and in vivo. Modern medicinal chemistry approaches are expected to generate improved PLA2 inhibitors as new agents to treat inflammatory diseases.

[8] *Ichikawa T, Miyaaki H, Miuma S et al.* **Changes in serum LDL, PCSK9 and microRNA-122 in patients with chronic HCV infection receiving Daclatasvir/Asunaprevir**. Biomedical reports 2019; 10:156-164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30906544
ABSTRACT
The present study evaluated the changes in lipid profile, and the associations between serum protein convertase subtilisin/kexin 9 (PCSK9), microRNA (miR)122 and low-density lipoprotein variation following treatment of hepatitis C virus (HCV) genotype 1b infection with Daclatasvir/Asunaprevir. A total of 39 patients with HCV genotype 1b infection with chronic hepatitis received a 24-week treatment regimen of Daclatasvir/Asunaprevir. Laboratory data were obtained for each subject every 4 weeks during treatment and every 12 weeks after treatment. Serum miR122 and PCSK9 were measured at the start of treatment (week 0), end of treatment (week 24), 4 weeks after the end of treatment (week 28), 12 weeks after the end of treatment (week 36) and 28 weeks after the end of treatment (week 52). LDL was increased at week 4 after the start of treatment to week 52. The increased LDL/HDL ratio at week 52 compared with week 4 was also associated with relative miR122 at week 52. At week 4, PCSK9-active form (A) was lower than that at other time points, and PCSK9-inactive form (I) exhibited the greatest increase. At week 52, PCSK9-A was higher than that during treatment, but PCSK9-I level at week 52 did not markedly differ from that any time point except for week 4. Relative miR122 at week 4 was associated with increased PCSK9-A at weeks 36 and 52 from the start of DAA. In summary, treatment of HCV with Daclatasvir/Asunaprevir resulted in elevated LDL, and relative miR122 and PCSK9-A levels in serum appeared to have some association with LDL increase.

[9] *Kim Y, Hatley O, Rhee SJ et al.* **Development of a Korean-specific virtual population for physiologically-based pharmacokinetic modeling and simulation**. Biopharmaceutics & drug disposition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30921829
ABSTRACT
Physiologically based pharmacokinetic (PBPK) modeling and simulation is a useful tool in predicting the PK profiles of a drug, assessing the effects of covariates such as demographics, ethnicity, genetic polymorphisms, and disease status on the PK, and evaluating the potential of drug-drug interactions. We developed a Korean-specific virtual population for the SimCYP(R) Simulator (version 15 used) and evaluated the population's predictive performance using six substrate drugs (midazolam, S-warfarin, metoprolol, omeprazole, lorazepam, and rosuvastatin) of five major DMEs and two transporters. Forty-three parameters including the proportion of phenotypes in DMEs and transporters were incorporated into the Korean-specific virtual population. The simulated concentration-time profiles in Koreans were overlapped with most of the observed concentrations for the selected substrate drugs with a <2-fold difference in clearance. Furthermore, we found some drug models within the SimCYP(R) library can be improved, e.g., the minor allele frequency of ABCG2 and the fraction metabolized by UGT2B15 should be incorporated for rosuvastatin and lorazepam, respectively. The Korean-specific population can be used to evaluate the impact of ethnicity on the pharmacokinetics of a drug, particularly in various stages of drug development.

[10] *Tramacere I, Boncoraglio GB, Banzi R et al.* **Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis**. BMC medicine 2019; 17:67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30914063
ABSTRACT
BACKGROUND: Statins may prevent recurrent ischemic events after ischemic stroke. Determining which statin to use remains controversial. We aimed to summarize the evidence for the use of statins in secondary prevention for patients with ischemic stroke by comparing benefits and harms of various statins. METHODS: We searched for randomized controlled trials (RCTs) assessing statins in patients with ischemic stroke or transient ischemic attack (TIA) in MEDLINE, EMBASE, and CENTRAL up to July 2017. Two authors extracted data and appraised risks of bias. We performed pairwise meta-analyses and trial sequential analyses (TSA) to compare statins versus placebo/no statin, and network meta-analyses using frequentist random-effects models to compare statins through indirect evidence. We used GRADE to rate the overall certainty of evidence. Primary outcomes were all-cause mortality and all strokes. Secondary outcomes were different types of strokes, cardiovascular events, and adverse events. RESULTS: We identified nine trials (10,741 patients). No head-to-head RCTs were found. The median follow-up period was 2.5 years. Statins did not seem to modify all stroke and all-cause mortality outcomes; they were associated with a decreased risk of ischemic stroke (odds ratio, OR, 0.81 [95% CI, 0.70 to 0.93]; absolute risk difference, ARD, - 1.6% [95% CI, - 2.6 to - 0.6%]), ischemic stroke or TIA (OR, 0.75 [95% CI, 0.64 to 0.87]; ARD, - 4.2% [95% CI, - 6.2 to - 2.1%]), and cardiovascular event (OR, 0.75 [95% CI, 0.69 to 0.83]; ARD, - 5.4% [95% CI, - 6.8 to -

3.6%]), and did not seem to modify rhabdomyolysis, myalgia, or rise in creatine kinase. In the comparison of different statins, moderate- to high-quality evidence indicated that differences between pharmaceutical products seemed modest, with high doses (e.g., atorvastatin 80 mg/day and simvastatin 40 mg/day) associated with the greatest benefits. TSA excluded random error as a cause of the findings for ischemic stroke and cardiovascular event outcomes. Evidence for increased risk of hemorrhagic stroke was sensitive to the exclusion of the SPARCL trial. CONCLUSIONS: Evidence strongly suggests that statins are associated with a reduction in the absolute risk of ischemic strokes and cardiovascular events. Differences in effects among statins were modest, signaling potential therapeutic equivalence. TRIAL REGISTRATION: PROSPERO CRD42018079112.

[11] *Bosch A, Ott C, Jung S et al.* **How does empagliflozin improve arterial stiffness in patients with type 2 diabetes mellitus? Sub analysis of a clinical trial**. Cardiovascular diabetology 2019; 18:44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30922297
ABSTRACT
BACKGROUND: Empagliflozin has been shown to reduce cardiovascular mortality, but the underlying pathogenetic mechanisms are poorly understood. It was previously demonstrated that empagliflozin improved arterial stiffness. METHODS: Our analysis comprising 58 patients with type 2 diabetes mellitus identifies factors triggering the improvement of arterial stiffness. All patients participated in an investigator-initiated, prospective, double-blind, randomized, placebo-controlled, interventional clinical trial (http://www.ClinicalTrials.gov : NCT02471963, registered 15th June 2015, retrospectively registered) and received either 6-weeks treatment with 25 mg empagliflozin orally once daily or placebo (crossover). Central systolic pressure and central pulse pressure were recorded by the SphygmoCor System (AtCor Medical). Now, we investigated the impact of parameters of glucose metabolism, volume status, sympathetic activation, lipids, uric acid, blood pressure and inflammation on vascular parameters of arterial stiffness using multivariate regression analysis. RESULTS: As previously reported, therapy with empagliflozin improved arterial stiffness as indicated by reduced central systolic blood pressure (113.6 +/- 12.1 vs 118.6 +/- 12.9 mmHg, $p < 0.001$), central pulse pressure (39.1 +/- 10.2 vs 41.9 +/- 10.7 mmHg, $p = 0.027$) forward (27.1 +/- 5.69 vs 28.7 +/- 6.23 mmHg, $p = 0.031$) as well as reflected wave amplitude (18.9 +/- 5.98 vs 20.3 +/- 5.97 mmHg, $p = 0.045$) compared to placebo. The multivariate regression analysis included age, sex and change between empagliflozin and placebo therapy of the following parameters: HbA1c, copeptin, hematocrit, heart rate, LDL-cholesterol, uric acid, systolic 24-h ambulatory blood pressure and high sensitive CRP (hsCRP). Besides the influence of age (beta = - 0.259, $p = 0.054$), sex (beta = 0.292, $p = 0.040$) and change in systolic 24-h ambulatory blood pressure (beta = 0.364, $p = 0.019$), the change of hsCRP (beta = 0.305, $p = 0.033$) emerged as a significant determinant of the empagliflozin induced reduction in arterial stiffness (placebo corrected). When replacing HbA1c with fasting plasma glucose in the multivariate regression analysis, a similar effect of the change in hsCRP (beta = 0.347, $p = 0.017$) on arterial stiffness parameters was found. CONCLUSION: Besides age and sex, change in systolic 24-h ambulatory blood pressure and change in hsCRP were determinants of the empagliflozin induced improvement of vascular parameters of arterial stiffness, whereas parameters of change in glucose metabolism and

volume status had no significant influence. Our analysis suggests that empagliflozin exerts, at least to some extent, its beneficial vascular effects via anti-inflammatory mechanisms. Trial registration http://www.ClinicalTrials.gov : NCT02471963, registered 15th June 2015, retrospectively registered.

[12] *Esper RJ, Nordaby RA*. **Cardiovascular events, diabetes and guidelines: the virtue of simplicity**. Cardiovascular diabetology 2019; 18:42.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30922303
ABSTRACT
Cardiovascular (CV) events or their minor syndromes, as various forms of ischemia, are medical emergencies that do not allow enough time for a guiding anamnesis or proper clinical examination, and lead to relying on Treatment Guidelines, but in many situations it is appropriate to deviate from them. Pathological studies have associated 75% of coronary artery events with atherosclerotic plaque rupture; it is now known that rupture alone is not enough for obstruction or occlusion of the vessel lumen. Concomitant conditions are required for the clinical manifestation of cardiovascular disease, including prothrombogenic and dysfunctional endothelium, less fibrinolytic capacity to protect it, increased platelet activation, increased adrenergic tone, microcirculation vasoconstriction, and other countless factors that contribute to thrombus formation, causing ischemia or infarction. But in most cases, repair of plaque rupture and re endothelization of the lesion are asymptomatic and silent. Atherosclerotic process is a chronic and progressive immune inflammation. Most of the therapeutic indications include statins, which cause side effects in 10% of patients, with a range varying between 7 and 21%, according to different authors. Many investigators have proved that statin use contribute to the genesis of diabetes, reports vary between 1 and 46%, where marked elevation of blood glucose fasting levels and glycosylated hemoglobin have been observed, be it by increased tissue resistance to insulin or by reduced beta-cell insulin secretion. Physicians should base their indications on the recommendations provided by Guidelines, but they should not forget that every patient is different, and they should not get confused due to lack of time in an emergency nor be influenced by the latest publications or techniques until they have been properly tested.

[13] *Bonaventura A, Montecucco F, Dallegri F et al.* **Novel findings in neutrophil biology and their impact on cardiovascular disease**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30918936
ABSTRACT
Neutrophils are the most abundant circulating leukocytes in healthy humans. These cells are central players during acute inflammatory responses, although a growing body of evidence supports a crucial role in chronic inflammation and chemokines and cytokines related to it as well. Thus, both humoral and cellular components are involved in the development of plaque formation and atherosclerosis. Accordingly, CANTOS trial using an interleukin-1beta antibody confirmed that inflammatory cytokines contribute to the occurrence of myocardial infarction and cardiac death independent of changes in lipids. Recent data revealed that neutrophils are a heterogeneous population with different subsets and functional characteristics (i.e. CD177+ cells, OLFM4+ neutrophils, proangiogenic neutrophils, neutrophils undergoing reverse

migration, and aged neutrophils). Importantly, neutrophils are able to synthesize de novo proteins. Neutrophil extracellular trap generation and NETosis have been considered as very important weapons in sterile inflammation. Neutrophil-derived microvesicles represent another mechanism by which neutrophils amplify inflammatory processes, being found at high levels both at the site of injury and in the bloodstream. Finally, neutrophil aging can influence their functions also in relation with host age. These recent acquisitions in the field of neutrophil biology might pave the way for new therapeutic targets to prevent or even treat patients experiencing cardiovascular diseases. Here, we discuss novel findings in neutrophil biology, their impact on cardiovascular and cerebrovascular diseases, and the potential implementation of these notions into daily clinical practice.

[14] *Gegotek A, Skrzydlewska E*. **Biological effect of protein modifications by lipid peroxidation products**. Chemistry and physics of lipids 2019; 221:46-52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30922835
ABSTRACT
The products of lipid peroxidation, resulting from cell metabolism as well as the action of external physical factors and xenobiotics, have a significant impact on cell functions. One of the mechanisms by which lipid peroxidation products influence cells is the formation of adducts with proteins, including enzymes and signaling molecules. This review describes the biological consequences of protein adduct formation with oxidative lipid fragmentation products such as 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), and acrolein, as well as cyclization products including isoprostanes, isoketals, and isolevuglandins. The generation of protein adducts with lipid peroxidation products can stimulate the antioxidant system, which may also possess proinflammatory or proapoptotic effects. However, the role of adducts between lipid peroxidation products and proteins depends on the condition of the cells and can range from the function of cytoprotective activity stimulation, to induction of toxicity involved in the development of degenerative diseases.

[15] *Lim S*. **(Retraction Request) Effect of Rosuvastatin on Cholesterol Efflux Capacity and Endothelial Function in Type 2 Diabetes Mellitus and Dyslipidemia**. Circulation journal : official journal of the Japanese Circulation Society 2019; 83:948.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30905909
ABSTRACT

[16] *Saglimbene VM, Wong G, van Zwieten A et al.* **Effects of omega-3 polyunsaturated fatty acid intake in patients with chronic kidney disease: Systematic review and meta-analysis of randomized controlled trials**. Clinical nutrition (Edinburgh, Scotland) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30905498
ABSTRACT
BACKGROUND & AIMS: Dietary and supplemental long chain omega-3 polyunsaturated fatty acids (n-3 PUFA) have shown vascular benefits for the general population, but effects among people with chronic kidney disease (CKD) are largely uncertain. We aimed to evaluate the effects of n-3 PUFA intake among patients with CKD. METHODS: We searched MEDLINE, Embase, and CENTRAL through January 12, 2018. Eligible studies were randomized controlled

trials evaluating n-3 PUFA intake (supplementation or dietary) compared with placebo, standard care, or other treatment, on cardiovascular and all-cause mortality, end stage kidney disease (ESKD), acute transplant rejection, and allograft loss. Risks of bias and evidence certainty were assessed using Cochrane and Grading of Recommendations Assessment, Development and Evaluation processes. RESULTS: Sixty trials (4129 participants) were eligible, all of supplementation, with a median follow-up of 6 months. Low to very low certainty evidence suggested that n-3 PUFA supplementation reduced cardiovascular death for participants on hemodialysis (39 events; relative risk (RR) 0.45, 95% confidence interval (CI) 0.23-0.89), prevented ESKD (29 events; RR 0.30, CI 0.09-0.98) in participants with CKD not receiving renal replacement therapy, and made little or no difference in all-cause mortality (215 events; RR 1.05, CI 0.84-1.33), acute transplant rejection (188 events; RR 0.98, CI 0.80-1.21) or allograft loss (39 events; RR 0.98, CI 0.54-1.81]). Risk of bleeding (44 events; RR 1.40, CI 0.78-2.49) and gastrointestinal side-effects (103 events; RR 1.14, CI 0.79-1.67) were uncertain. CONCLUSIONS: n-3 PUFA supplementation may reduce cardiovascular mortality in patients on hemodialysis but it is uncertain whether supplementation prevents mortality or ESKD in patients with CKD.

[17] *Bowen J, Luscombe-Marsh ND, Stonehouse W et al.* **Effects of almond consumption on metabolic function and liver fat in overweight and obese adults with elevated fasting blood glucose: A randomised controlled trial**. Clinical nutrition ESPEN 2019; 30:10-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30904207

ABSTRACT

BACKGROUND: Almonds are a rich source of bioactive components. This study examined the effects of daily almond consumption on glycaemic regulation, liver fat concentration and function, adiposity, systemic inflammation and cardiometabolic health. METHODS: 76 adults with elevated risk of type 2 diabetes (T2D) or T2D (age: 60.7 +/- 7.7 years, body mass index: 33.8 +/- 5.6 kg/m(2)) were randomly assigned to daily consumption of either 2 servings of almonds (AS:56 g/day) or an isocaloric, higher carbohydrate biscuit snack (BS) for 8 weeks. Glycosylated haemoglobin (HbA1c), glycaemic variability (GV), liver fat, serum aminotransferases, body weight and composition, markers of cardio-metabolic risk and systemic inflammation were assessed at baseline and week 8. RESULTS: No group differential effects were observed on HbA1c, GV, body weight and composition, liver fat and aminotransferases, cardio-metabolic health and inflammatory markers (all $P > 0.05$). For serum TC/HDL-C ratio a significant gender x treatment x time interaction occurred ($P < 0.01$), such that in women TC/HDL-C ratio was significantly reduced after AS compared to BS (-0.36 [0.26] mmol/L [n = 14] vs. -0.14 [0.32] mmol/L [n = 17]; $P = 0.05$), but not in men ($P = 0.52$). CONCLUSIONS: Compared to BS, AS consumed between meals did not substantially alter glycaemic regulation, liver fat or function, adiposity, and metabolic health and inflammatory markers. Serum TC/HDL-C ratio improved in women, but not in men with AS; but as this sub-analysis was not defined a priori the results should be interpreted with caution. Further research should examine the longer-term health effects of regular almond consumption and differential gender responses. CLINICAL TRIAL REGISTRY NUMBER AND WEBSITE: Australia New Zealand Clinical Trial Registry: ACTRN12616000571471 (https://www.anzctr.org.au).

Literature update week 13 (2019)

[18] *Turner-McGrievy GM, Wirth MD, Shivappa N et al.* **Impact of a 12-month Inflammation Management Intervention on the Dietary Inflammatory Index, inflammation, and lipids**. Clinical nutrition ESPEN 2019; 30:42-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30904228
ABSTRACT
BACKGROUND AND AIMS: The objective of this study was to assess the feasibility (ability to recruit participants and develop the 12-month intervention), acceptability (retention of participants in the intervention), and impact on systemic inflammation and Dietary Inflammatory Index (DII(R)) scores over a 12-month DII-based intervention. METHODS: Adults were recruited to participate in a self-selection trial (intervention: n = 61, in-person classes; control: n = 34, newsletters). Classes included participatory cooking and dietary recommendations focused on consuming a plant-based diet rich in anti-inflammatory foods (spices, vegetables, etc.). Changes in markers of inflammation, lipids, and DII were analyzed using general linear models with repeated measurements. RESULTS: At 3 months, intervention participants had significantly lower DII scores (-2.66 +/- 2.44) compared to controls (-0.38 +/- 2.56) ($p < 0.01$); but not at 12 months ($P = 0.10$). The only biomarker to approach a significant group effect or group-by-time interaction was CRP ($P = 0.11$ for the group-by-time interaction). CRP decreased by -0.65 mg/L (95%CI = 0.10-1.20, $P = 0.02$) at 12 months in the intervention group; no significant decrease was seen for the control group. With both groups combined at 3 months, those with the greatest decrease/improvement in DII score (tertile 1) compared with those whose scores increased (tertile 3) had greater reductions in CRP (-1.09 vs. +0.52 mg/L, $P = 0.04$), total cholesterol (-9.38 vs. +12.02 mg/dL, $P = 0.01$), and LDL cholesterol (-11.99 vs. +7.16 mg/dL, $P = 0.01$). CONCLUSIONS: Although the intervention group had reductions in DII and CRP, main inflammation and lipid outcomes did not differ between groups. Overall, those participants with the largest reduction in DII scores had the largest reductions in CRP and LDL and total cholesterol. Future interventions may need to have more components in place to support maintenance and continued reductions in the DII. CLINICALTRIALS. GOV IDENTIFIER: NCT02382458.

[19] *Bergman A, Bi YA, Mathialagan S et al.* **Effect of hepatic OATP1B inhibition and chronic kidney disease on the pharmacokinetics of a liver-targeted glucokinase activator: A model-based evaluation**. Clinical pharmacology and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30919935
ABSTRACT
PF-04991532 [(S)-6-(3-Cyclopentyl-2-(4-(trifluoromethyl)-1H-imidazol-1-yl) propanamido) nicotinic acid] is a glucokinase activator designed to achieve hepato-selectivity via OATPs, so as to minimize systemic hypoglycemic effects. This study investigated the effect of OATP1B1/1B3 inhibition and renal impairment on PF-04991532 oral pharmacokinetics. Cyclosporine (600mg single dose) increased mean area under the plasma curve (AUC) of PF-04991532 by approximately 3-fold in healthy subjects. In renal impairment study, PF-04991532 AUC values were approximately 2.3-fold greater in subjects with mild, moderate and severe kidney dysfunction, compared to healthy subjects. PBPK model parameterizing hepatic and renal transporter-mediated disposition based on in vitro inputs, and verified using first-in-human data, indicated key role of OATP-mediated hepatic uptake in the systematic and target-tissue

exposure of PF-04991532. Mechanistic evaluation of the clinical data suggest reduced hepatic OATPs (~35%) and renal OAT3 (80-90%) function with renal impairment. This study illustrates the adequacy and utility of PBPK approach in assessing impact of drug interactions and kidney dysfunction on transporter-mediated disposition. This article is protected by copyright. All rights reserved.

[20] *Werba JP, Vigo LM, Veglia F et al.* **Trials in "true" dyslipidemic patients are urged to reconsider comprehensive lipid management as a means to reduce residual cardiovascular risk**. Clinical pharmacology and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30916778
ABSTRACT
Randomized cardiovascular trials aimed to reduce the excessive residual risk in high-risk patients through a more aggressive LDL-cholesterol control or targeting triglycerides or HDL-cholesterol levels have shown a null or, at best, limited incremental benefit. In some cases, the treatment produced meaningful effects only in study subgroups. As a consequence, some compounds were withdrawn (e.g. nicotinic acid derivatives and CETP inhibitors), whereas others (fibrates) are utilized with reluctance due to the low level of evidence-based data. By reviewing these trials analytically, we identified a common feature that might explain their meagre results: most of them involved patients generically at high cardiovascular risk with normal or near normal lipid levels and not patients with "true" dyslipidemia, who would receive the treatment if it were part of usual care. These observations may warrant reexamining a central criterion of pragmatism, eligibility, in the outline of forthcoming cardiovascular trials with novel lipid-modifying drugs. This article is protected by copyright. All rights reserved.

[21] *Kim TS, Rha SW, Kim SY et al.* **Efficacy and Tolerability of Telmisartan/Amlodipine and Rosuvastatin Coadministration in Hypertensive Patients with Hyperlipidemia: A Phase III, Multicenter, Randomized, Double-blind Study**. Clinical therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30904178
ABSTRACT
PURPOSE: Dyslipidemia and hypertension increase the risk for cardiovascular disease. Combination therapy improves patient compliance. This study was conducted to compare the efficacy and tolerability of the combination therapies telmisartan/amlodipine + rosuvastatin, telmisartan/amlodipine, and telmisartan + rosuvastatin in patients with hypercholesterolemia and hypertension. METHODS: In this Phase III, multicenter, 8-week randomized, double-blind study, participants with hypertension and dyslipidemia (defined as a sitting systolic blood pressure [sitSBP] of >/=140 mm Hg, a low-density lipoprotein-cholesterol [LDL-C] level of </=250 mg/dL, and a triglyceride level of </=400 mg/dL) were screened. After a 4-week washout/run-in period involving therapeutic lifestyle changes and telmisartan 80 mg once a day, eligible patients had a sitSBP of >/=140 mm Hg and met the LDL-C level criteria according to the National Cholesterol Education Program Adult Treatment Panel III cardiovascular disease risk category. Patients were randomly assigned to 1 of 3 groups: (1) telmisartan/amlodipine 80/10 mg + rosuvastatin 20 mg (TAR group); (2) telmisartan/amlodipine 80/10 mg (TA group); or (3) telmisartan 80 mg + rosuvastatin 20 mg (TR group). The primary efficacy end points were the percentage changes from baseline in LDL-C in the TAR and TA groups and the mean changes

in sitSBP in the TAR and TR groups at week 8 compared to baseline. Continuous variables were compared using the unpaired t test or the Wilcoxon rank sum model, and categorical variables were compared using the chi(2) or Fisher exact test. Tolerability was assessed based on adverse events found on physical examination including vital sign measurements, laboratory evaluations, and 12-lead ECG. FINDINGS: A total of 134 patients were enrolled. The least squares mean percentage changes in LDL-C at 8 weeks after administration of the drug compared to baseline were -51.9% (3.0%) in the TAR group and -3.2% (2.9%) in the TA group (P < 0.001). At 8 weeks after baseline, the least squares mean (SE) changes sitSBP were -28.3 (2.4) mm Hg in the TAR group and -10.7 (2.1) mm Hg in the TR group (P < 0.001). The prevalence rates of treatment-emergent adverse events were 15.0%, 25.0%, and 12.2% in the TAR, TA, and TR groups, respectively; those of adverse drug reactions were 15.0%, 22.7%, and 10.2%. None of the differences in rates were significant among 3 groups. IMPLICATIONS: Triple therapy with TAR can be an effective treatment in patients with dyslipidemia and hypertension. The TAR combination has value for hypertensive patients with hyperlipidemia in terms of convenience, tolerability, and efficacy. ClinicalTrials.gov identifier: NCT03566316.

[22] *Clair C, Mueller Y, Livingstone-Banks J et al.* **Biomedical risk assessment as an aid for smoking cessation**. The Cochrane database of systematic reviews 2019; 3:Cd004705.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30912847

ABSTRACT

BACKGROUND: A possible strategy for increasing smoking cessation rates could be to provide smokers with feedback on the current or potential future biomedical effects of smoking using, for example, measurement of exhaled carbon monoxide (CO), lung function, or genetic susceptibility to lung cancer or other diseases. OBJECTIVES: The main objective was to determine the efficacy of providing smokers with feedback on their exhaled CO measurement, spirometry results, atherosclerotic plaque imaging, and genetic susceptibility to smoking-related diseases in helping them to quit smoking. SEARCH METHODS: For the most recent update, we searched the Cochrane Tobacco Addiction Group Specialized Register in March 2018 and ClinicalTrials.gov and the WHO ICTRP in September 2018 for studies added since the last update in 2012. SELECTION CRITERIA: Inclusion criteria for the review were: a randomised controlled trial design; participants being current smokers; interventions based on a biomedical test to increase smoking cessation rates; control groups receiving all other components of intervention; and an outcome of smoking cessation rate at least six months after the start of the intervention. DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane. We expressed results as a risk ratio (RR) for smoking cessation with 95% confidence intervals (CI). Where appropriate, we pooled studies using a Mantel-Haenszel random-effects method. MAIN RESULTS: We included 20 trials using a variety of biomedical tests interventions; one trial included two interventions, for a total of 21 interventions. We included a total of 9262 participants, all of whom were adult smokers. All studies included both men and women adult smokers at different stages of change and motivation for smoking cessation. We judged all but three studies to be at high or unclear risk of bias in at least one domain. We pooled trials in three categories according to the type of biofeedback provided: feedback on risk exposure (five studies); feedback on smoking-related disease risk (five studies); and feedback on smoking-related harm (11 studies). There was no

evidence of increased cessation rates from feedback on risk exposure, consisting mainly of feedback on CO measurement, in five pooled trials (RR 1.00, 95% CI 0.83 to 1.21; I(2) = 0%; n = 2368). Feedback on smoking-related disease risk, including four studies testing feedback on genetic markers for cancer risk and one study with feedback on genetic markers for risk of Crohn's disease, did not show a benefit in smoking cessation (RR 0.80, 95% CI 0.63 to 1.01; I(2) = 0%; n = 2064). Feedback on smoking-related harm, including nine studies testing spirometry with or without feedback on lung age and two studies on feedback on carotid ultrasound, also did not show a benefit (RR 1.26, 95% CI 0.99 to 1.61; I(2) = 34%; n = 3314). Only one study directly compared multiple forms of measurement with a single form of measurement, and did not detect a significant difference in effect between measurement of CO plus genetic susceptibility to lung cancer and measurement of CO only (RR 0.82, 95% CI 0.43 to 1.56; n = 189). AUTHORS' CONCLUSIONS: There is little evidence about the effects of biomedical risk assessment as an aid for smoking cessation. The most promising results relate to spirometry and carotid ultrasound, where moderate-certainty evidence, limited by imprecision and risk of bias, did not detect a statistically significant benefit, but confidence intervals very narrowly missed one, and the point estimate favoured the intervention. A sensitivity analysis removing those studies at high risk of bias did detect a benefit. Moderate-certainty evidence limited by risk of bias did not detect an effect of feedback on smoking exposure by CO monitoring. Low-certainty evidence, limited by risk of bias and imprecision, did not detect a benefit from feedback on smoking-related risk by genetic marker testing. There is insufficient evidence with which to evaluate the hypothesis that multiple types of assessment are more effective than single forms of assessment.

[23] *Spolitu S, Dai W, Zadroga JA, Ozcan L*. **Proprotein convertase subtilisin/kexin type 9 and lipid metabolism**. Current opinion in lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30925519
ABSTRACT
PURPOSE OF REVIEW: The purpose of this review is to highlight the recent findings of one of the most promising therapeutic targets in LDL cholesterol (LDL-C) management, proprotein convertase subtilisin/kexin type 9 (PCSK9). RECENT FINDINGS: Endoplasmic reticulum cargo receptor, surfeit locus protein 4 interacts with PCSK9 and regulates its exit from endoplasmic reticulum and its secretion. Once secreted, PCSK9 binds to heparin sulfate proteoglycans on the hepatocyte surface and this binding is required for PCSK9-LDL receptor (LDLR) complex formation and LDLR degradation. Posttranscriptionally, recent work has shown that PCSK9 gets degraded in lysosomes by activation of the glucagon receptor signaling, providing more data on the hormonal regulation of PCSK9. Finally, human studies with PCSK9 inhibitors offered more evidence on their benefits and safe use. SUMMARY: Recent work on the regulation of PCSK9 has enhanced our understanding of its biology, which may provide important information for future PCSK9-based therapies.

[24] *Hu Y, Li TT, Zhou W et al.* **Lipoprotein-associated phospholipase A2 is a risk factor for diabetic kidney disease**. Diabetes Res Clin Pract 2019; 150:194-201.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30904742
ABSTRACT

AIMS: This study aimed to determine the association between lipoprotein-associated phospholipase A2 (Lp-PLA2), a marker for inflammation in the vessel wall and independently associated with atherosclerosis, and the incidence of diabetic kidney disease (DKD) in patients with type 2 diabetes (T2D). METHODS: A total of 1452 patients were enrolled in this retrospective crosssectional study. We recruited patients with T2D who were tested for glycated hemoglobin, fasting and 2h post-meal serum C-peptide, blood lipid profile, 24h urine albumin excretion rate (UAER), blood creatine, blood albumin, uric acid, and Lp-PLA2. RESULTS: Among the patients with T2D, 40.3% were diagnosed with DKD and the correlation between DKD and Lp-PLA2 was the most significant one compared to other diabetic complications (odds ratio=1.651, P<0.001). Plasma Lp-PLA2 level in patients with DKD was significantly higher and increased Lp-PLA2 level was independently associated with the incidence of DKD after adjustment for age, gender, duration of diabetes, glycated hemoglobin, body mass index, blood lipids, blood pressure, presence of coronary heart disease and carotid plaque, and use of statins (odds ratio=1.545, P=0.013). Lp-PLA2 was found to be positively correlated with UAER (r=0.123, P<0.001) and negatively correlated with estimated glomerular filtration rate (eGFR) (r=-0.71, P=0.009). CONCLUSIONS: Increased plasma level of Lp-PLA2 is associated with incidence and development of DKD in patients with T2D. Lp-PLA2 should be considered as a biomarker for early detection and follow-up of DKD. TRIAL REGISTRATION: clinicaltrials.gov, No. NCT03362112, Registered 30 November 2017, retrospectively registered.

[25] *De La Cruz JA, Mihos CG, Horvath SA, Santana O*. **The Pleiotropic Effects of Statins in Endocrine Disorders**. Endocrine, metabolic & immune disorders drug targets 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30924424

ABSTRACT

BACKGROUND: The 3-Hydroxy-3-MethylGlutaryl-CoA reductase inhibitors, better known as statins, are used extensively in the treatment of dyslipidemia and cardiovascular risk reduction. They have also demonstrated a variety of non-lipid lowering, or pleiotropic effects. Pertaining to the endocrine system the benefits of statins can extend to patients with polycystic ovarian syndrome and thyroid disease. However, there is also increasing evidence that statin use can lead to deleterious effects in different organs, including worsening glycemia and the development of diabetes mellitus. OBJECTIVE: The aim of this review is to describe the most relevant and updated evidence regarding the pleiotropic effects of statins in endocrine disorders. METHOD: We did a systematic review of scientific articles published in PubMed regarding the effects of statins on the different aspects of the endocrine system up until June 5th of 2018. RESULTS: We identified preliminarily 61 publications, of which 4 were excluded due to having abstract format only, and 5 were excluded for not containing pertinent information to the study. CONCLUSION: Several aspects of the endocrine system have been shown to be influenced by the pleiotropic effects that statins exert, however, the benefits of statins on cardiovascular morbidity and mortality largely outweigh this deleterious effect, and statin therapy should continue to be recommended.

[26] *Wewer Albrechtsen NJ, Pedersen J, Galsgaard KD et al.* **The liver-alpha cell axis and type 2 diabetes**. Endocrine reviews 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30920583

ABSTRACT
Both type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) strongly associate with increasing body mass index (BMI) and together these metabolic diseases affect millions of individuals. In patients with T2D, increased secretion of glucagon (hyperglucagonemia) contributes to the diabetic hyperglycemia as proven by the significant lowering of fasting plasma glucose levels following glucagon receptor antagonist (GRA) administration. Emerging data now indicate that the elevated plasma concentrations of glucagon may also be associated with hepatic steatosis and not necessarily with the presence or absence of T2D. Thus, fatty liver disease, most often secondary to overeating, may result in impaired amino acid turnover, leading to increased plasma concentrations of certain glucagonotropic amino acids (e.g. alanine). This, in turn, causes increased glucagon secretion which may help to restore amino acid turnover and ureagenesis, but may eventually also led to increased hepatic glucose production, a hallmark of T2D. Early experimental findings support the hypothesis that hepatic steatosis impairs glucagon's actions on amino acid turnover and ureagenesis. Hepatic steatosis also impairs hepatic insulin sensitivity and clearance which, together with hyperglycemia and hyperaminoacidemia, lead to peripheral hyperinsulinemia; systemic hyperinsulinemia may itself contribute to worsen peripheral insulin resistance. In addition, obesity is accompanied by an impaired incretin effect, causing meal-related glucose intolerance. Lipid-induced impairment of hepatic sensitivity, not only to insulin but potentially also to glucagon, resulting in both hyperinsulinemia and hyperglucagonemia, may therefore contribute to the development of T2D at least in a subset of individuals with NAFLD.

[27] *Stralberg T, Nordenskjold A, Cao Y et al.* **Proprotein convertase subtilisin/kexin type 9 and mortality in patients starting hemodialysis**. European journal of clinical investigation 2019:e13113.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30921469

ABSTRACT
BACKGROUND: Cardiovascular events are the leading cause of death in end stage renal disease (ESRD), but traditional markers of dyslipidemia are not clearly associated with cardiovascular risk in this population. Proprotein Convertase Subtilsin/Kexin type 9 (PCSK-9) could be of interest as a novel cardiovascular risk marker in ESRD due to the emergence of lipid lowering therapy based on PCSK-9 inhibition. The aim of the present study was to investigate if the convertase PCSK-9 is a potential risk marker for mortality among patients starting hemodialysis treatment. MATERIALS AND METHODS: This is a cohort study of 265 patients starting hemodialysis between 1991-2009, with three years follow-up. The association between baseline PCSK-9 levels and mortality was assessed using Cox proportional hazards- and quantile regression models, with adjustment for potential confounders. RESULTS: PCSK-9 levels at initiation of hemodialysis were associated to mortality in multivariable adjusted analysis. PCSK-9 levels exhibited an U-shaped association to mortality. Inclusion of the quadratic term of PCSK-9 in regression modeling optimized model performance. At baseline, PCSK-9 levels had positive correlations to Davies comorbidity score, hemoglobin and C-reactive protein while negative correlations were found for high-density lipoprotein and total cholesterol. PCSK-9 levels were higher in statin users and patients with a history of cardiovascular disease. CONCLUSIONS: This study shows, for the first time, that the level of PCSK-9 is associated with all-cause mortality in

hemodialysis patients, independently of a number of potential confounders. This article is protected by copyright. All rights reserved.

[28] *Cesaro A, Gragnano F, Fimiani F et al.* **Impact of PCSK9 inhibitors on the quality of life of patients at high cardiovascular risk**. European journal of preventive cardiology 2019:2047487319839179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30913901
ABSTRACT

[29] *Reiner Z*. **The association between lipid-lowering drugs and circulating concentration of PCSK9**. European journal of preventive cardiology 2019:2047487319840179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30922114
ABSTRACT

[30] *van Koeverden ID, Scholtes VPW, den Ruijter HM et al.* **The Impact of Diabetes and Time on the Atherosclerotic Plaque and Cardiovascular Outcome in Patients Undergoing Iliofemoral Endarterectomy**. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30910497
ABSTRACT
OBJECTIVE: The incidence of diabetes is rapidly increasing and diabetes is associated with an increased risk of peripheral artery disease. Recent studies have shown a time dependent decline in vulnerable plaque features and secondary cardiovascular events in iliofemoral endarterectomy (IFE) patients. IFE patients with diabetes have a high risk of cardiovascular events. It is not known, however, whether vulnerable plaque features and cardiovascular events reduce over time in IFE patients with diabetes. METHODS: Between 2003 and 2014, 691 atherosclerotic plaques were obtained by IFE, from 212 patients with and 479 patients without diabetes. Plaques were immunohistochemically stained and analysed for the presence of intraplaque haemorrhage, lipid core, calcification, collagen, smooth muscle cells, and macrophages. Patients were stratified according to their diabetic status and year of inclusion. All patients had a follow up of three years in which cardiovascular adverse events were recorded. RESULTS: A time dependent decrease was observed in intraplaque haemorrhage, plaque lipid core, and percentage of macrophages in IFE patients with diabetes. After multivariable correction for changes in risk factors over time, intraplaque haemorrhage (64.2% [2002-2005] vs. 39.6% [2012-2014], p = .01) became significantly less prevalent. Interestingly, the percentage of severely calcified plaques remained high over time. The number of secondary events decreased over time in patients without diabetes (HR 1.80, 95% CI 1.15-2.81 (p = .010) for 2002-2005 vs. 2012-2014), but remained high and unchanged in patients with diabetes. CONCLUSION: In patients with diabetes undergoing IFE, a time dependent stabilisation of atherosclerotic plaque features was found in line with previous observations in patients with severe atherosclerosis. The presence of severely calcified lesions remained high and unchanged. The secondary event rate remained high in patients with diabetes in contrast to a significant decrease in patients without diabetes. These findings stress the need for improvement of care in IFE patients with diabetes.

[31] *Miao XY, Liu HZ, Jin MM et al.* **A comparative meta-analysis of the efficacy of statin-ezetimibe co-therapy versus statin monotherapy in reducing cardiovascular and cerebrovascular adverse events in patients with type 2 diabetes mellitus**. European review for medical and pharmacological sciences 2019; 23:2302-2310.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30915779
ABSTRACT
OBJECTIVE: This study evaluates the efficacy of statin-ezetimibe co-therapy compared to statin monotherapy in reducing cardiovascular and/or cerebrovascular disease (CVD) prevalence in diabetes and non-diabetes patients. PATIENTS AND METHODS: Literature search was conducted in electronic databases and study selection was based on pre-determined eligibility criteria. Random-effects metanalyses were performed to examine the risk of CVD incidence between statin-ezetimibe co-therapy and statin monotherapy and subgroups were performed to examine the significance of differences between diabetic and non-diabetic individuals. A pooled analysis of hazard ratios of statin-ezetimibe combination versus statin monotherapy in the prevalence of CVD reported by the individual studies was also performed. RESULTS: 8 studies (136893 individuals; 80790 diabetics, 85555 non-diabetics; age 63.5 years [95% confidence interval (CI) 61.2, 65.8]; 61.5% [95% CI 55.2, 67.8] males) were included. Follow-up duration was 45 months [95% CI 27.5, 62.5]. Risk of CVD prevalence was significantly less with ezetimibe-statin than with statin alone in both diabetes (RR 0.69 [95% CI 0.67, 0.73]; p<0.00001) and in non-diabetes (RR 0.68 [95% CI 0.52, 0.90]; p=0.006) subjects (subgroup difference: chi2=0.00; p=0.97). Risk of prevalence of stroke was significantly less with ezetimibe-statin than with statin monotherapy in diabetes (RR 0.74 [95% CI 0.56, 0.98]; p=0.03) but non-significantly less in non-diabetes patients (RR 0.74 [95% CI 0.39, 1.41]; p=0.39) and this sub-group difference was also not statistically significant (chi2=0.00; p=0.99). CONCLUSIONS: Statin-ezetimibe co-therapy is found more efficacious than statin monotherapy in reducing the incidence of CVD with no significant difference between diabetic and non-diabetic individuals.

[32] *Ma YB, Chan P, Zhang Y et al.* **Evaluating the efficacy and safety of atorvastatin + ezetimibe in a fixed-dose combination for the treatment of hypercholesterolemia**. Expert opinion on pharmacotherapy 2019:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30908086
ABSTRACT
INTRODUCTION: Cardiovascular disease is a major cause of morbidity and mortality throughout the world and hypercholesterolemia is one of the key risk factors. Statins are the first line treatment to reduce atherogenic lipids and there is substantial and robust evidence with atorvastatin for reduction of cardiovascular events and mortality. Ezetimibe can be combined with any dose of atorvastatin for incremental lipid-lowering effects. Areas covered: In this review, the authors summarize the pharmacokinetics, pharmacodynamics and clinical efficacy of the components and the combination of ezetimibe and atorvastatin. Clinical benefits have been seen with ezetimibe combined with simvastatin but studies of its combination with atorvastatin are generally limited to the effects on lipid parameters where the addition of ezetimibe to atorvastatin is generally more effective than titrating the atorvastatin dose. Expert opinion: Although there are no cardiovascular outcomes studies with the combination of

ezetimibe and atorvastatin, the greater reduction in atherogenic lipids can be assumed to have greater benefits in reducing cardiovascular events. The ezetimibe-atorvastatin combination is very effective in this respect and well tolerated. Fixed-dose combinations improve medication adherence and this combination should be useful for patients who cannot reach their lipid targets with maximally tolerated statin doses.

[33] *Ellis KL, Chakraborty A, Moses EK, Watts GF*. **To test, or not to test: that is the question for the future of lipoprotein(a)**. Expert review of cardiovascular therapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30916582
ABSTRACT
INTRODUCTION: Lipoprotein(a) [Lp(a)] is a potent, highly heritable and common risk factor for atherosclerotic cardiovascular disease (ASCVD). Evidence for a causal association between elevated Lp(a) and ASCVD has been provided by large epidemiological investigations that have demonstrated a curvilinear association with increased risk, as well as from genetic examinations and cellular and transgenic animal studies. Although there are several therapies available for lowering Lp(a), none are selective for Lp(a) and there is no clinical trial data that has specifically shown that lowering Lp(a) reduces the risk of ASCVD. Hence, screening for elevated Lp(a) is not routinely incorporated into clinical practice. Areas covered: This paper reviews the current evidence supporting the causal role of Lp(a) in the primary and secondary prevention of ASCVD, screening approaches for high Lp(a), current guidelines on testing Lp(a), and barriers to the routine screening of elevated Lp(a) in clinical practice. Expert opinion: At present there is a moderate level of evidence supporting the routine screening of elevated Lp(a). Current guidelines recommend testing for elevated Lp(a) in individuals at intermediate or high risk of ASCVD.

[34] *Mancuso P, Bouchard B*. **The Impact of Aging on Adipose Function and Adipokine Synthesis**. Frontiers in endocrinology 2019; 10:137.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30915034
ABSTRACT
During the last 40 years, there has been a world-wide increase in both the prevalence of obesity and an increase in the number of persons over the age of 60 due to a decline in deaths from infectious disease and the nutrition transition in low and middle income nations. While the increase in the elderly population indicates improvements in global public health, this population may experience a diminished quality of life due to the negative impacts of obesity on age-associated inflammation. Aging alters adipose tissue composition and function resulting in insulin resistance and ectopic lipid storage. A reduction in brown adipose tissue activity, declining sex hormones levels, and abdominal adipose tissue expansion occur with advancing years through the redistribution of lipids from the subcutaneous to the visceral fat compartment. These changes in adipose tissue function and distribution influence the secretion of adipose tissue derived hormones, or adipokines, that promote a chronic state of low-grade systemic inflammation. Ultimately, obesity accelerates aging by enhancing inflammation and increasing the risk of age-associated diseases. The focus of this review is the impact of aging on adipose tissue distribution and function and how these effects influence the elaboration of pro and anti-inflammatory adipokines.

[35] *Smitka K, Nedvidkova J, Vondra K et al.* **Acipimox Administration With Exercise Induces a Co-feedback Action of the GH, PP, and PYY on Ghrelin Associated With a Reduction of Peripheral Lipolysis in Bulimic and Healthy-Weight Czech Women: A Randomized Study**. Frontiers in endocrinology 2019; 10:108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30915029
ABSTRACT
Objective: Anti-lipolytic drugs and exercise are enhancers of growth hormone (GH) secretion. Decreased circulating free fatty acids (FFA) have been proposed to exert ghrelin-GH feedback loop after administration of an anti-lipolytic longer-acting analog of nicotinic acid, Acipimox (OLB, 5-Methylpyrazine-2-carboxylic acid 4-oxide, molecular weight of 154.1 Da). OLB administration strongly suppresses plasma FFA during exercise. Neuroendocrine perturbations of the adipose tissue (AT), gut, and brain peptides may be involved in the etiopathogenesis of eating disorders including bulimia nervosa (BN) and anorexia nervosa. BN is characterized by binge eating, self-induced vomiting or excessive exercise. Approach: To test the hypothesis that treatment with OLB together with exercise vs. exercise alone would induce feedback action of GH, pancreatic polypeptide (PP), peptide tyrosine tyrosine (PYY), and leptin on ghrelin in Czech women with BN and in healthy-weight Czech women (HW). The lipolysis rate (as glycerol release) in subcutaneous abdominal AT was assessed with microdialysis. At an academic medical center, 12 BN and 12 HW (the control group) were randomized to OLB 500 mg 1 h before a single exercise bout (45 min, 2 W/kg of lean body mass [LBM]) once a week vs. identical placebo over a total of 2 weeks. Blood plasma concentrations of GH, PP, PYY, leptin, ghrelin, FFA, glycerol, and concentrations of AT interstitial glycerol were estimated during the test by RIA utilizing (125)I-labeled tracer, the electrochemiluminescence technique (ECLIA) or colorimetric kits. Results: OLB administration together with short-term exercise significantly increased plasma GH ($P < 0.0001$), PP ($P < 0.0001$), PYY, and leptin concentrations and significantly decreased plasma ghrelin ($P < 0.01$) concentrations in both groups, whereas short-term exercise with placebo resulted in plasma ghrelin ($P < 0.05$) decrease exclusively in BN. OLB administration together with short-term exercise significantly lowered local subcutaneous abdominal AT interstitial glycerol ($P < 0.0001$) to a greater extent in BN. Conclusion: OLB-induced suppression of plasma ghrelin concentrations together with short-term exercise and after the post-exercise recovering phase suggests a potential negative co-feedback of GH, PP, PYY, and leptin on ghrelin secretion to a greater extent in BN. Simultaneously, the exercise-induced elevation in AT interstitial glycerol leading to a higher inhibition of peripheral lipolysis by OLB in BN. Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT03338387.

[36] *Colombo M, Lleo A, Lleo A*. **Lights and Shadows on Fibrates as Second-Line Therapy of Primary Biliary Cholangitis**. Gastroenterology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30926340
ABSTRACT

[37] *Laufs U, Banach M, Mancini GBJ et al.* **Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance**. Journal of the American Heart Association 2019; 8:e011662.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30922146

ABSTRACT

Background Inability to tolerate statins because of muscle symptoms contributes to uncontrolled cholesterol levels and insufficient cardiovascular risk reduction. Bempedoic acid, a prodrug that is activated by a hepatic enzyme not present in skeletal muscle, inhibits ATP - citrate lyase, an enzyme upstream of beta-hydroxy beta-methylglutaryl-coenzyme A reductase in the cholesterol biosynthesis pathway. Methods and Results The phase 3, double-blind, placebo-controlled CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) Serenity study randomized 345 patients with hypercholesterolemia and a history of intolerance to at least 2 statins (1 at the lowest available dose) 2:1 to bempedoic acid 180 mg or placebo once daily for 24 weeks. The primary end point was mean percent change from baseline to week 12 in low-density lipoprotein cholesterol. The mean age was 65.2 years, mean baseline low-density lipoprotein cholesterol was 157.6 mg/dL, and 93% of patients reported a history of statin-associated muscle symptoms. Bempedoic acid treatment significantly reduced low-density lipoprotein cholesterol from baseline to week 12 (placebo-corrected difference, -21.4% [95% CI, -25.1% to -17.7%]; P<0.001). Significant reductions with bempedoic acid versus placebo were also observed in non-high-density lipoprotein cholesterol (-17.9%), total cholesterol (-14.8%), apolipoprotein B (-15.0%), and high-sensitivity C-reactive protein (-24.3%; P<0.001 for all comparisons). Bempedoic acid was safe and well tolerated. The most common muscle-related adverse event, myalgia, occurred in 4.7% and 7.2% of patients who received bempedoic acid or placebo, respectively. Conclusions Bempedoic acid offers a safe and effective oral therapeutic option for lipid lowering in patients who cannot tolerate statins. Clinical Trial Registration URL : https://www.clinicaltrials.gov . Unique identifier: NCT 02988115.

[38] *Barrett HE, Van der Heiden K, Farrell E et al.* **Calcifications in atherosclerotic plaques and impact on plaque biomechanics**. Journal of biomechanics 2019; 87:1-12.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30904335

ABSTRACT

The catastrophic mechanical rupture of an atherosclerotic plaque is the underlying cause of the majority of cardiovascular events. The infestation of vascular calcification in the plaques creates a mechanically complex tissue composite. Local stress concentrations and plaque tissue strength properties are the governing parameters required to predict plaque ruptures. Advanced imaging techniques have permitted insight into fundamental mechanisms driving the initiating inflammatory-driven vascular calcification of the diseased intima at the (sub-) micron scale and up to the macroscale. Clinical studies have potentiated the biomechanical relevance of calcification through the derivation of links between local plaque rupture and specific macrocalcification geometrical features. The clinical implications of the data presented in this review indicate that the combination of imaging, experimental testing, and computational modelling efforts are crucial to predict the rupture risk for atherosclerotic plaques. Specialised experimental tests and modelling efforts have further enhanced the knowledge base for calcified plaque tissue mechanical properties. However, capturing the temporal instability and rupture causality in the plaque fibrous caps remains elusive. Is it necessary to move our experimental efforts down in scale towards the fundamental (sub-) micron scales in order to interpret the true mechanical behaviour of calcified plaque tissue interactions that is presented

on a macroscale in the clinic and to further optimally assess calcified plaques in the context of biomechanical modelling.

[39] *Barkas F, Elisaf M, Liberopoulos E et al.* **Atherogenic dyslipidemia increases the risk of incident diabetes in statin-treated patients with impaired fasting glucose or obesity**. J Cardiol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30910387
ABSTRACT
AIM: To investigate which metabolic factors increase the risk of incident diabetes (T2D) in statin-treated patients. METHODS: A retrospective study conducted in Greece including 1241 consecutive individuals with dyslipidemia attending a lipid clinic for >/=3 years. After defining associations with incident T2D, we assessed the risk of new-onset T2D based on the presence of impaired fasting glucose (IFG), atherogenic dyslipidemia, and overweight/obesity. RESULTS: After excluding 166 patients with baseline T2D and 193 subjects taking lipid-lowering therapy at the baseline visit, 882 participants were included in the study. Eleven percent (n=94) developed T2D during their follow-up (median 6 years; IQR: 4-10). Baseline patients' age (OR: 1.05; 95% CI: 1.02-1.08, p<0.01), family history of diabetes (OR: 3.58; 95% CI: 1.86-6.91, p<0.01), IFG (OR: 6.56; 95% CI: 3.53-12.12, p<0.01), overweight/obesity (OR: 2.65; 95% CI: 1.39-5.05, p<0.01), atherogenic dyslipidemia (OR: 3.27; 95% CI: 1.50-7.15, p<0.01), and treatment with high-intensity statins (OR: 3.51; 95% CI: 1.89-6.51, p<0.01) were independently associated with increased risk of T2D in statin-treated patients. Among the IFG subjects, atherogenic dyslipidemia (OR: 3.44; 95% CI: 1.31-9.04, p=0.01) and overweight/obesity (OR: 2.54; 95% CI: 1.14-5.66, p<0.05) independently increased the risk of T2D. Among the overweight/obese ones, atherogenic dyslipidemia independently increased the risk of T2D (adjusted OR: 5.60; 95% CI: 2.19-14.30, p<0.01). CONCLUSION: Atherogenic dyslipidemia appears to be an independent risk factor for new-onset T2D in statin-treated patients, while IFG, overweight/obesity and family history of diabetes remain risk factors for new-onset T2D in this group.

[40] *Pappa E, Rizos CV, Filippatos TD, Elisaf MS*. **Emerging Fixed-Dose Combination Treatments for Hyperlipidemia**. Journal of cardiovascular pharmacology and therapeutics 2019:1074248419838506.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30909733
ABSTRACT
Low-density lipoprotein cholesterol targets may not be achieved by statin monotherapy, especially in high-risk patients. Furthermore, in some patient subgroups, atherogenic dyslipidemia is observed. As a result, a combination of a statin with other hypolipidemic drugs may have additional benefits, especially in the form of a single tablet. The aim of this review is to present the novel fixed-dose drug combinations for the management of hyperlipidemia. Statins, ezetimibe, and fibrates have established their efficacy and safety in the treatment of hypercholesterolemia and hypertriglyceridemia. Clinical trials have shown that these hypolipidemic drug classes can be safely combined in order to augment the lipid-lowering efficacy. Furthermore, novel hypolipidemic drugs such as bembedoic acid and berberine have shown some promising initial results. The combination of different hypolipidemic regimens in a fixed-dose formulation can enhance the adherence to hypolipidemic treatment leading to

improved outcomes. Moreover, complementary mechanisms of action of the combined hypolipidemic drugs may also provide additional benefits such as improvement in carbohydrate metabolism. As a result, fixed-dose combinations of hypolipidemic agents may provide an attractive option for the effective and safe management of hypercholesterolemia.

[41] *Stasinopoulou M, Kadoglou NPE, Christodoulou E et al.* **Statins' Withdrawal Induces Atherosclerotic Plaque Destabilization in Animal Model-A "Rebound" Stimulation of Inflammation**. Journal of cardiovascular pharmacology and therapeutics 2019:1074248419838499.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30905179
ABSTRACT
BACKGROUND:: To evaluate the impact of atorvastatin discontinuation on the progression and stability of atherosclerotic plaques in a valid animal model of atherosclerosis. METHODS:: Seventy ApoE(-/-) male mice fed with high-fat diet were randomly assigned into: (1) long-term intervention groups: (i) ATL, received atorvastatin for 12 weeks, (ii) CO-12W, control received vehicle for 12 weeks, (iii) ATW-6W, received atorvastatin for 6 weeks which was withdrawn for another 6 weeks. (2) Short-term intervention groups: (i) ATS received atorvastatin for 6 weeks, (ii) CO-6W, control receiving vehicle for 6 weeks, (iii) ATW-3D, ATW-7D, received atorvastatin for 6 weeks which was withdrawn for 3 days and 7 days, respectively. Daily dosage of atorvastatin was 20 mg/kg. Mice were killed and aortic samples were obtained for histological evaluation. RESULTS:: Long-term atorvastatin treatment (ATL) induced atherosclerosis regression and stabilization compared to control ($P < .05$). Atorvastatin's withdrawal was associated with acute (ATW-3D) reduction in connective tissue and collagen contents within plaques compared to ATS ($P < .05$). Those changes were almost restored after a while (ATW-7D) and started appearing again after longer cessation (ATW-6W). Moreover, atorvastatin withdrawal induced shortly (ATW-3D) a peak in inflammatory markers (macrophages, MCP-1, tumor necrosis factor-alpha) and matrix metalloproteinases (MMP-3, MMP-9) concentrations within plaques, which sustained but to a lesser extent along time (ATW-7D, ATW-6W). CONCLUSION:: Short-term withdrawal of atorvastatin seems to compromise its antiatherosclerotic effects, leading to an unstable phenotype of the atherosclerotic lesions and a rebound increase in inflammatory mediators. The clinical relevance of our findings requires further investigation.

[42] *Bogsrud MP, Graesdal A, Johansen D et al.* **LDL-cholesterol goal achievement, cardiovascular disease, and attributed risk of Lp(a) in a large cohort of predominantly genetically verified familial hypercholesterolemia**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30910667
ABSTRACT
BACKGROUND: Current treatment goals for familial hypercholesterolemia (FH) recommended by the European Atherosclerosis Society (EAS) are LDL-C </=2.5 mmol/L (approximately 100 mg/dL) or </=1.8 mmol/L (approximately 70 mg/dL) in very high-risk subjects. OBJECTIVE: The objective of the present study was to investigate characteristics and treatment status in subjects with genetically verified FH followed at specialized lipid clinics in Norway. METHODS: Data from treatment registries of 714 adult (>18 years) subjects with FH. RESULTS: Fifty-seven

percent were female. Mean age (SD) at last visit was 44 (16.3) years, and the subjects had been followed at a lipid clinic for 11.1 (7.9) years. Two hundred forty-five (34%) were classified as very-high-risk, and 44% of these had established coronary heart disease. Very-high-risk FH subjects more often received maximal statin dose (54% vs 33%, P < .001), ezetimibe (76% vs 48%, P < .001) or resins (23% vs 9%, P < .001), and achieved LDL-C was lower (3.2 vs 3.5 mmol/L [124 vs 135 mg/dL], P = .003) than normal-risk FH. LDL-C treatment goal was achieved in 25% and 8% of subjects with normal-risk and very-high-risk FH, respectively. Lp(a) levels were available in 599 subjects, and they were divided into 2 groups: >/=90 mg/dL (n = 96) and <90 mg/dL (n = 503). Despite similar lipid levels, body mass index, smoking status, presence of diabetes, and blood pressure, prevalence of coronary heart disease was doubled in the high- compared to low-Lp(a) group (30% vs 14%, P < .001). CONCLUSION: Very few FH subjects achieve their LDL-C treatment goal. New treatment modalities are needed. Independent of LDL-C and other risk factors, high Lp(a) seem to be an important additional risk factor in genetically verified FH.

[43] *Gualtierotti R, De Lucia O*. **Efficacy and Metabolic Effect on Serum Lipids of Apremilast in Psoriatic Arthritis: A Case Report**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30909370
ABSTRACT
Psoriatic arthritis (PsA) is a chronic immune-mediated disease manifesting as joint inflammation with functional impairment associated with psoriasis. Recently, PsA has emerged as a systemic disease with several comorbidities, such as cardiovascular diseases and metabolic disorders. Apremilast is a targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD) directed against phosphodiesterase 4 (PDE4) with demonstrated efficacy and safety in PsA and psoriasis. We report the case of a patient with PsA manifesting as arthritis, dactylitis, mild psoriasis and a significantly reduced health-related quality of life (HRQoL). Treatment with apremilast in association with methotrexate led to a quick improvement of joint and skin involvement with a stable amelioration of HRQoL. Furthermore, we observed a persistent favorable shift of serum lipid profile. Our observations suggest that apremilast is effective in controlling mild skin and joint involvement, including dactylitis, and suggest a potentially advantageous metabolic effect in patients with PsA.

[44] *Bruno A, Pandolfo G, Crucitti M et al.* **Effect of Red Yeast Rice on Cognitive Functioning in Schizophrenia: Data From a Pilot Study**. Journal of clinical psychopharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30921099
ABSTRACT
BACKGROUND: Cognitive deficits (CDs) in schizophrenia affect poor outcome and real-world community functioning. Because redox imbalance has been implicated, among other factors, in the pathophysiology of CDs, antioxidant compounds may have a beneficial effect in their treatment. Red yeast rice (RYR), besides its lipid-lowering effect, exhibit antioxidant and anti-inflammatory. METHODS: Thirty-five schizophrenia outpatients (age range, 18-60 years) on stable antipsychotic treatment and assessed by neuropsychological (Wisconsin Card Sorting Test [WCST], Verbal Fluency, and Stroop task) and psychodiagnostic instruments (Brief Psychiatric Rating Scale) received RYR at daily dosage of 200 mg/d (total monacolin K/capsule

content, 11.88 mg) for 12 weeks. RESULTS: Red yeast rice supplementation significantly improved WCST "perseverative errors" (P = 0.015), "total errors" (P = 0.017, P = 0.001), and phonemic fluency test (P = 0.008); a trend for improvement on other WCST variables ("nonperseverative errors," "perseverative responses," and "categories") was observed. Effect sizes, according to Cohen's suggestions, were small in all explored cognitive dimensions. There were no significant change in clinical symptoms and no subject-reported adverse effects. CONCLUSIONS: Despite several limitations (open design, lack of a control group, short period of observation, small sample size, mode of controlling patients' compliance, the lack of assessment of patients' functional improvement), results suggest that RYR supplementation may be a potentially promising strategy for addressing CDs in schizophrenia; further randomized, placebo-controlled studies are needed to better evaluate the potential role of RYR for the treatment of CDs in schizophrenia.

[45] *Dongiovanni P, Meroni M, Baselli GA et al.* **PCSK7 gene variation bridges atherogenic dyslipidemia with hepatic inflammation in NAFLD patients**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30918065
ABSTRACT
Dyslipidemia and altered iron metabolism are typical features of non-alcoholic fatty liver disease (NAFLD). Proprotein Convertase Subtilisin/Kexin Type 7 (PCSK7) gene variation has been associated with circulating lipids and liver damage during iron overload. Aim of this study was to examine the impact of the PCSK7 rs236918 variant on NAFLD-related traits in 1,801 individuals from the Liver Biopsy Cohort (LBC), 500,000 from the UK Biobank Cohort (UKBBC), and 4,580 from the Dallas Heart Study (DHS). The minor PCSK7 rs236918 C allele was associated with higher triglycerides, aminotransferases and hepatic inflammation in the LBC ($p<0.05$) and with hypercholesterolemia and liver disease in the UKBBC. In the DHS, PCSK7 missense variants were associated with circulating lipids. PCSK7 was expressed in hepatocytes and its hepatic expression correlated with that of lipogenic genes ($p<0.05$). The rs236918 C allele was associated with upregulation of a new 'intra-PCSK7' lnc-RNA predicted to interact with the protein, higher hepatic and circulating PCSK7 protein ($p<0.01$), and the latter correlated with triglycerides ($p=0.04$). In HepG2, PCSK7 deletion reduced lipogenesis, fat accumulation, inflammation, TGFB pathway activation and fibrogenesis. In conclusion, PCSK7 gene variation is associated with dyslipidemia and more severe liver disease in high risk individuals, likely by modulating PCSK7 expression/activity.

[46] *Meital LT, Windsor MT, Ramirez Jewell RML et al.* **n-3 PUFAs improve erythrocyte fatty acid profile in patients with small abdominal aortic aneurysms: a randomised controlled trial**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30914500
ABSTRACT
Abdominal aortic aneurysm (AAA) is an important cause of death in older adults which has no current drug therapy. Inflammation and abnormal redox status are believed to be key pathogenic mechanisms for AAA. In light of evidence correlating inflammation with aberrant fatty acid profiles, this study compared erythrocyte fatty acid content in 43 AAA patients (diameter 3.0-4.5 cm) and 52 healthy controls. In addition, the effect of omega-3

polyunsaturated fatty acid (n-3 PUFA) supplementation on erythrocyte fatty acid content was examined in a cohort of 30 AAA patients as part of a 12-week randomised placebo-controlled clinical trial. Blood analyses identified associations between AAA and decreased linoleic acid, and AAA and increased Delta6-desaturase activity and biosynthesis of arachidonic acid from linoleic acid. n-3 PUFA supplementation (1.5g DHA+0.3g EPA/day) decreased red blood cell distribution width (RDW, 14.8+/-0.4% to 13.8+/-0.2%, p=0.003) and levels of pro-inflammatory n-6 PUFAs (arachidonic acid, 12.46+/-0.23% to 10.14+/-0.3%, P<0.001; adrenic acid 2.12+/-0.13% to 1.23+/-0.09%, p<0.001). In addition, Delta4-desaturase activity increased (docosahexaenoic/docosapentaenoic acid ratio, 1.85+/-0.14 to 3.93+/-0.17, P<0.001) and elongase 2/5 activity decreased (adrenic acid/arachidonic acid ratio, 0.17+/-0.01 to 0.12+/-0.01, P<0.01) following supplementation. The findings suggest n-3 PUFAs improve fatty acid profiles and ameliorate factors associated with inflammation in AAA patients.

[47] *Zarei B, Mousavi M, Mehdizadeh S et al.* **Early Effects of Atorvastatin on Vitamin D and Parathyroid Hormone Serum Levels Following Acute Myocardial Infarction**. Journal of research in pharmacy practice 2019; 8:7-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30911557
ABSTRACT
Objective: High Vitamin D serum level after acute myocardial infarction (aMI) has shown to increase cardiac reconstruction by increasing cell survival and enhancing angiogenesis. Atorvastatin has a well-defined role in both primary and secondary prevention of cardiovascular diseases. It is suggested that this effect may partly be attributable to raising 25-hydroxyvitamin D concentrations. The aim of this study was to evaluate atorvastatin effects on Vitamin D and parathyroid hormone (PTH) levels early after aMI. Methods: All patients admitted with aMI in Imam Reza Hospital, Mashhad, Iran, from July 2014 to March 2015, were included in this pre- and postintervention study. Serum levels of Vitamin D and PTH were measured on admission and the 3(rd) day after administration of atorvastatin 80 mg/day. Findings: A total of 69 post-aMI patients (47 males and 22 females) were enrolled in this study. Serum levels of Vitamin D and PTH were significantly higher (23.52 ng/ml and 46.04 pg/ml, respectively) after 72 h of atorvastatin therapy compared to the baseline (19.66 ng/ml and 31.19 pg/ml, respectively) (P = 0.004 and 0.002, respectively). Conclusion: The early post-aMI beneficial effects of atorvastatin can be attributed to increased serum Vitamin D level; however, atorvastatin cannot significantly decrease serum PTH level after aMI. Further studies are needed to elucidate the clinical effect of atorvastatin.

[48] *Anagnostis P, Vaitsi K, Veneti S et al.* **Management of dyslipidaemias in the elderly population-A narrative review**. Maturitas 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30910278
ABSTRACT
The impact of dyslipidaemias on the risk of cardiovascular disease (CVD) is well documented. However, it is often under-estimated and, sometimes, suboptimally managed in the elderly population. The prevalence of dyslipidaemias seems to decline from the 7(th) decade of life in both genders. The association of dyslipidaemias with CVD weakens after the 7th decade, perhaps due to other age-related comorbidities. Low-density lipoprotein cholesterol remains

the main target in the management of CVD risk. Although the evidence is not robust for the elderly, statins are the cornerstone of the management of CVD. Statins do have a potentially beneficial role in elderly individuals with established CVD and/or a history of type 2 diabetes mellitus. Data on their use in other elderly populations are inconsistent. There is no clear evidence for a beneficial effect of other hypolipidaemic drug categories in the elderly, such as ezetimibe, fibrates, niacin, omega-3 fatty acids and the new proprotein convertase subtilisin/kexin type 9 inhibitors. Their use should be balanced against possible adverse effects, such as the increased risk of myopathy with fibrates. Potential drug-drug interactions should be also taken into account. In conclusion, there is a need to establish the most effective lipid-lowering strategy in the elderly population with respect to CVD risk reduction, in future well-designed trials.

[49] *Bi Y, Chen J, Hu F et al.* **M2 Macrophages as a Potential Target for Antiatherosclerosis Treatment**. Neural plasticity 2019; 2019:6724903.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30923552
ABSTRACT
Atherosclerosis is a chronic progressive inflammation course, which could induce life-threatening diseases such as stroke and myocardial infarction. Optimal medical treatments for atherosclerotic risk factors with current antihypertensive and lipid-lowering drugs (for example, statins) are widely used in clinical practice. However, many patients with established disease still continue to have recurrent cardiovascular events in spite of treatment with a state-of-the-art therapy. Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality worldwide. Hence, current treatment of atherosclerosis is still far from being satisfactory. Recently, M2 macrophages have been found associated with atherosclerosis regression. The M2 phenotype can secrete anti-inflammatory factors such as IL-10 and TGF-beta, promote tissue remodeling and repairing through collagen formation, and clear dying cells and debris by efferocytosis. Therefore, modulators targeting macrophages' polarization to the M2 phenotype could be another promising treatment strategy for atherosclerosis. Two main signaling pathways, the Akt/mTORC/LXR pathway and the JAK/STAT6 pathway, are found playing important roles in M2 polarization. In addition, researchers have reported several potential approaches to modulate M2 polarization. Inhibiting or activating some kinds of enzymes, affecting transcription factors, or acting on several membrane receptors could regulate the polarization of the M2 phenotype. Besides, biomolecules, for example vitamin D, were found to affect the process of M2 polarization. Pomegranate juice could promote M2 polarization via unclear mechanism. In this review, we will discuss how M2 macrophages affect atherosclerosis regression, signal transduction in M2 polarization, and outline potential targets and compounds that affect M2 polarization, thus controlling the progress of atherosclerosis.

[50] *Lu D, Shen L, Mai H et al.* **HMG-CoA Reductase Inhibitors Attenuate Neuronal Damage by Suppressing Oxygen Glucose Deprivation-Induced Activated Microglial Cells**. Neural plasticity 2019; 2019:7675496.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30911291
ABSTRACT

Ischemic stroke is usually followed by inflammatory responses mediated by microglia. However, the effect of statins on directly preventing posthypoxia microglia inflammatory factors to prevent injury to surrounding healthy neurons is unclear. Atorvastatin and rosuvastatin, which have different physical properties regarding their lipid and water solubility, are the most common HMG-CoA reductase inhibitors (statins) and might directly block posthypoxia microglia inflammatory factors to prevent injury to surrounding neurons. Neuronal damage and microglial activation of the peri-infarct areas were investigated by Western blotting and immunofluorescence after 24 hours in a middle cerebral artery occlusion (MCAO) rat model. The decrease in neurons was in accordance with the increase in microglia, which could be reversed by both atorvastatin and rosuvastatin. The effects of statins on blocking secretions from posthypoxia microglia and reducing the secondary damage to surrounding normal neurons were studied in a coculture system in vitro. BV2 microglia were cultured under oxygen glucose deprivation (OGD) for 3 hours and then cocultured following reperfusion for 24 hours in the upper wells of transwell plates with primary neurons being cultured in the bottom wells. Inflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), and cyclooxygenase-2 (COX2), which are activated by the nuclear factor-kappa B (NF-kappaB) signaling pathway in OGD-induced BV2 microglia, promoted decreased release of the anti-inflammatory cytokine IL-10 and apoptosis of neurons in the coculture systems according to ELISA and Western blotting. However, pretreatment with atorvastatin or rosuvastatin significantly reduced neuronal death, synaptic injury, and amyloid-beta (Abeta) accumulation, which might lead to increased low-density lipoprotein receptors (LDLRs) in BV2 microglia. We concluded that the proinflammatory mediators released from postischemia damage could cause damage to surrounding normal neurons, while HMG-CoA reductase inhibitors prevented neuronal apoptosis and synaptic injury by inactivating microglia through blocking the NF-kappaB signaling pathway.

[51] *Gai Z, Wang T, Visentin M et al.* **Lipid Accumulation and Chronic Kidney Disease**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30925738

ABSTRACT

Obesity and hyperlipidemia are the most prevalent independent risk factors of chronic kidney disease (CKD), suggesting that lipid accumulation in the renal parenchyma is detrimental to renal function. Non-esterified fatty acids (also known as free fatty acids, FFA) are especially harmful to the kidneys. A concerted, increased FFA uptake due to high fat diets, overexpression of fatty acid uptake systems such as the CD36 scavenger receptor and the fatty acid transport proteins, and a reduced beta-oxidation rate underlie the intracellular lipid accumulation in non-adipose tissues. FFAs in excess can damage podocytes, proximal tubular epithelial cells and the tubulointerstitial tissue through various mechanisms, in particular by boosting the production of reactive oxygen species (ROS) and lipid peroxidation, promoting mitochondrial damage and tissue inflammation, which result in glomerular and tubular lesions. Not all lipids are bad for the kidneys: polyunsaturated fatty acids (PUFA) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) seem to help lag the progression of chronic kidney disease (CKD). Lifestyle interventions, especially dietary adjustments, and lipid-lowering drugs can contribute to improve the clinical outcome of patients with CKD.

[52] *Casula M, Olmastroni E, Boccalari MT et al.* **CARDIOVASCULAR EVENTS WITH PCSK9 INHIBITORS: AN UPDATED META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30926528

ABSTRACT

The therapy with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors efficiently reduces plasma cholesterol levels, which has been recently associated with improvement in cardiovascular outcomes. This meta-analysis aimed at investigating the safety and efficacy of treatment with the clinically available anti-PCSK9 monoclonal antibodies (mAbs) in all published randomized clinical trials (RCTs), updating the available results with the recently published ODYSSEY OUTCOMES trial. Data search was carried out using PubMed/MEDLINE and EMBASE (inception - January 2019). Inclusion criteria were: (1) phase 2 or 3 RCTs; (2) comparing anti-PCSK9 mAbs (specifically evolocumab and alirocumab) with placebo; (3) with effects on outcomes reported; (4) with treatment duration longer than 8 weeks. Odds ratios (ORs) with 95% CIs were used as summary statistics. We pooled the estimates by using both the DerSimonian & Laird method (random-effects model). Between-study heterogeneity was tested by Cochrane's Q test and measured with the I2 statistics. Twenty-eight RCTs comprising 62,281 participants (33,204 in the mAb arm, 29,077 in the placebo arm) were included in the meta-analysis. The treatment follow-up ranged from 8 weeks up to 208 weeks. Overall, no significant difference in all-cause mortality was observed between the two groups (OR 0.93 [95% CI, 0.85-1.03]). The treatment with an anti-PCSK9 mAb was associated with a significant reduction of CV events compared with placebo (OR 0.83 [95% CI, 0.78-0.87]), being the FOURIER and ODYSSEY OUTCOMES studies the major contributors. Both myocardial infarction and stroke were significantly reduced following the treatment with an anti-PCSK9 mAb. No significant difference was observed in cardiovascular mortality (OR 0.94 [95% CI, 0.83-1.07]). The incidence of serious adverse events was similar in the two groups (OR: 0.95, [95% CI, 0.91-0.99]). Thus, the pharmacological approach with anti-PCSK9 mAbs significantly and safely improves cardiovascular outcomes. Despite that, the pooled analysis failed to show a significant cardiovascular mortality benefit with anti-PCSK9 mAb treatment, suggesting that specific longer-term studies are warranted to address this issue. We suggest that the observed delay between the rapid effect on plasma cholesterol levels and the emergence of the clinical benefit, observed both in FOURIER and ODYSSEY OUTCOMES trials, might explain this finding.

[53] *Hajighasemi S, Mahdavi Gorabi A, Bianconi V et al.* **A review of gene- and cell-based therapies for familial hypercholesterolemia**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019; 143:119-132.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30910740

ABSTRACT

Familial hypercholesterolemia (FH) is a genetic autosomal dominant disorder caused by an impaired receptor-mediated low-density lipoprotein (LDL) removal from the circulation, mainly due to disruptive autosomal co-dominant mutations in the LDL receptor (LDLr) gene, but also less frequently in the apolipoprotein B100 (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes. A rare form of autosomal recessive FH has been also described due to

LDLr adaptor protein 1 (LDLRAP1) gene mutations. FH is characterized by very high levels of plasma LDL cholesterol associated with the high incidence of premature atherosclerotic cardiovascular disease (CVD). Despite heterozygous FH (HeFH) patients are still poorly recognized and treated, there is today a large availability of drugs (i.e., statins, ezetimibe and PCSK9 inhibitors) allowing theoretically the normalization of plasma LDL cholesterol levels in this population. Homozygous FH patients (HoFH) have a more severe form of FH, characterized by low responsiveness to the conventional lipid-lowering treatment and often associated with unfavorable prognosis in the young age. Inspired by promising outcomes obtained by orthotopic liver transplantation (OLT), scientists are investigating the possibility of correcting the defective LDLr in these patients by using gene therapy approaches to achieve a novel therapeutic solution with high efficiency. In this article, we tried to review the in vitro, ex vivo, and in vivo attempts conducted to correct FH-causing LDLr gene mutations by using different methods of gene delivery, gene editing, and stem cell manipulation. We also discussed some clinical trials performed in this context.

[54] *Kim MJ, Bible KL, Regnier M et al.* **Simvastatin provides long-term improvement of left ventricular function and prevents cardiac fibrosis in muscular dystrophy**. Physiological reports 2019; 7:e14018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30912308
ABSTRACT
Duchenne muscular dystrophy (DMD), caused by absence of the protein dystrophin, is a common, degenerative muscle disease affecting 1:5000 males worldwide. With recent advances in respiratory care, cardiac dysfunction now accounts for 50% of mortality in DMD. Recently, we demonstrated that simvastatin substantially improved skeletal muscle health and function in mdx (DMD) mice. Given the known cardiovascular benefits ascribed to statins, the aim of this study was to evaluate the efficacy of simvastatin on cardiac function in mdx mice. Remarkably, in 12-month old mdx mice, simvastatin reversed diastolic dysfunction to normal after short-term treatment (8 weeks), as measured by echocardiography in animals anesthetized with isoflurane and administered dobutamine to maintain a physiological heart rate. This improvement in diastolic function was accompanied by increased phospholamban phosphorylation in simvastatin-treated mice. Echocardiography measurements during long-term treatment, from 6 months up to 18 months of age, showed that simvastatin significantly improved in vivo cardiac function compared to untreated mdx mice, and prevented fibrosis in these very old animals. Cardiac dysfunction in DMD is also characterized by decreased heart rate variability (HRV), which indicates autonomic function dysregulation. Therefore, we measured cardiac ECG and demonstrated that short-term simvastatin treatment significantly increased heart rate variability (HRV) in 14-month-old conscious mdx mice, which was reversed by atropine. This finding suggests that enhanced parasympathetic function is likely responsible for the improved HRV mediated by simvastatin. Together, these findings indicate that simvastatin markedly improves cardiac health and function in dystrophic mice, and therefore may provide a novel approach for treating cardiomyopathy in DMD.

[55] *Viecelli AK, Polkinghorne KR, Pascoe EM et al.* **Fish oil and aspirin effects on arteriovenous fistula function: Secondary outcomes of the randomised omega-3 fatty acids (Fish oils) and**

Aspirin in Vascular access OUtcomes in REnal Disease (FAVOURED) trial. PloS one 2019; 14:e0213274.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30913208
ABSTRACT
BACKGROUND: Arteriovenous fistulas (AVF) for haemodialysis often experience early thrombosis and maturation failure requiring intervention and/or central venous catheter (CVC) placement. This secondary and exploratory analysis of the FAVOURED study determined whether omega-3 fatty acids (fish oils) or aspirin affected AVF usability, intervention rates and CVC requirements. METHODS: In 567 adult participants planned for AVF creation, all were randomised to fish oil (4g/d) or placebo, and 406 to aspirin (100mg/d) or placebo, starting one day pre-surgery and continued for three months. Outcomes evaluated within 12 months included AVF intervention rates, CVC exposure, late dialysis suitability failure, and times to primary patency loss, abandonment and successful cannulation. RESULTS: Final analyses included 536 participants randomised to fish oil or placebo (mean age 55 years, 64% male, 45% diabetic) and 388 randomised to aspirin or placebo. Compared with placebo, fish oil reduced intervention rates (0.82 vs 1.14/1000 patient-days, incidence rate ratio [IRR] 0.72, 95% confidence interval [CI] 0.54-0.97), particularly interventions for acute thrombosis (0.09 vs 0.17/1000 patient-days, IRR 0.53, 95% CI 0.34-0.84). Aspirin significantly reduced rescue intervention rates (IRR 0.45, 95% CI 0.27-0.78). Neither agent significantly affected CVC exposure, late dialysis suitability failure or time to primary patency loss, AVF abandonment or successful cannulation. CONCLUSION: Although fish oil and low-dose aspirin given for 3 months reduced intervention rates in newly created AVF, they had no significant effects on CVC exposure, AVF usability and time to primary patency loss or access abandonment. Reduction in access interventions benefits patients, reduces costs and warrants further study.

[56] *Lee YP, Cho Y, Kim EJ et al.* **Reduced expression of pyruvate kinase in kidney proximal tubule cells is a potential mechanism of pravastatin altered glucose metabolism**. Scientific reports 2019; 9:5318.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30926836
ABSTRACT
Recent studies have reported that statins are associated with increased incidence of diabetes. Although several mechanisms have been proposed, the role of the kidney's glucose metabolism upon statin treatment is still unclear. Thus, we investigated the role of pravastatin in gluconeogenesis and glycolysis. HK-2 and HepG2 cells were treated with pravastatin and cultured under either high- or normal-cholesterol conditions. In HK-2 cells treated with pravastatin under both high- and normal-cholesterol conditions, the protein expression of only pyruvate kinase isozymes L/R (PKLR) decreased in a dose-dependent manner, while the protein expression of other glucose metabolism related enzymes remained unchanged. Within the in vivo experiment, male C57BL/6 mice were fed either pravastatin-treated normal-fat diets for 2 or 4 weeks or pravastatin-treated high-fat diets for 16 weeks. Protein expression of PKLR in the kidneys from mice that consumed pravastatin-treated high-fat diets decreased significantly compared to the controls. Upon the treatments of pravastatin, only the PKLR expression decreased in lean mice. Furthermore, PKLR activity decreased significantly in the kidney after pravastatin treatments. However, there was no change in enzyme activity in the liver,

suggesting that pravastatin decreased PKLR activity only in the kidney. This change may be associated with the hyperglycemic effect of statins.

[57] *Sharma R, Matsuzaka T, Kaushik MK et al.* **Octacosanol and policosanol prevent high-fat diet-induced obesity and metabolic disorders by activating brown adipose tissue and improving liver metabolism**. Scientific reports 2019; 9:5169.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30914769
ABSTRACT
Brown adipose tissue (BAT) is an attractive therapeutic target for treating obesity and metabolic diseases. Octacosanol is the main component of policosanol, a mixture of very long chain aliphatic alcohols obtained from plants. The current study aimed to investigate the effect of octacosanol and policosanol on high-fat diet (HFD)-induced obesity. Mice were fed on chow, or HFD, with or without octacosanol or policosanol treatment for four weeks. HFD-fed mice showed significantly higher body weight and body fat compared with chow-fed mice. However, mice fed on HFD treated with octacosanol or policosanol (HFDo/p) showed lower body weight gain, body fat gain, insulin resistance and hepatic lipid content. Lower body fat gain after octacosanol or policosanol was associated with increased BAT activity, reduced expression of genes involved in lipogenesis and cholesterol uptake in the liver, and amelioration of white adipose tissue (WAT) inflammation. Moreover, octacosanol and policosanol significantly increased the expression of Ffar4, a gene encoding polyunsaturated fatty acid receptor, which activates BAT thermogenesis. Together, these results suggest that octacosanol and policosanol ameliorate diet-induced obesity and metabolic disorders by increasing BAT activity and improving hepatic lipid metabolism. Thus, these lipids represent promising therapeutic targets for the prevention and treatment of obesity and obesity-related metabolic disorders.

[58] *Brown M, Ahmed S.* **Emerging role of proprotein convertase subtilisin/kexin type-9 (PCSK-9) in inflammation and diseases**. Toxicology and applied pharmacology 2019; 370:170-177.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30914377
ABSTRACT
Proprotein convertase subtilisin/kexin type-9 (PCSK9) is most recognized serine protease for its role in cardiovascular diseases (CVD). PCSK9 regulates plasma low-density lipoprotein cholesterol (LDL-C) levels by selectively targeting hepatic LDL receptors (LDLR) for degradation, thereby serving as a potential therapeutic target for CVD. New pharmacological agents under development aim to lower the risk of CVD by inhibiting PCSK9 extracellularly, although secondary effects of this approach are not yet studied. Here we review the history of PCSK9 and rationale behind developing inhibitors for CVD. Importantly, we summarized the studies investigating the role and impact of modulated PCSK9 levels in inflammation, specifically in sepsis, rheumatoid arthritis and other chronic inflammatory conditions. Furthermore, we summarized studies that investigated the interactions of PCSK9 with pro-inflammatory pathways, such as scavenger receptor CD36 and thrombospondin 1 (TSP-1) in inflammatory diseases. This review highlights the conflicting role that PCSK9 plays in different inflammatory disease states and postulates that any unwanted effects of PCSK9 inhibition in early clinical testing should critically be examined.

[59] *Hollstein T, Vogt A, Grenkowitz T et al.* **Treatment with PCSK9 inhibitors reduces atherogenic VLDL remnants in a real-world study**. Vascular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30910670

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin-kexin type 9 inhibitors (PCSK9-I) reduce low-density lipoprotein (LDL) cholesterol in human studies. Previous studies suggest that PCSK9-I may also affect very-low-density lipoproteins (VLDL). We therefore studied VLDL size and composition in a "real-world" study population with the use of beta-quantification. SUBJECTS AND METHODS: 350 patients (62+/-11years old, 58% men, 22% with diabetes mellitus) with different concomitant lipid lowering therapies, and in whom PCSK9-I treatment was indicated, received either evolocumab (140mg) or alirocumab (75 or 150mg). The major lipoprotein fractions were separated by beta-quantification and lipid and apolipoprotein compositions were determined before and 4weeks after initiation of PCSK9-I treatment. RESULTS: After 4weeks of PCSK9-I treatment, the ratio of triglycerides to apolipoprotein B in VLDL particles (VLDL-TG/apoB ratio) increased by 40% (p<.0001). VLDL-associated apolipoproteins E, CII, and CIII were reduced by 29.4%, 16.4%, and 12.4%, respectively (all p<.0001). CONCLUSION: PCSK9-I treatment increased VLDL size (estimated by an increased VLDL-TG/apoB ratio) and reduced VLDL-associated apolipoproteins in a heterogeneous "real-world" study-population, reflecting a higher clearance of small atherogenic VLDL remnant particles by PCSK9-I. This may potentially lower cardiovascular risk in clinical routine patients beyond low-density cholesterol (LDL-C) reduction.