Literature update week 37 (2019)

[1] *de Havenon A, Muhina HJ, Parker DL et al.* **Effect of Time Elapsed since Gadolinium Administration on Atherosclerotic Plaque Enhancement in Clinical Vessel Wall MR Imaging Studies**. AJNR. American journal of neuroradiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31515211
ABSTRACT
Vessel wall MR imaging is a useful tool for the evaluation of intracranial atherosclerotic disease. Enhancement can be particularly instructive. This study investigated the impact of the duration between contrast administration and image acquisition. The cohort with the longest duration had the greatest increase in signal intensity change. When using vessel wall MR imaging to assess intracranial atherosclerotic disease, protocols should be designed to maximize the duration between contrast administration and image acquisition to best demonstrate enhancement.

[2] *Ray KK, Nicholls SJ, Ginsberg HD et al.* **Effect of selective BET protein inhibitor apabetalone on cardiovascular outcomes in patients with acute coronary syndrome and diabetes: Rationale, design, and baseline characteristics of the BETonMACE trial**. American heart journal 2019; 217:72-83.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31520897
ABSTRACT
After an acute coronary syndrome (ACS), patients with diabetes remain at high risk for additional cardiovascular events despite use of current therapies. Bromodomain and extra-terminal (BET) proteins are epigenetic modulators of inflammation, thrombogenesis, and lipoprotein metabolism implicated in atherothrombosis. The BETonMACE trial tests the hypothesis that treatment with apabetalone, a selective BET protein inhibitor, will improve cardiovascular outcomes in patients with diabetes after an ACS. DESIGN: Patients (n=2425) with ACS in the preceding 7 to 90 days, with type 2 diabetes and low HDL cholesterol (</=40 mg/dl for men, </=45 mg/dl for women), receiving intensive or maximum-tolerated therapy with atorvastatin or rosuvastatin, were assigned in double-blind fashion to receive apabetalone 100 mg orally twice daily or matching placebo. Baseline characteristics include female sex (25%), myocardial infarction as index ACS event (74%), coronary revascularization for index ACS (76%), treatment with dual anti-platelet therapy (87%) and renin-angiotensin system inhibitors (91%), median LDL cholesterol 65 mg per deciliter, and median HbA1c 7.3%. The primary efficacy measure is time to first occurrence of cardiovascular death, non-fatal myocardial infarction, or stroke. Assumptions include a primary event rate of 7% per annum in the placebo group and median follow-up of 1.5 years. Patients will be followed until at least 250 primary endpoint events have occurred, providing 80% power to detect a 30% reduction in the primary endpoint with apabetalone. SUMMARY: BETonMACE will determine whether the addition of the selective BET protein inhibitor apabetalone to contemporary standard of care for ACS reduces cardiovascular morbidity and mortality in patients with type 2 diabetes. Results are expected in 2019.

[3] *Packer M*. **Epicardial Adipose Tissue Inflammation Can Cause the Distinctive Pattern of Cardiovascular Disorders Seen in Psoriasis**. The American journal of medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31520623

ABSTRACT
Psoriasis is a systemic inflammatory disorder that can target adipose tissue; the resulting adipocyte dysfunction is manifest clinically as the metabolic syndrome, which is present in approximately 20-40% of patients. Epicardial adipose tissue inflammation is likely responsible for a distinctive pattern of cardiovascular disorders, consisting of(1): accelerated coronary atherosclerosis leading to myocardial infarction,(2) atrial myopathy leading to atrial fibrillation and thromboembolic stroke, and(3) ventricular myopathy leading to heart failure with a preserved ejection fraction. If cardiovascular inflammation drives these risks, then treatments that focus on blood pressure, lipids and glucose will not ameliorate the burden of cardiovascular disease in patients with psoriasis, especially in those who are young and have severe inflammation. Instead, interventions that alleviate systemic and adipose tissue inflammation may not only minimize the risks of atrial fibrillation and heart failure, but may also have favorable effects on the severity of psoriasis. Viewed from this perspective, the known link between psoriasis and cardiovascular disease is not related to the influence of the individual diagnostic components of the metabolic syndrome.

[4] *Rebalka IA, Cao AW, May L et al.* **Statin administration activates System Xc(-) in skeletal muscle: a potential mechanism explaining statin-induced muscle pain**. Am J Physiol Cell Physiol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31509447

ABSTRACT
Statins are a cholesterol-lowering drug class that significantly reduce cardiovascular disease risk. Despite their safety and effectiveness, musculoskeletal side-effects, particularly myalgia, are prominent and the most common reason for discontinuance. The cause of statin-induced myalgia is unknown, so defining the underlying mechanism(s) and potential therapeutic strategies is of clinical importance. Here we tested the hypothesis that statin administration activates skeletal muscle system xC(-), a cystine/glutamate antiporter, to increase intracellular cysteine and therefore glutathione synthesis to attenuate statin-induced oxidative stress. Increased system xC(-)activity would increase interstitial glutamate; an amino acid associated with peripheral nociception. Consistent with our hypothesis, atorvastatin treatment significantly increased mitochondrial reactive oxygen species (ROS; 41%) and glutamate efflux (up to 122%) in C2C12 mouse skeletal muscle myotubes. Statin-induced glutamate efflux was confirmed to be the result of system xC(-)activation, as co-treatment with sulfasalazine (system xC(-)inhibitor) negated this rise in extracellular glutamate. These findings were reproduced in primary human myotubes but, consistent with being muscle-specific, were not observed in primary human dermal fibroblasts. To further demonstrate that statin-induced increases in ROS triggered glutamate efflux, C2C12 myotubes we co-treated with atorvastatin and various antioxidants. Alpha-tocopherol and cysteamine bitartrate reversed the increase in statin-induced glutamate efflux, bringing glutamate levels between 50-92% of control-treated levels. N-acetylcysteine (a system xC(-) substrate) increased glutamate efflux above statin treatment alone; up to 732% greater than control treatment. Taken together, we provide a mechanistic foundation for statin-induced myalgia and offer therapeutic insights to alleviate this particular statin-associated side-effect.

[5] *Wang L, Hou H, Zi D et al.* **Novel apoE receptor mimetics reduce LPS-induced microglial inflammation**. American journal of translational research 2019; 11:5076-5085.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31497223
ABSTRACT
Apolipoprotein E (apoE) and apoE-mimetic peptides exert prominent anti-inflammatory effects. We determined the anti-inflammatory effects of novel apoE receptor mimetics, composed of the LDL receptor-binding domain of apoE (aa 133-152, ApoEp) or ApoEp with 6 lysines (6KApoEp) or 6 aspartates added at the N-terminus (6DApoEp). BV2 microglia and human THP-1 monocytes were treated with lipopolysaccharide (LPS) in the absence or presence of ApoEp, 6KApoEp or 6DApoEp, followed by determination of pro-inflammatory tumor necrosis factor alpha (TNFalpha) and interleukin-6 (IL-6) release by ELISA. As signaling intermediates of inflammation, Signal Transducer and Activator of Transcription 3 (STAT3), Janus-Activated Kinase2 (JAK2) and p38 and p44/42 MAPK phosphorylation levels were determined by Western blot analysis. In addition, we isolated splenocytes from female htau mice treated with 6KApoEp or 6K for 28 weeks, followed by determination of concanavalinA (conA)-mediated interferon gamma (IFNgamma) release. 6KApoEp starting at 2.5 microM significantly reduced LPS-mediated TNFalpha and IL-6 secretion in BV2 and THP-1 cells in a dose-dependent manner. In BV2 cells, 6KApoEp reduced TNFalpha secretion more effectively than 6DApoEp and ApoEp, which was blocked by PCSK9 treatment, suggesting a role for LDL receptors. 6KApoEp also inhibited LPS-induced p44/42 MAPK, JAK2 and STAT3 phosphorylation, while enhancing p38 MAPK phosphorylation. In addition, conA induced significantly less IFNgamma release in splenocytes derived from htau mice treated with 6KApoEp compared with those treated with 6K. Thus, 6KApoEp most effectively reduces LPS-mediated neuroinflammation by interacting with LDL receptors, thus representing a novel anti-inflammatory agent for treatment of neurodegenerative disease.

[6] *Cokkinos DV, Cokkinos P, Kolovou G*. **Proprotein convertase subtilisin/kexin type 9 inhibitors: New insights into cardiovascular atherosclerotic pathophysiology with therapeutic implications**. Archives of cardiovascular diseases 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31495741
ABSTRACT

[7] *Sanchez-Hernandez RM, Di Taranto MD, Benito-Vicente A et al.* **The Arg499His gain-of-function mutation in the C-terminal domain of PCSK9**. Atherosclerosis 2019; 289:162-172.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31518966
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is a monogenic disease characterized by high levels of low-density lipoprotein cholesterol and premature atherosclerotic cardiovascular disease. FH is caused by loss of function mutations in genes encoding LDL receptor (LDLR), and Apolipoprotein B (APOB) or gain of function (GOF) mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9). In this study, we identified a novel variant in PCSK9, p.(Arg499His), located in the C-terminal domain, in two unrelated FH patients from Spain and Italy. METHODS: We studied familial segregation and determined variant activity in vitro. RESULTS: We determined PCSK9 expression, secretion and activity of the

variant in transfected HEK293cells; extracellular activity of the recombinant p.(Arg499His) PCSK9 variant in HEK 293 and HepG2 cells; PCSK9 affinity to the LDL receptor at neutral and acidic pH; the mechanism of action of the p.(Arg499His) PCSK9 variant by co-transfection with a soluble construct of the LDL receptor and by determining total PCSK9 intracellular accumulation when endosomal acidification is impaired and when an excess of soluble LDLr is present in the culture medium. Our results show high LDL-C concentrations and FH phenotype in p.(Arg499His) carriers. In vitro functional characterization shows that p.(Arg499His) PCSK9 variant causes a reduction in LDLr expression and LDL uptake. An intracellular activity for this variant is also shown when blocking the activity of secreted PCSK9 and by inhibiting endosomal acidification. CONCLUSIONS: We demonstrated that p.(Arg499His) PCSK9 variant causes a direct intracellular degradation of LDLr therefore causing FH by reducing LDLr availability.

[8] *Xie W, Li L, Gong D et al.* **Kruppel-like factor 14 inhibits atherosclerosis via mir-27a-mediated down-regulation of lipoprotein lipase expression in vivo**. Atherosclerosis 2019; 289:143-161.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31518965
ABSTRACT
BACKGROUND AND AIMS: Kruppel-like factor 14 (KLF14) is known to play a role in atherosclerosis, but the underlying mechanisms are still largely unknown. The aim of our study was to explore the effects of KLF14 on lipid metabolism and inflammatory response, providing a potential target for lowering the risk of atherosclerosis-causing disease. METHODS AND RESULTS: mRNA and protein levels of KLF14 were significantly decreased in oxidized low-density lipoprotein (oxLDL)-treated macrophages and in the atherosclerotic lesion area. Chromatin immunoprecipitation (ChIP) and luciferase reporter gene assays were used to confirm that KLF14 positively regulated miR-27a expression by binding to its promoter. We also found that KLF14 could restored appropriate cellular lipid homeostasis and inflammatory responses via negatively regulating lipoprotein lipase (LPL) expression in THP1-derived macrophages through miR-27a. In addition, gypenosides (GP), a KLF14 activator, delayed the development of atherosclerosis in apolipoprotein E deficient (apoE(-/-)) mice. CONCLUSIONS: KLF14 plays an antiatherogenic role via the miR-27a-dependent down-regulation of LPL and subsequent inhibition of proinflammatory cytokine secretion and lipid accumulation.

[9] *Li S, Yu Y, Jin Z et al.* **Prediction of pharmacokinetic drug-drug interactions causing atorvastatin-induced rhabdomyolysis using physiologically based pharmacokinetic modelling**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2019; 119:109416.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31518878
ABSTRACT
Atorvastatin and its lactone form metabolite are reported to be associated with statin-induced myopathy (SIM) such as myalgia and life-threatening rhabdomyolysis. Though the statin-induced rhabdomyolysis is not common during statin therapy, its incidence will significantly increase due to pharmacokinetic drug-drug interactions (DDIs) with inhibitor drugs which inhibit atorvastatin's and its lactone's metabolism and hepatic uptake. Thus, the quantitative analysis of DDIs of atorvastatin and its lactone with cytochrome P450 3A4 (CYP3A4) and organic anion-transporting polypeptide (OATP) inhibitors is of great importance. This study aimed to

predict pharmacokinetic DDIs possibly causing atorvastatin-induced rhabdomyolysis using Physiologically Based Pharmacokinetic (PBPK) Modelling. Firstly, we refined the PBPK models of atorvastatin and atorvastatin lactone for predicting the DDIs with CYP3A4 and OATP inhibitors. Thereafter, we predicted the exposure changes of atorvastatin and atorvastatin lactone originating from the case reports of atorvastatin-induced rhabdomyolysis using the refined models. The simulation results show that pharmacokinetic DDIs of atorvastatin and its lactone with fluconazole, palbociclib diltiazem and cyclosporine are significant. Consequently, clinicians should be aware of necessary dose adjustment of atorvastatin being used with these four inhibitor drugs.

[10] *Zhang C, He J, Li J et al.* **A novel light-electricity sensing method for PCSK9 detection based on s-PdNFs with multifunctional property**. Biosensors & bioelectronics 2019; 144:111575.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31513960
ABSTRACT
Amounts of studies show that proprotein convertase subtilisin/kexin type 9 (PCSK9) can increase the low-density lipoprotein cholesterol ((LDL-C), leading to the progression and development of atherosclerosis. Hence, design an effective method to detect serum PCSK9 is meaningful for the prevention, monitor and diagnosis of cardiovascular diseases. Here, we reported a dual-signal method for detecting PCSK9 using a signal label, sulphur-doped palladium nanoflowers (s-PdNFs), inspired by its multifunctional properties of quenching and catalysis, which would simultaneously achieve electrochemiluminescence (ECL) analysis and electrochemical detection. For the ECL analysis, s-PdNFs could effectively quench the ECL intensity of peroxydisulfate/oxygen (S2O8(2-)/O2) system via ECL resonance energy transfer (ECL-RET). Importantly, the donor-acceptor pair (s-PdNFs-S2O8(2-) pair) was firstly reported in the ECL-RET field. For the electrochemical detection, s-PdNFs with peroxidase-like activity, produce electric signals by catalyzing H2O2. Herein, a novel light-electricity dual signal immunosensor based on s-PdNFs was developed, and with a broad linear range of 5fgmL(-1) to 50ngmL(-1) (ECL channel) and 500fgmL(-1) to 50ngmL(-1) (electrochemical channel). Furthermore, the ECL channel and electrochemical channel can achieve the detection respectively which can meet different testing instruments. The two channels can also be combined to improve the accuracy of the detection. More importantly, the immunosensor realized the detection of PCSK9 in real serum samples demonstrated by good correlations with ELISA method. Our findings can promote the application of multifunctional materials in sensor and biomedicine field and provide a novel strategy for the detection of serum molecular.

[11] *Kristiansen O, Vethe NT, Fagerland MW et al.* **A novel direct method to determine adherence to atorvastatin therapy in patients with coronary heart disease**. British journal of clinical pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31495943
ABSTRACT
AIMS: Objective methods to monitor statin adherence are needed. We have established a liquid chromatography-tandem mass spectrometry assay for quantification of atorvastatin and its metabolites in blood. This study aimed to develop an objective drug exposure variable with cut-off values to discriminate among adherence, partial adherence and non-adherence to

atorvastatin therapy in patients with coronary heart disease. METHODS: Twenty-five patients treated with atorvastatin 10 mg (N=5), 20 mg (N=6), 40 mg (N=7) and 80 mg (N=7) participated in a directly observed atorvastatin therapy (DOT) study to confirm baseline adherence. After the DOT, half of the patients (test-group) were instructed to stop taking atorvastatin and return for blood sample collection the subsequent 3 days. Levels of atorvastatin and metabolites were compared between the test-group and the adherent control group. RESULTS: The sum of parent drug and all measured primary metabolites correlated well with the atorvastatin dose administered (Spearman's rho=0.71, 95% CI 0.44 to 0.87). The dose-normalized atorvastatin plus metabolites concentrations completely separated the partially adherent test-group from the controls at 0.18 (nmol/L)/mg after 3 days without atorvastatin. To reduce the risk of misinterpreting adherent patients as partially adherent, a corresponding cut-off at 0.10 (nmol/L)/mg is proposed. A metabolite level of 2-OH atorvastatin acid <0.014 nmol/L provided the optimal cut-off for non-adherence. CONCLUSION: A direct method to discriminate among adherence, partial adherence and non-adherence to atorvastatin therapy in patients with coronary heart disease has been developed. This tool may be important for novel studies on adherence and potentially useful in clinical practice.

[12] *Ruyter B, Sissener NH, Ostbye TK et al.* **Omega-3 canola oil effectively replaces fish oil as a new safe dietary source of docosahexaenoic acid (DHA) in feed for juvenile Atlantic salmon**. The British journal of nutrition 2019:1-43.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31506120
ABSTRACT
Limited availability of fish oils (FO), rich in omega-3 long-chain (>/=C20) polyunsaturated fatty acids (FA), is a major constraint for further growth of the aquaculture industry. Long-chain omega-3 rich oils from crops genetically modified with algal genes are promising new sources for the industry. This project studied the use of a newly developed omega-3 canola oil (DHA-CA) in diets of Atlantic salmon fingerlings in freshwater. The DHA-CA oil has high proportions of the omega-3 FA 18:3n-3 and DHA and lower proportions of omega-6 FA than conventional plant oils. Levels of phytosterols, vitamin E, and minerals in the DHA-CA were within the natural variation of commercial canola oils. Pesticides, mycotoxins, polyaromatic hydrocarbons, and heavy metals were below lowest qualifiable concentration. Two feeding trials were conducted to evaluate effects of two dietary levels of DHA-CA compared to two dietary levels of FO at two water temperatures. Fish increased their weight approximately 20-fold at 16 degrees C and 12-fold at 12 degrees C during the experimental periods, with equal growth in salmon fed the FO diets compared to DHA-CA diets. Salmon fed DHA-CA diets had approximately the same EPA+DHA content in whole body as salmon fed FO diets. Gene expression, lipid composition, and oxidative stress related enzyme activities showed only minor differences between the dietary groups and the effects were mostly a result of dietary oil level, rather than the oil source. The results demonstrated that DHA-CA is a safe and effective replacement for FO in diets of Atlantic salmon during the sensitive fingerling life-stage.

[13] *Sriranjan RS, Tarkin JM, Evans NR et al.* **Atherosclerosis Imaging Using Positron Emission Tomography (PET): Insights and Applications**. Br J Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31517992

ABSTRACT
Positron emission tomography (PET) imaging is able to harness biological processes to characterise high-risk features of atherosclerotic plaque prone to rupture. Current radiotracers are able to track inflammation, microcalcification, hypoxia and neoangiogenesis within vulnerable plaque. (18) F-fluorodeoxyglucose ((18) F-FDG) is the most commonly used radiotracer in vascular studies and is employed as a surrogate marker of plaque inflammation. Increasingly, (18) F-FDG and other PET tracers are also being used to provide imaging endpoints in cardiovascular interventional trials. The evolution of novel PET radiotracers, imaging protocols and hybrid scanners are likely to enable more efficient and accurate characterisation of high-risk plaque. This review explores the role of PET imaging in atherosclerosis with a focus on PET tracers utilised in clinical research and the applications of PET imaging to cardiovascular drug development.

[14] *Syed MB, Fletcher AJ, Forsythe RO et al.* **Emerging techniques in atherosclerosis imaging**. Br J Radiol 2019:20180309.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31502858
ABSTRACT
Atherosclerosis is a chronic immunomodulated disease that affects multiple vascular beds and results in a significant worldwide disease burden. Conventional imaging modalities focus on the morphological features of atherosclerotic disease such as the degree of stenosis caused by a lesion. Modern CT, MR and positron emission tomography scanners have seen significant improvements in the rapidity of image acquisition and spatial resolution. This has increased the scope for the clinical application of these modalities. Multimodality imaging can improve cardiovascular risk prediction by informing on the constituency and metabolic processes within the vessel wall. Specific disease processes can be targeted using novel biological tracers and "smart" contrast agents. These approaches have the potential to inform clinicians of the metabolic state of atherosclerotic plaque. This review will provide an overview of current imaging techniques for the imaging of atherosclerosis and how various modalities can provide information that enhances the depiction of basic morphology.

[15] *Ihara M, Saito S*. **[Drug Repositioning for Alzheimer's Disease]**. Brain and nerve = Shinkei kenkyu no shinpo 2019; 71:961-970.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31506398
ABSTRACT
To date, all clinical trials of disease-modifying drugs for Alzheimer's disease (AD) have been unsuccessful, making investments into AD drug development very risky despite the high unmet need. Drug repositioning or repurposing approaches are relatively less expensive and more promising compared to novel drug development in AD. About 40% of clinical trials for AD currently in progress across the world use the drug repositioning method. They are expected to be a trigger for AD drug discovery that breaks the current deadlock situation. By using drugs approved for other indications, these clinical trials target dysregulated pathways of AD with different or a combination of modes of action, including anti-amyloid, anti-tau, anti-inflammatory, metabolic, neuroprotective, and neurotransmission-based approaches. In these clinical trials, cardiovascular drugs such as insulin, cilostazol, probucol, telmisartan, and

dabigatran are tested for their effect on different mechanisms of AD pathology. This is in line with the recent emphasis that AD should be studied as a complex multifactorial disorder, not dominated by one dominant biological factor such as beta-amyloid, and without disregarding any relevant pathologic factor, such as vascular dysregulation. It is strongly expected that drug repositioning approaches will create a paradigm shift in treatment approaches for AD patients.

[16] *Blom DJ, Breedt J, Burgess LJ et al.* **Long-term safety and efficacy of alirocumab in South African patients with heterozygous familial hypercholesterolaemia: the ODYSSEY Open-Label Extension study**. Cardiovasc J Afr 2019; 30:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31512717
ABSTRACT
BACKGROUND: Alirocumab reduces low-density lipoprotein cholesterol (LDL-C) levels by up to 61%. The ODYSSEY Open-Label Extension study investigated the effect of alirocumab in patients with heterozygous familial hypercholesterolaemia (HeFH) over 144 weeks. METHODS: Eligible patients with HeFH had completed an earlier double-blind, randomised, placebo-controlled parent study. Patients were initiated on 75 mg alirocumab Q2W subcutaneous (SC) unless baseline LDL-C was > 8.9 mmol/l, in which case they received 150 mg alirocumab Q2W. Dose titration to 150 mg Q2W was at the investigator's discretion. RESULTS: The study enrolled 167 patients and the parent study mean (+/- SD) baseline LDL-C level was 3.65 +/- 1.9 mmol/l. Mean LDL-C level was reduced by 48.7% at week 144; mean on-treatment LDL-C was 2.30 +/- 1.24 mmol/l. Eight patients reported injection-site reactions, with one treatment discontinuation. Treatment emergent anti-drug antibodies were identified in five patients but these did not affect the efficacy. CONCLUSIONS: Alirocumab effectively and safely reduced LDL-C in these patients.

[17] *Newman JL, Stone JR*. **Immune checkpoint inhibition alters the inflammatory cell composition of human coronary artery atherosclerosis**. Cardiovasc Pathol 2019; 43:107148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31518915
ABSTRACT
BACKGROUND: Immune checkpoint inhibition (ICI) has emerged as a promising new approach to treat malignancy. Such therapies can result in autoimmune-related complications such as myocarditis and hepatitis. The impact of ICI on sites of preexisting chronic inflammation has been less clear. Atherosclerosis is a chronic vascular disease with a significant inflammatory component. METHODS: To determine the effect of ICI on the inflammatory infiltrate in coronary artery atherosclerotic plaques, 11 patients who had recently been treated with ICI and subsequently underwent autopsy were matched with 11 cancer patients who had not received ICI treatment. The amount of CD3(+) T-lymphocytes, CD8(+) cytotoxic T-lymphocytes, and CD68(+) macrophages and the ratios of the various cell types in the coronary artery atherosclerotic plaques were compared. RESULTS: There was no significant difference in the absolute numbers of CD3(+), CD8(+), or CD68(+) cells in the atherosclerotic plaques. In the plaques of the ICI-treated patients, there was a significant increase in the ratio of CD3(+) cells to CD68(+) cells (CD3/CD68) (P=.002) and a trend towards an increased CD8/CD68 ratio. The increased CD3/CD68 ratio in the ICI-treated patients resulted in 6 of the 11 patients having lymphocyte-predominate inflammation in contrast to the macrophage-predominate

inflammation typically found in atherosclerotic plaques. CONCLUSIONS: These findings indicate that ICI alters the inflammatory composition of human atherosclerotic plaque and, thus, may influence plaque progression and/or clinical coronary events. SUMMARY: In cancer patients, treatment with immune checkpoint inhibition is associated with an altered inflammatory cell composition in coronary artery atherosclerotic plaques with an increased ratio of CD3(+) T cells to CD68(+) macrophages. Thus, immune checkpoint inhibition may influence plaque progression and/or clinical coronary events.

[18] *Hoogendoorn A, Kok AM, Hartman EMJ et al.* **Multidirectional wall shear stress promotes advanced coronary plaque development - comparing five shear stress metrics**. Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31504238
ABSTRACT
AIMS: Atherosclerotic plaque development has been associated with wall shear stress (WSS). However, the multidirectionality of blood flow, and thus of WSS, is rarely taken into account. The purpose of this study was to comprehensively compare five metrics that describe (multidirectional) WSS behaviour and assess how WSS multidirectionality affects coronary plaque initiation and progression. METHODS AND RESULTS: Adult familial hypercholesterolemic pigs (n = 10) that were fed a high-fat diet, underwent imaging of the three main coronary arteries at three time points (3 (T1), 9 (T2) and 10-12 (T3) months). A 3D-geometry of the arterial lumen, in combination with local flow velocity measurements, was used to calculate WSS at T1 and T2. For analysis, arteries were divided into 3mm/45 degrees sectors (n = 3648). Changes in wall thickness, and final plaque composition were assessed with near-infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) and optical coherence tomography (OCT) imaging, and histology. Both in pigs with advanced and mild disease, the highest plaque progression rate was exclusively found at low TAWSS or high multidirectional WSS regions at both T1 and T2. However, the eventually largest plaque growth was located in regions with initial low time-averaged WSS or high multidirectional WSS, that, over time, became exposed to high time-averaged WSS or low multidirectional WSS at T2. Besides plaque size, also the presence of vulnerable plaque components at the last time point was related to low and multidirectional WSS. Almost all WSS metrics had good predictive values for the development of plaque (47-50%), and for advanced fibrous cap atheroma development (59-61%). CONCLUSIONS: This study demonstrates that low and multidirectional WSS promote both initiation and progression of coronary atherosclerotic plaques. The high predictive values of the multidirectional WSS metrics for fibrous cap atheroma development indicate their potential as an additional clinical marker for vulnerable disease. TRANSLATIONAL PERSPECTIVE: Wall shear stress (WSS) plays a key role in coronary atherosclerotic plaque development and destabilization. However, the multidirectionality of WSS is rarely taken into account. In this pre-clinical study, we demonstrated that both plaque initiation and progression were related to low and multidirectional WSS. Therefore, regions exposed to low and/or multidirectional WSS regions throughout disease development, continue to be at risk for further plaque progression. The high predictive values of almost all multidirectional WSS metrics for plaque progression and advanced plaque composition demonstrated the potential of multidirectional WSS as an additional predictive clinical marker for vulnerable disease.

[19] *Kelly L, Matsumoto CL, Schreiber Y et al.* **Prevalence of chronic kidney disease and cardiovascular comorbidities in adults in First Nations communities in northwest Ontario: a retrospective observational study**. CMAJ open 2019; 7:E568-e572.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31501170

ABSTRACT

BACKGROUND: The prevalence of adult chronic kidney disease and cardiovascular comorbidities in Canadian Indigenous communities is largely unknown. We conducted a study to document the prevalence of chronic kidney disease and concurrent diabetes mellitus, hypertension and dyslipidemia in a First Nations population in northwest Ontario. METHODS: In this observational study, we used retrospective data collected from regional electronic medical records of 16 170 adults (age >/= 18 yr) from 26 First Nations communities in northwest Ontario from May 2014 to May 2017. Demographic and laboratory data included age, gender, prescribed medications, estimated glomerular filtration rate, urine albumin:creatinine ratio, low-density lipoprotein cholesterol (LDL-C) level and glycated hemoglobin (HbA1c) concentration. We identified patients with diabetes by an HbA1c concentration of 6.5% or higher, or the use of a diabetic medication, those with dyslipidemia by an elevated LDL-C level (>/= 2.0 mmol/L) or use of lipid-lowering medication, and those with hypertension by use of antihypertensive medication. RESULTS: Of the 16 170 adults residing in the communities, 5224 unique patients (32.3%) had renal testing (albumin:creatinine ratio and/or estimated glomerular filtration rate). The age-adjusted prevalence of chronic kidney disease was 14.5%, and the prevalence of stage 3-5 chronic kidney disease (estimated glomerular filtration rate < 60 mL/min) was 7.0%. Most patients with chronic kidney disease (1487 [80.0%]) had at least 1 cardiovascular comorbidity. A total of 1332 patients (71.6%) had diabetes, 1313 (70.6%) had dyslipidemia, and 1098 (59.1%) had hypertension; all 3 comorbidities were present in 716 patients (38.5%). INTERPRETATION: We document a high prevalence of advanced chronic kidney disease in this First Nations population, 7.0%, double the rate in the general population. High rates of cardiovascular comorbidities were also common in these patients with chronic kidney disease, which places them at increased risk for cardiovascular disease.

[20] *Choi HR, Lee JH, Lee HK et al.* **Association Between Dyslipidemia and Dry Eye Syndrome Among the Korean Middle-Aged Population**. Cornea 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31517720

ABSTRACT

PURPOSE: Dry eye syndrome (DES) is a common eye disease caused by tear deficiency or excessive tear evaporation. Because the tear film layers play a major role in the pathogenesis of the evaporative dry eye, some previous articles have suggested the possible mechanism of dyslipidemia and DES. However, the previous results were inconsistent and few studies were conducted to find the independent relationship between dyslipidemia and DES. Therefore, we investigated the association of dyslipidemia with DES in middle-aged Korean adults. METHODS: This study was conducted on 2272 participants (854 men and 1418 women) enrolled in the Study Group for Environmental Eye Disease (2013-2017) after excluding people who have taken lipid-lowering medication. Participants with total cholesterol >/=240 mg/dL or high-density lipoprotein cholesterol <40 mg/dL or low-density lipoprotein cholesterol >/=160 mg/dL or

triglycerides >/=200 mg/dL are defined as having dyslipidemia. Using the ocular surface disease index, we measured the DES severity and defined DES as an ocular surface disease index score >/=13. RESULTS: Men with dyslipidemia had an odds ratio of 1.29 (95% confidence interval, 0.97-1.71) for DES in an unadjusted model compared with those without DES. After adjusting for age, body mass index, hypertension, diabetes, occupations, smoking and drinking status, exercise, contact lens use, computer use, study cohorts, and calendar year of examinations, the adjusted odds ratio for DES was 1.40 (1.03-1.90) in men. However, there was no significant association between dyslipidemia and DES in women, even after stratifying by menopausal status. CONCLUSIONS: Our findings suggest that dyslipidemia may be associated with the prevalence of DES in Korean men, but not in women.

[21] *Segar MW, Vaduganathan M, Patel KV et al.* **Machine Learning to Predict the Risk of Incident Heart Failure Hospitalization Among Patients With Diabetes: The WATCH-DM Risk Score**. Diabetes Care 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31519694
ABSTRACT
OBJECTIVE: To develop and validate a novel, machine learning-derived model to predict the risk of heart failure (HF) among patients with type 2 diabetes mellitus (T2DM). RESEARCH DESIGN AND METHODS: Using data from 8,756 patients free at baseline of HF, with <10% missing data, and enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, we used random survival forest (RSF) methods, a nonparametric decision tree machine learning approach, to identify predictors of incident HF. The RSF model was externally validated in a cohort of individuals with T2DM using the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). RESULTS: Over a median follow-up of 4.9 years, 319 patients (3.6%) developed incident HF. The RSF models demonstrated better discrimination than the best performing Cox-based method (C-index 0.77 [95% CI 0.75-0.80] vs. 0.73 [0.70-0.76] respectively) and had acceptable calibration (Hosmer-Lemeshow statistic chi(2) = 9.63, P = 0.29) in the internal validation data set. From the identified predictors, an integer-based risk score for 5-year HF incidence was created: the WATCH-DM (Weight [BMI], Age, hyperTension, Creatinine, HDL-C, Diabetes control [fasting plasma glucose], QRS Duration, MI, and CABG) risk score. Each 1-unit increment in the risk score was associated with a 24% higher relative risk of HF within 5 years. The cumulative 5-year incidence of HF increased in a graded fashion from 1.1% in quintile 1 (WATCH-DM score </=7) to 17.4% in quintile 5 (WATCH-DM score >/=14). In the external validation cohort, the RSF-based risk prediction model and the WATCH-DM risk score performed well with good discrimination (C-index = 0.74 and 0.70, respectively), acceptable calibration (P >/=0.20 for both), and broad risk stratification (5-year HF risk range from 2.5 to 18.7% across quintiles 1-5). CONCLUSIONS: We developed and validated a novel, machine learning-derived risk score that integrates readily available clinical, laboratory, and electrocardiographic variables to predict the risk of HF among outpatients with T2DM.

[22] *Emelyanova L, Sra A, Schmuck EG et al.* **Impact of statins on cellular respiration and de-differentiation of myofibroblasts in human failing hearts**. ESC heart failure 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31520523
ABSTRACT

AIMS: Fibroblast to myofibroblast trans-differentiation with altered bioenergetics precedes cardiac fibrosis (CF). Either prevention of differentiation or promotion of de-differentiation could mitigate CF-related pathologies. We determined whether 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors-statins, commonly prescribed to patients at risk of heart failure (HF)-can de-differentiate myofibroblasts, alter cellular bioenergetics, and impact the human ventricular fibroblasts (hVFs) in HF patients. METHODS AND RESULTS: Either in vitro statin treatment of differentiated myofibroblasts (n = 3-6) or hVFs, isolated from human HF patients under statin therapy (HF + statin) vs. without statins (HF) were randomly used (n = 4-12). In vitro, hVFs were differentiated by transforming growth factor-beta1 (TGF-beta1) for 72 h (TGF-72 h). Differentiation status and cellular oxygen consumption rate (OCR) were determined by alpha-smooth muscle actin (alpha-SMA) expression and Seahorse assay, respectively. Data are mean +/- SEM except Seahorse (mean +/- SD); $P < 0.05$, considered significant. In vitro, statins concentration-dependently de-differentiated the myofibroblasts. The respective half-maximal effective concentrations were 729 +/- 13 nmol/L (atorvastatin), 3.6 +/- 1 mumol/L (rosuvastatin), and 185 +/- 13 nmol/L (simvastatin). Mevalonic acid (300 mumol/L), the reduced product of HMG-CoA, prevented the statin-induced de-differentiation (alpha-SMA expression: 31.4 +/- 10% vs. 58.6 +/- 12%). Geranylgeranyl pyrophosphate (GGPP, 20 mumol/L), a cholesterol synthesis-independent HMG-CoA reductase pathway intermediate, completely prevented the statin-induced de-differentiation (alpha-SMA/GAPDH ratios: 0.89 +/- 0.05 [TGF-72 h + 72 h], 0.63 +/- 0.02 [TGF-72 h + simvastatin], and 1.2 +/- 0.08 [TGF-72 h + simvastatin + GGPP]). Cellular metabolism involvement was observed when co-incubation of simvastatin (200 nmol/L) with glibenclamide (10 mumol/L), a KATP channel inhibitor, attenuated the simvastatin-induced de-differentiation (0.84 +/- 0.05). Direct inhibition of mitochondrial respiration by oligomycin (1 ng/mL) also produced a de-differentiation effect (0.33 +/- 0.02). OCR (pmol O2 /min/mug protein) was significantly decreased in the simvastatin-treated hVFs, including basal ($P = 0.002$), ATP-linked ($P = 0.01$), proton leak-linked ($P = 0.01$), and maximal ($P < 0.001$). The OCR inhibition was prevented by GGPP (basal OCR [$P = 0.02$], spare capacity OCR [$P = 0.008$], and maximal OCR [$P = 0.003$]). Congruently, hVFs from HF showed an increased population of myofibroblasts while HF + statin group showed significantly reduced cellular respiration (basal OCR [$P = 0.021$], ATP-linked OCR [$P = 0.047$], maximal OCR [$P = 0.02$], and spare capacity OCR [$P = 0.025$]) and myofibroblast differentiation (alpha-SMA/GAPDH: 1 +/- 0.19 vs. 0.23 +/- 0.06, $P = 0.01$). CONCLUSIONS: This study demonstrates the de-differentiating effect of statins, the underlying GGPP sensitivity, reduced OCR with potential activation of KATP channels, and their impact on the differentiation magnitude of hVFs in HF patients. This novel pleiotropic effect of statins may be exploited to reduce excessive CF in patients at risk of HF.

[23] *Knuuti J, Wijns W, Saraste A et al.* **2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31504439
ABSTRACT

[24] *Luscher TF*. **Frontiers in lipid research: lipoprotein(a), apolipoprotein C-III and E, and PCSK9 and inflammation**. European heart journal 2019; 40:2741-2744.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31505607

Literature update week 37 (2019)

ABSTRACT

[25] *Patel BM, Goyal RK*. **Liver and insulin resistance: New wine in old bottle!!!** European journal of pharmacology 2019; 862:172657.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31499040
ABSTRACT
Hepatic and systemic insulin resistance form the core of metabolic syndrome which is also associated with cardiovascular abnormalities, inflammation, and dyslipidemia. Skeletal muscles and adipose tissues are two main target organs for glucose disposal and hence have been studied for insulin resistance too. The liver is the first organ where insulin reaches after being secreted from pancreas and liver regulates glucose storage and disposal as per the body's demand in response to insulin. There are multiple mechanisms, which regulate hepatic insulin signaling and liver is now emerging as an important target involving several intracellular players. In the current review, we would like to put forward the data and facts deploying liver and its action on lipid regulation and insulin resistance. The liver is known as organ mediating insulin resistance (old bottle) but with advanced research and understanding of detailed and novel mechanisms (new wine), future research can be directed towards developing target-specific agents.

[26] *Bacquer D, Smedt D, Reiner Z et al.* **Percentage low-density lipoprotein-cholesterol response to a given statin dose is not fixed across the pre-treatment range: Real world evidence from clinical practice: Data from the ESC-EORP EUROASPIRE V Study**. European journal of preventive cardiology 2019:2047487319874898.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31500460
ABSTRACT
AIMS: Recent European guidelines recommend in patients with atherosclerotic cardiovascular disease to achieve a reduction of low-density lipoprotein-cholesterol of at least 50% if the baseline low-density lipoprotein-cholesterol level is between 1.8 and 3.5 mmol/L. Systematic reviews have associated a given statin/dose combination with a fixed percentage low-density lipoprotein-cholesterol response. Algorithms for detecting cases and estimating the prevalence of familial hypercholesterolaemia often rely on such fixed percentage reductions. METHODS AND RESULTS: We used data from 915 coronary patients participating in the EUROASPIRE V study in whom atorvastatin or rosuvastatin therapy was initiated at hospital discharge and who were still using these drugs at the same dose at a follow-up visit 6 or more months later. Pre and on-treatment low-density lipoprotein-cholesterol levels were compared across the full low-density lipoprotein-cholesterol range. The prevalence of FH was estimated using the Dutch Lipid Clinic Network criteria, once using observed pre-treatment low-density lipoprotein-cholesterol and once using imputed pre-treatment low-density lipoprotein-cholesterol by following the common strategy of applying fixed correction factors to on-treatment low-density lipoprotein-cholesterol. Inter-individual variation in the low-density lipoprotein-cholesterol response to a fixed statin and dose was considerable, with a strong inverse relation of percentage reductions to pre-treatment low-density lipoprotein-cholesterol. The percentage low-density lipoprotein-cholesterol response was markedly lower at the left end of the pre-treatment low-density lipoprotein-cholesterol range especially for levels less than 3 mmol/L.

The estimated prevalence of familial hypercholesterolaemia was 2% if using observed pre-treatment low-density lipoprotein-cholesterol and 10% when using imputed low-density lipoprotein-cholesterol. CONCLUSION: The inter-individual variation in the percentage low-density lipoprotein-cholesterol response to a given dose of a statin is largely dependent on the pre-treatment level: the lower the pre-treatment low-density lipoprotein-cholesterol level the smaller the percentage low-density lipoprotein-cholesterol reduction. The use of uniform correction factors to estimate pre-treatment low-density lipoprotein-cholesterol is not justified.

[27] *Gutierrez MDM, Mateo MG, Corbacho N et al.* **Drug-drug interactions when treating HIV-related metabolic disorders**. Expert opinion on drug metabolism & toxicology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31512529
ABSTRACT
Introduction: Drug-drug interactions (DDI) between antiretroviral drugs and drugs for the treatment of metabolic disturbances in people living with human immunodeficiency virus (HIV) (PLWH) have represented a problem of paramount importance in the recent times. The problem has been mainly driven by sharing common metabolizing pathways. This problem has classically been worsened by the frequent use of pharmacokinetic boosters to enhance protease inhibitors and some integrase inhibitors plasma levels. These boosters block the metabolizing routes of many antiretroviral drugs. Areas covered: This article focuses on the interactions between antiretroviral drugs and those drugs used to treat metabolic disturbances which frequently appear in people living with human immunodeficiency virus (PLWH). These include drugs for the treatment of dyslipidemia, insulin resistance, and diabetes mellitus, hyperuricemia, and finally, drugs for the treatment of overweight and clinical obesity. To this end, references from PubMed, Embase, or Web of Science, among others, were reviewed. Expert opinion: The advent of safer drugs, in terms of DDI, in the antiretroviral and the metabolic field, has been due to the increased use of non-boosted antiretrovirals and to the use of drugs with divergent metabolizing paths. Besides, learning by the caregivers on how to decrease the potential for DDI and how to manage interactions once they appear, together with the extensive use of online updated DDI databases, has undoubtedly minimized the problem. The foreseeable increase in the burden of HIV-associated comorbidities and their associated treatments anticipates further complexities in the management of DDI in PLWH.

[28] *Alkhouri N, Lawitz E, Noureddin M et al.* **GS-0976 (Firsocostat): an investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH)**. Expert opinion on investigational drugs 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31519114
ABSTRACT
Introduction: De novo lipogenesis (DNL) plays a major role in fatty acid metabolism and contributes significantly to triglyceride accumulation within the hepatocytes in patients with nonalcoholic steatohepatitis (NASH). Acetyl-CoA carboxylase (ACC) converts acetyl-CoA to malonyl CoA, and is a rate-controlling step in DNL. Furthermore, malonyl-CoA is an important regulator of hepatic mitochondrial fat oxidation through its ability to inhibit carnitine palmitoyltransferase I. Therefore, inhibiting ACC pharmacologically represents an attractive approach to treating NASH. Areas Covered: This article summarizes preclinical and clinical data

on the efficacy and safety of the liver targeted ACC inhibitor GS-0976 (Firsocostat) for the treatment of NASH. In a phase 2 trial that included 126 patients with NASH and fibrosis, GS-0976 20 mg daily for 12 weeks showed significant relative reduction in liver fat by 29%; however, treatment was associated with an increase in plasma triglycerides with 16 patients having levels > 500 mg/dL. Expert Opinion: Preclinical and preliminary clinical data support the development of GS-0976 as treatment for NASH. ACC-induced hypertriglyceridemia can be mitigated by fish oil or fibrates, but the long-term cardiovascular effects require further investigations.

[29] *Sudun, Liu S, Xiao C et al.* **Probiotic strains improve high-fat diet-induced hypercholesterolemia through modulating gut microbiota in ways different from atorvastatin**. Food & function 2019; 10:6098-6109.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31495848
ABSTRACT
Hypercholesterolemia is a major risk factor for cardiovascular disease (CVD). Probiotics are one of the most popular dietary supplements for hypercholesterolemia, but there are questions as to whether there are differences between probiotics and cholesterol-lowering drugs like atorvastatin (ATO) both in effectiveness and in the underlying mechanisms. In this study, the hypocholesterolemia effects of 4 probiotic strains were investigated and compared with ATO, focusing on their impacts on the gut microbiota. A hypercholesterolemia model was established via high-fat diet (HFD) in golden hamsters after which ATO and the 4 probiotics were orally administered individually for 8 weeks. All probiotics were effective, but less than ATO, on body weight, serum parameters (TG, TC, LDL, INS, HbA1c) and expression of inflammatory factors (INF-alpha, IL-1beta, CRP), with strain JQII-5 being most significant. Besides, these effects were associated with restoration of microbiota dysbiosis induced by HFD. It was worth noting that ATO and probiotics induced different shifts of the gut microbiota in both structure and key phylotypes. Most interestingly, Allobaculum, a HFD-suppressed genus, reported to be involved in alleviating oxidative stress, was enriched by all tested probiotic strains, but not by ATO. Furthermore, Prevotella, also a HFD-suppressed genus, was uniquely reversed by JQII-5. Importantly, most of the alerted genera and reversed genera were found to be correlated with the inflammatory state and serum lipid level. Compared with ATO, the probiotic strains were less effective on body weight, hypercholesterolemia, and inflammation. However, probiotics exert additional favorable effects on the gut microbiota, making them excellent potential complements to cholesterol-lowering drugs like ATO.

[30] *Sokolowska E, Blachnio-Zabielska A*. **The Role of Ceramides in Insulin Resistance**. Frontiers in endocrinology 2019; 10:577.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31496996
ABSTRACT
Resistance to insulin is a pathophysiological state related to the decreased response of peripheral tissues to the insulin action, hyperinsulinemia and raised blood glucose levels caused by increased hepatic glucose outflow. All the above precede the onset of full-blown type 2 diabetes. According to the World Health Organization (WHO), in 2016 more than 1.9 billion people over 18 years of age were overweight and about 600 million were obese. Currently, the

primary hypothesis explaining the probability of occurrence of insulin resistance assigns a fundamental role of lipids accumulation in adipocytes or nonadipose tissue (muscle, liver) and the locally developing chronic inflammation caused by adipocytes hypertrophy. However, the major molecular pathways are unknown. The sphingolipid ceramide is the main culprit that combines a plethora of nutrients (e.g., saturated fatty acids) and inflammatory cytokines (e.g., TNFalpha) to the progression of insulin resistance. The accumulation of sphingolipid ceramide in tissues of obese humans, rodents and Western-diet non-human primates is in line with diabetes, hypertension, cardiac failure or atherosclerosis. In hypertrophied adipose tissue, after adipocytes excel their storage capacity, neutral lipids begin to accumulate in nonadipose tissues, inducing organ dysfunction. Furthermore, obesity is closely related to the development of chronic inflammation and the release of cytokines directly from adipocytes or from macrophages that infiltrate adipose tissue. Enzymes taking part in ceramide metabolism are potential therapeutic targets to manipulate sphingolipids content in tissues, either by inhibition of their synthesis or through stimulation of ceramides degradation. In this review, we will evaluate the mechanisms responsible for the development of insulin resistance and possible therapeutic perspectives.

[31] *Milionis H, Ntaios G, Korompoki E et al.* **Statin-based therapy for primary and secondary prevention of ischemic stroke: A meta-analysis and critical overview**. Int J Stroke 2019:1747493019873594.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31496436
ABSTRACT
BACKGROUND AND AIMS: To reassess the effect of statin-based lipid-lowering therapy on ischemic stroke in primary and secondary prevention trials with regard to achieved levels of low-density lipoprotein-cholesterol in view of the availability of novel potent hypolipidemic agents. METHODS: English literature was searched (up to November 2018) for publications restricted to trials with a minimum enrolment of 1000 and 500 subjects for primary and secondary prevention, respectively, meeting the following criteria: adult population, randomized controlled design, and recorded outcome data on ischemic stroke events. Data were meta-analyzed and curve-estimation procedure was applied to estimate regression statistics and produce related plots. RESULTS: Four primary prevention trials and four secondary prevention trials fulfilled the eligibility criteria. Lipid-lowering therapy was associated with a lower risk of ischemic stroke in primary (risk ratio, RR 0.70, 95% confidence interval, CI, 0.60-0.82; $p < 0.001$) and in the secondary prevention setting (RR 0.80, 95% CI 0.70-0.90; $p < 0.001$). Curve-estimation procedure revealed a linear relationship between the absolute risk reduction of ischemic stroke and active treatment-achieved low-density lipoprotein-cholesterol levels in secondary prevention (adjusted R-square 0.90) in support of "the lower the better" hypothesis for stroke survivors. On the other hand, the cubic model followed the observed data well in primary prevention (adjusted R-square 0.98), indicating greater absolute risk reduction in high-risk cardiovascular disease-free individuals. CONCLUSIONS: Statin-based lipid-lowering is effective both for primary and secondary prevention of ischemic stroke. Most benefit derives from targeting disease-free individuals at high cardiovascular risk, and by achieving low treatment targets for low-density lipoprotein-cholesterol in stroke survivors.

[32] *Sivashanmugarajah A, Fulcher J, Sullivan D et al.* **Suggested clinical approach for the diagnosis and management of 'statin intolerance' with an emphasis on muscle-related side-effects**. Internal medicine journal 2019; 49:1081-1091.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31507054
ABSTRACT
Hyperlipidaemia is a major risk factor for cardiovascular morbidity and mortality. 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors ('statins') are first-line therapies for hyperlipidaemia. For each 1.0 mmoL/L reduction in low-density lipoprotein (LDL)-cholesterol, statins reduce the risk of major vascular events by 21% and all-cause mortality by 9%. Owing to their clinical effectiveness and excellent safety profile, many Australians are prescribed statins. There has been widespread reporting of possible side-effects, particularly muscle pains. Conversely, statin cessation relating to possible side-effects exposes patients to increased risk of vascular events and death. Although there is clinical consensus for diagnosing rare side-effects (e.g. myopathy or rhabdomyolysis), confirming that statins cause other less common side-effects (e.g. memory impairment) is difficult as strong randomised trial evidence related to statins and non-muscle-related side-effects is lacking. A stepwise approach to possible statin intolerance, consistent definitions and a simple flowchart may improve diagnosis and management. An increasing array of potential treatments is emerging, including intermittent statin dosing, new LDL-lowering drugs, LDL apheresis and supplements. Optimal statin use and management of statin intolerance should improve cardiovascular care and clinical outcomes.

[33] *Adawi M, Firas S, Blum A*. **Rheumatoid Arthritis and Atherosclerosis**. The Israel Medical Association journal : IMAJ 2019; 21:460-463.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31507121
ABSTRACT
BACKGROUND: Inflammation is the basic mechanism leading to many pathological processes, including degenerative diseases, atherosclerosis, and cancer. We found an interesting link connecting rheumatoid arthritis and atherosclerosis that may explain the high cardiovascular event rate among patients with rheumatoid arthritis, but also may lead to a new way of thinking and a better understanding of atherosclerosis. Rheumatoid arthritis could serve as a model of accelerated atherosclerosis. Understanding the basic mechanisms of rheumatoid arthritis may solve some of the complexity of atherosclerosis.

[34] *Hackler E, 3rd, Lew J, Gore MO et al.* **Racial Differences in Cardiovascular Biomarkers in the General Population**. Journal of the American Heart Association 2019; 8:e012729.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31514563
ABSTRACT
Background The incidence and clinical manifestations of cardiovascular disease (CVD) differ between blacks and whites. Biomarkers that reflect important pathophysiological pathways may provide a window to allow deeper understanding of racial differences in CVD. Methods and Results The study included 2635 white and black participants from the Dallas Heart Study who were free from existing CVD. Cross-sectional associations between race and 32 biomarkers were evaluated using multivariable linear regression adjusting for age, traditional CVD risk factors, imaging measures of body composition, renal function, insulin resistance, left

ventricular mass, and socioeconomic factors. In fully adjusted models, black women had higher lipoprotein(a), leptin, d-dimer, osteoprotegerin, antinuclear antibody, homoarginine, suppression of tumorigenicity-2, and urinary microalbumin, and lower adiponectin, soluble receptor for advanced glycation end products and N-terminal pro-B-type natriuretic peptide versus white women. Black men had higher lipoprotein(a), leptin, d-dimer, high-sensitivity C-reactive protein, antinuclear antibody, symmetrical dimethylarginine, homoarginine, high-sensitivity cardiac troponin T, suppression of tumorigenicity-2, and lower adiponectin, soluble receptor for advanced glycation end products, and N-terminal pro-B-type natriuretic peptide versus white men. Adjustment for biomarkers that were associated with higher CVD risk, and that differed between blacks and whites, attenuated the risk for CVD events in black women (unadjusted hazard ratio 2.05, 95% CI 1.32, 3.17 and adjusted hazard ratio 1.15, 95% CI 0.69, 1.92) and black men (unadjusted hazard ratio 2.39, 95% CI 1.64, 3.46, and adjusted hazard ratio 1.21, 95% CI 0.76, 1.95). Conclusions Significant racial differences were seen in biomarkers reflecting lipids, adipokines, and biomarkers of endothelial function, inflammation, myocyte injury, and neurohormonal stress, which may contribute to racial differences in the development and complications of CVD.

[35] *Nakamura T, Uematsu M, Yoshizaki T et al.* **Improvement of endothelial dysfunction is mediated through reduction of remnant lipoprotein after statin therapy in patients with coronary artery disease**. J Cardiol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31500961
ABSTRACT
BACKGROUND: Remnant lipoproteinemia with high levels of low-density lipoprotein cholesterol (LDL-C) is a high risk for endothelial dysfunction. Statins are the first-line lipid-lowering drugs for this combined hyperlipidemia. However, it remains undetermined whether reduction of remnant lipoprotein mediates the relationship between improvement in endothelial dysfunction and reduction of LDL-C level after statin treatment. METHODS: A total of 122 coronary artery disease (CAD) patients with impaired flow-mediated dilation (FMD; <5.5%), high levels of LDL-C (>/=100mg/dL), and remnant-like lipoprotein particle cholesterol (RLP-C) (>/=5mg/dL) were examined in this study. The lipid profiles and FMD were measured before and after 6-9 months of statin treatment. The association between changes in LDL-C levels and its relationship with changes in FMD was investigated. Furthermore, mediation analysis was performed to assess the changes in RLP-C level as a mediator of the relationship between the reduction in LDL-C level and improvement of FMD. RESULTS: Treatment with statins improved FMD in 69 (56.5%) patients. Patients with improved FMD showed lower percent changes of LDL-C, triglyceride (TG), RLP-C, RLP-C/TG, and C-reactive protein (CRP) levels, and higher percent change of HDL-C level, compared to patients who did not show improved FMD. The percent changes in FMD levels had a significant inverse correlation with the percent changes in LDL-C, (r=-0.18, p= 0.03), RLP-C (r=-0.39, p<0.001), RLP-C/TG (r=-0.34, p<0.001), and CRP (r=-0.27, p<0.01). Mediation analysis showed that the relationship between reduction in LDL-C and improvement of FMD was mediated by reduction of RLP-C (34.5%), RLP-C/TG (24.4%), and CRP (24.9%) levels. CONCLUSION: Improvement of remnant lipoproteinemia may be an important mediator for the relationship between improvement of endothelial dysfunction and LDL-lowering after statin treatment in patients with CAD.

[36] *Yano H, Horinaka S, Ishimitsu T*. **Effect of evolocumab therapy on coronary fibrous cap thickness assessed by optical coherence tomography in patients with acute coronary syndrome**. J Cardiol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31495548
ABSTRACT
BACKGROUND: The addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab, to statin therapy produced incremental regression of atherosclerotic plaques and a collaborative prevention of cardiovascular events in patients with coronary artery disease. The effect on fibrous-cup thickness, or extension of the atherosclerotic plaque with PCSK9-inhibitor, for several weeks after onset of acute coronary syndrome (ACS) has never been reported. METHODS: This study aimed to examine the effect of evolocumab on fibrous-cap thickness, as well as the extent of the atherosclerotic plaque, by serial optical coherence tomography (OCT) analysis in patients with ACS. All patients received rosuvastatin 5mg/day from at least 24h after onset of ACS. Patients received evolocumab (140mg every 2 weeks) 1 week after the onset of ACS in the statin plus evolocumab group. Patients took only rosuvastatin in the statin monotherapy group. OCT was performed to assess intermediate, non-culprit lesions just 4 and 12 weeks after emergent percutaneous coronary intervention. RESULTS: OCT analysis revealed that the increase in fibrous-cap thickness and decrease in macrophage grade were greater with a narrower lipid arc and shorter lipid length, which were associated with lower low-density lipoprotein cholesterol (LDL-C) in the statin plus evolocumab group than in the statin alone treatments, even for a short term after ACS onset. CONCLUSIONS: Addition of the PCSK9-inhibitor evolocumab to statin therapy might produce incremental growth in fibrous-cap thickness and regression of the lipid-rich plaque, which were associated with greater reduction of LDL-C even for a short term in the early phase of ACS.

[37] *Virani SS, Akeroyd JM, Ahmed ST et al.* **The use of structured data elements to identify ASCVD patients with statin-associated side effects: Insights from the Department of Veterans Affairs**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31501043
ABSTRACT
BACKGROUND: Accurate identification of patients with statin-associated side effects (SASEs) is critical for health care systems to institute strategies to improve guideline-concordant statin use. OBJECTIVE: The objective of this study was to determine whether adverse drug reaction (ADR) entry by clinicians in the electronic medical record can accurately identify SASEs. METHODS: We identified 1,248,214 atherosclerotic cardiovascular disease (ASCVD) patients seeking care in the Department of Veterans Affairs. Using an ADR data repository, we identified SASEs in 15 major symptom categories. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed using a chart review of 256 ASCVD patients with identified SASEs, who were not on high-intensity statin therapy. RESULTS: We identified 171,189 patients (13.71%) with documented SASEs over a 15-year period (9.9%, 2.7%, and 1.1% to 1, 2, or >2 statins, respectively). Statin use, high-intensity statin use, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol levels were 72%, 28.1%, 99 mg/dL, and 129 mg/dL among those with vs 81%, 31.1%, 84 mg/dL, and 111 mg/dL among those

without SASEs. Progressively lower statin and high-intensity statin use, and higher low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol levels were noted among those with SASEs to 1, 2, or >2 statins. Two-thirds of SASEs were related to muscle symptoms. Sensitivity, specificity, PPV, NPV compared with manual chart review were 63.4%, 100%, 100%, and 85.3%, respectively. CONCLUSION: A strategy of using ADR entry in the electronic medical record is feasible to identify SASEs with modest sensitivity and NPV but high specificity and PPV. Health care systems can use this strategy to identify ASCVD patients with SASEs and operationalize efforts to improve guideline-concordant lipid-lowering therapy use in such patients. The sensitivity of this approach can be further enhanced by the use of unstructured text data.

[38] *Mefford MT, Marcovina SM, Bittner V et al.* **PCSK9 loss-of-function variants and Lp(a) phenotypes among black US adults**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31511398
ABSTRACT
Pharmacologic inhibition of proprotein convertase subtilisin-kexin type-9 (PCSK9) lowers lipoprotein(a) [Lp(a)] concentrations. However, the impact of genetic PCSK9 loss-of-function variants (LOFV) on Lp(a) is uncertain.We determined the association of PCSK9 LOFV with Lp(a) measures among black adults. Genotyping for PCSK9 LOFV was conducted in 10,196 black Reasons for Geographic And Racial Differences in Stroke study participants. Among 241 participants with and 723 randomly selected participants without PCSK9 LOFV, Lp(a) concentations, apo(a) kringle IV (KIV) repeats - a proxy for isoform size - and oxidized phospholipid (OxPL-apoB) levels were measured using validated methods. Median Lp(a) concentrations among participants with and without PCSK9 LOFV were 63.2 and 80.4 nmol/L, respectively (p=0.016). After adjustment for age, sex, estimated glomerular filtration rate, LDL-C and statin use, participants with versus without a PCSK9 LOFV had lower median Lp(a) concentration (Delta=-18.8 nmol/L [95%CI -34.2, -3.3]). Median apo(a) isoform sizes were 24 and 23 KIV repeats (p=0.12) among participants with and without PCSK9 LOFV, respectively (Delta= 1.1 [95%CI 0.2, 2.0] after adjustment). Median OxPL-apoB levels among participants with and without PCSK9 LOFV were 3.4 and 4.1 nM (p=0.20), respectively (Delta=-1.2 nM [95%CI -2.4, -0.04] after adjustment). Among black adults, PCSK9 LOFV were associated with lower Lp(a) concentration and OxPL-apoB levels.

[39] *Tulbah AS, Pisano E, Landh E et al.* **Simvastatin Nanoparticles Reduce Inflammation in LPS-Stimulated Alveolar Macrophages**. Journal of pharmaceutical sciences 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31494116
ABSTRACT
Simvastatin (SV) is widely used as lipid- lowering medication that has also been found to have beneficial immuno-modulatory effects for treatment of chronic lung diseases. Although its anti-inflammatory activity has been investigated, its underlying mechanisms have not yet been clearly elucidated. In this study, the anti-inflammatory and anti-oxidant effects and mechanism of simvastatin nanoparticles (SV-NPs) on lipopolysaccharide (LPS)-stimulated alveolar macrophages (AM) NR8383 cells were investigated. Quantitative cellular uptake of SV-NPs, the production of inflammatory mediators (interleukin (IL)-6, tumour necrosis factor (TNF) and

monocyte chemoattractant protein-1 (MCP-1)), and oxidative stress (nitric oxide, NO) were tested. Furthermore, the involvement of the Nuclear factor KB (NF-KB) signaling pathway in activation of inflammation in AM and the efficacy of SV were visualized using immunofluorescence. Results indicated that SV-NPs exhibit a potent inhibitory effect on NO production and secretion of inflammatory cytokine in inflamed AM, without affecting cell viability. The enhanced anti-inflammatory activity of SV-NPs is likely due to SV improved chemical- physical stability and higher cellular uptake into AM. The study also indicates that SV targets the inflammatory and oxidative response of AM, through inactivation of the NF-KappaB signalling pathway, supporting the pharmacological basis of SV for treatment of chronic inflammatory lung diseases.

[40] *Saleh Y, Herzallah K, Hassanein M, Chang HT*. **Statin-induced necrotizing autoimmune myopathy: An uncommon complication of a commonly used medication**. Journal of the Saudi Heart Association 2019; 31:269-272.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31516306
ABSTRACT
A well-known side effect of statin therapy is myopathy. We report a case of statin induced necrotizing autoimmune myopathy, a rare variant of statin-induced myopathy. A 64-year-old gentleman on atorvastatin presented with muscle weakness. Initial laboratory results showed elevated liver function tests, a creatine phosphokinase (CPK) of 8200IU/L, and positive urine myoglobin. Despite discontinuing atorvastatin, his CPK remained persistently elevated. Muscle biopsy was consistent with necrotizing myopathy. Anti-HMG CoA reductase antibody was strongly positive. Steroids followed by intravenous immunoglobulin were given. The patient's muscle weakness, CPK, and liver functions gradually improved, and he was eventually discharged on oral steroids. Statin induced necrotizing autoimmune myopathy should be considered when discontinuing statin does not lead to muscle recovery and improvement in CPK. Diagnosis is confirmed by positive anti-HMG-CoA reductase autoantibody.

[41] *Feng Q, Wei WQ, Chaugai S et al.* **A Genetic Approach to the Association Between PCSK9 and Sepsis**. JAMA network open 2019; 2:e1911130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31509211
ABSTRACT
Importance: Whether the PCSK9 gene is associated with the progress from infection to sepsis is unknown to date. Objective: To test the associations between PCSK9 genetic variants, a PCSK9 genetic risk score (GRS), or genetically estimated PCSK9 expression levels and the risk of sepsis among patients admitted to a hospital with infection. Design, Setting, and Participants: This retrospective cohort study used deidentified electronic health records to identify patients admitted to Vanderbilt University Medical Center, Nashville, Tennessee, with infection. Patients were white adults, had a code indicating infection from the International Classification of Diseases, Ninth Revision, Clinical Modification, or the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification, and received an antibiotic within 1 day of hospital admission (N = 61 502). Data were collected from January 1, 1993, through December 31, 2017, and analyzed from April 1, 2018, to March 16, 2019. Exposures: Four known PCSK9 functional variants, a GRS for PCSK9, and genetically estimated PCSK9 expression. Main

Outcomes and Measures: The primary outcome was sepsis; secondary outcomes included cardiovascular failure and in-hospital death. Results: Of patients with infection, genotype information was available in 10 922 white patients for PCSK9 functional variants (5628 men [51.5%]; mean [SD] age, 60.1 [15.7] years), including 7624 patients with PCSK9 GRS and 6033 patients with estimated PCSK9 expression. Of these, 3391 developed sepsis, 835 developed cardiovascular failure, and 366 died during hospitalization. None of the 4 functional PCSK9 variants were significantly associated with sepsis, cardiovascular failure, or in-hospital death, with or without adjustment for (1) age and sex or (2) age, sex, and Charlson-Deyo comorbidities (in model adjusted for age, sex, and comorbidities, odds ratios for any loss-of function variant were 0.96 [95% CI, 0.88-1.04] for sepsis, 1.05 [95% CI, 0.90-1.22] for cardiovascular failure, and 0.89 [95% CI, 0.72-1.11] for death). Similarly, neither the PCSK9 GRS nor genetically estimated PCSK9 expression were significantly associated with sepsis, cardiovascular failure, or in-hospital death in any of the analysis models. For GRS, in the full model adjusted for age, sex, and comorbidities, the odds ratios were 1.01 for sepsis (95% CI, 0.96-1.06; P = .70), 1.03 for cardiovascular failure (95% CI, 0.95-1.12; P = .48), and 1.05 for in-hospital death (95% CI, 0.92-1.19; P = .50). For genetically estimated PCSK9 expression, in the full model adjusted for age, sex, and comorbidities, the odds ratios were 1.01 for sepsis (95% CI, 0.95-1.06; P = .86), 0.96 for cardiovascular failure (95% CI, 0.88-1.05; P = .41), and 0.99 for in-hospital death (95% CI, 0.87-1.14; P = .94). Conclusions and Relevance: In this study, PCSK9 genetic variants were not significantly associated with risk of sepsis or the outcomes of sepsis in patients hospitalized with infection.

[42] *Schanuel FS, Romana-Souza B, Monte-Alto-Costa A*. **Short-Term Administration of a High-Fat Diet Impairs Wound Repair in Mice**. Lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31509252
ABSTRACT
High intake of dietary fat plays an important role in obesity development in animals and humans, and prolonged intake of high-fat diet might lead to low-grade chronic inflammation. Previous study showed that diet-induced overweight delays cutaneous wound healing in both obesity-prone and obesity-resistant animals, highlighting the importance of diet composition in the wound healing process. This study evaluated the hypothesis that a short-term administration of high-fat diet could affect cutaneous wound healing. Male mice (C57/bl6) were randomly divided into standard (10% energy from fat) or high-fat (60% energy from fat) chow groups. After 10 days of diet administration, an excisional lesion was performed and the animals were sacrificed 6 or 10 days later. There was no difference in the fasting blood glucose between groups. Ten days after wounding, high-fat chow group presented increased inflammatory infiltrate, levels of inducible nitric oxide synthase and cyclo-oxygenase-2 proteins, and lipid peroxidation. The high-fat chow group presented delayed wound closure, increased amount of myofibroblasts and vessels, and decreased deposition of type I collagen. These findings support the hypothesis that short-term administration of high-fat diet exerts negative effects on mice cutaneous wound healing, due to the interference in the inflammatory phase.

[43] *Badawy NA, Labeeb SA, Alsamdan MF, Alazemi BF*. **Prevalence and Risk of Polypharmacy Among Community-Dwelling, Elderly Kuwaiti Patients**. Medical principles and practice : international journal of the Kuwait University, Health Science Centre 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31509828
ABSTRACT
OBJECTIVES: To estimate the prevalence of polypharmacy in community-dwelling, older Kuwaiti patients, describe the number and types of drugs used and to identify risk factors associated with polypharmacy. SUBJECTS AND METHODS: This was a descriptive cross-sectional questionnaire-based survey in which we interviewed 500 community-dwelling, Kuwaiti adults over 65 years of age. The data collection occurred during a four-month period from March to July 2017. RESULTS: Fifty-two percent (n = 260) of the patients were males, with a mean age of 71.73 +/- 5.32 years. The prevalence of polypharmacy (5-8 drugs) and excessive polypharmacy (> 8 drugs) were 58.4% (n = 292) and 10.2% (n = 51) respectively. The risk factors associated with an increased number of used medicines were female gender (p = 0.019), a lower level of education (p = 0.003), and a high number of hospital admissions (p =0.000), clinics visited by the patient (p = 0.000), and number of comorbidities (p = 0.000). The most commonly used medications were blood glucose-lowering agents excluding insulin, which were used by 82.6% of the study population. Other commonly used medications were antihypertensive drugs and lipid-modifying agents. CONCLUSION: A significant sector of the older Kuwaiti patient population has a high prevalence of polypharmacy and thus are exposed to its potential hazards. The current study highlights the need to revise the drug-dispensing policy among community-dwelling, older Kuwaiti people, as well as to initiate educational programs among healthcare practitioners concerning prescribing issues in older individuals.

[44] *Faubion SS, Kapoor E, Moyer AM et al.* **Statin therapy: does sex matter?** Menopause (New York, N.Y.) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31513091
ABSTRACT
OBJECTIVE: Statins are a class of drugs that competitively bind to the active site of HMG-CoA reductase enzyme, thereby inhibiting the initial steps in cholesterol synthesis. Originally approved for use in lowering serum cholesterol, a risk factor for developing atherosclerosis and coronary heart disease, statins have subsequently been noted to have myriad extrahepatic effects, including potential effects on cognition, diabetes, breast cancer, bone, and muscle. This narrative review assesses the current state of the science regarding the risks and benefits of statin therapy in women to identify areas where additional research is needed. METHODS: Basic and clinical studies were identified by searching PubMed with particular attention to inclusion of female animals, women, randomized controlled trials, and sex-specific analyses. RESULTS: Statin therapy is generally recommended to reduce the risk of cardiovascular disease. None of the current clinical guidelines, however, offer sex-specific recommendations for women due to lack of understanding of sex differences and underlying mechanisms of disease processes. In addition, conclusions regarding efficacy of treatments do not consider lipid solubility for the drug, dosing, duration of treatment, interactions with estrogen, or comorbidities. Pleiotropic effects of statins are often derived from secondary analysis of studies with cardiovascular events as primary outcomes. CONCLUSIONS: Many of the trials that have

established the efficacy and safety of statins were conducted predominantly or entirely in men, with results extrapolated to women. Additional research is needed to guide clinical recommendations specific to women. : Video Summary:http://links.lww.com/MENO/A462.

[45] *Makrides M, Best K, Yelland L et al.* **A Randomized Trial of Prenatal n-3 Fatty Acid Supplementation and Preterm Delivery**. The New England journal of medicine 2019; 381:1035-1045.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31509674
ABSTRACT
BACKGROUND: Previous studies have suggested that maternal supplementation with n-3 long-chain polyunsaturated fatty acids may reduce the incidence of preterm delivery but may also prolong gestation beyond term; however, more data are needed regarding the role of n-3 long-chain polyunsaturated fatty acids in pregnancy. METHODS: We performed a multicenter, double-blind, randomized trial in which women who were pregnant with single or multiple fetuses were assigned to receive either fish-oil capsules that contained 900 mg of n-3 long-chain polyunsaturated fatty acids (n-3 group) or vegetable-oil capsules that contained trace n-3 long-chain polyunsaturated fatty acids (control group) daily, beginning before 20 weeks of gestation and continuing to 34 weeks of gestation or delivery, whichever occurred first. The primary outcome was early preterm delivery, defined as delivery before 34 completed weeks of gestation. Other pregnancy and neonatal outcomes were also assessed. RESULTS: A total of 5544 pregnancies in 5517 women were randomly assigned at six centers in Australia; 5486 pregnancies were included in the primary analysis. Early preterm delivery occurred in the case of 61 of 2734 pregnancies (2.2%) in the n-3 group and 55 of 2752 pregnancies (2.0%) in the control group; the between-group difference was not significant (adjusted relative risk, 1.13; 95% confidence interval [CI], 0.79 to 1.63; P = 0.50). There were no significant differences between the groups in the incidence of interventions in post-term (>41 weeks of gestation) deliveries, in adverse events, or in other pregnancy or neonatal outcomes, except that a higher percentage of infants born to women in the n-3 group than in the control group were very large for gestational age at birth (adjusted relative risk, 1.30; 95% CI, 1.02 to 1.65). Percentages of serious adverse events did not differ between the groups. Minor gastrointestinal disturbances were more commonly reported in the n-3 group than in the control group. CONCLUSIONS: Supplementation with n-3 long-chain polyunsaturated fatty acids from early pregnancy (<20 weeks of gestation) until 34 weeks of gestation did not result in a lower incidence of early preterm delivery or a higher incidence of interventions in post-term deliveries than control. (Funded by the Australian National Health and Medical Research Council and the Thyne Reid Foundation; ORIP Australian New Zealand Clinical Trials Registry number, ACTRN12613001142729.).

[46] *Grzegorczyk E, Ksiazek M, Kurek K et al.* **Effect of Sleeve Gastrectomy on Proprotein Convertase Subtilisin/Kexin Type 9 (Pcsk9) Content and Lipid Metabolism in the Blood Plasma and Liver of Obese Wistar Rats**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31510106
ABSTRACT

Nowadays, obesity and its complications are heavy burdens to western civilization. Surgical procedures remain one of the available therapies for obesity and obesity-associated diseases treatment. Among them, sleeve gastrectomy is the most common bariatric procedure. Despite the well-established fact that sleeve gastrectomy results in significant weight loss, some of its other divergent effects still need to be established. To fulfill this knowledge gap, we examined whether sleeve gastrectomy affects lipid metabolism in the plasma and liver of obese rats. We demonstrated that chronic high-fat diet feeding led to an increment in the level of Proprotein Convertase Subtilisin/Kexin (PCSK)-a regulator of plasma cholesterol concentration-in the liver, which was decreased after the gastrectomy. Moreover, we noticed significant increases in both plasma and liver contents of free fatty acids, diacylgycerides and triacylglycerides in the obese animals, with their reduction after the bariatric surgery. In conclusion, we revealed, presumably for the first time, that sleeve gastrectomy affects lipid metabolism in the liver of obese rats.

[47] *Coste J, Karras A, Rudnichi A et al.* **Statins for primary prevention of cardiovascular disease and the risk of acute kidney injury**. Pharmacoepidemiology and drug safety 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31517431
ABSTRACT
PURPOSE: To investigate the risk of acute kidney injury (AKI) in subjects initiating statin therapy for primary prevention of cardiovascular disease (CVD). METHODS: A nationwide cohort study using French hospital discharge and claims databases was performed, studying subjects from the general population aged 40 to 75 years in 2009, with no history of CVD and no lipid-lowering drugs during the preceding 3-year period, followed for up to 7 years. Exposure to statins (type, dose, and time since first use) and to other drugs for CVD risk was assessed. The primary outcome was hospital admission for AKI. RESULTS: The cohort included 8 236 279 subjects, 818 432 of whom initiated a statin for primary prevention. During 598 487 785 person-months exposed to statins, 700 events were observed, corresponding to an incidence of AKI of 4.59 per 10 000 person-years (7.01 in men, 3.01 in women). AKI mainly occurred in the context of organ failure, sepsis, and genitourinary disease. A 19% increased rate of AKI (hazard ratio = 1.19, 95%CI: 1.08-1.31) was observed in men exposed to statins, whereas no increase in the overall risk of AKI was observed in women. However, exposure to high-potency statins was associated with a 72% to 116% increased risk in both genders and a dose-effect relationship observed for rosuvastatin and atorvastatin. No temporal pattern of occurrence nor interaction with drugs for CVD risk was observed. CONCLUSIONS: Although the overall risk of AKI appears moderately increased, more attention should be paid to renal function in subjects taking statins for primary prevention both in clinical practice and from a research viewpoint.

[48] *Feng X, Zhang L, Xu S, Shen AZ*. **ATP-citrate lyase (ACLY) in lipid metabolism and atherosclerosis: An updated review**. Progress in lipid research 2019:101006.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31499095
ABSTRACT
ATP citrate lyase (ACLY) is an important enzyme linking carbohydrate to lipid metabolism by generating acetyl-CoA from citrate for fatty acid and cholesterol biosynthesis. Mendelian randomization of large human cohorts has validated ACLY as a promising target for low-density-lipoprotein-cholesterol (LDL-C) lowering and cardiovascular protection. Among current ACLY

inhibitors, Bempedoic acid (ETC-1002) is a first-in-class, prodrug-based direct competitive inhibitor of ACLY which regulates lipid metabolism by upregulating hepatic LDL receptor (LDLr) expression and activity. ACLY deficiency in hepatocytes protects from hepatic steatosis and dyslipidemia. In addition, pharmacological inhibition of ACLY by bempedoic acid, prevents dyslipidemia and attenuates atherosclerosis in hypercholesterolemic ApoE(-/-) mice, LDLr(-/-) mice, and LDLr(-/-) miniature pigs. Convincing data from clinical trials have revealed that bempedoic acid significantly lowers LDL-C as monotherapy, combination therapy, and add-on with statin therapy in statin-intolerant patients. More recently, a phase 3 CLEAR Harmony clinical trial ("Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol") has shown that bempedoic acid reduces the level of LDL-C in hypercholesterolemic patients receiving guideline-recommended statin therapy with a good safety profile. Hereby, we provide a updated review of the expression, regulation, genetics, functions of ACLY in lipid metabolism and atherosclerosis, and highlight the therapeutic potential of ACLY inhibitors (such as bempedoic acid, SB-204990, and other naturally-occuring inhibitors) to treat atherosclerotic cardiovascular diseases. It must be pointed out that long-term large-scale clinical trials in high-risk patients, are warranted to validate whether ACLY represent a promising therapeutic target for pharmaceutic intervention of dyslipidemia and atherosclerosis; and assess the safety and efficacy profile of ACLY inhibitors in improving cardiovascular outcome of patients.

[49] *Chen Y, Zhan X, Zhao Q et al.* **Serum lipoprotein(a) and risk of hemorrhagic stroke among incident peritoneal dialysis patients: a large study from a single center in China**. Renal failure 2019; 41:800-807.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31498021

ABSTRACT

Background: This retrospective study investigated whether baseline serum lipoprotein(a) (Lp(a)) may predict subsequent stroke in patients under chronic peritoneal dialysis (PD). Methods: Eight hundred and sixty incident PD patients, treated from 1 November 2005 to 28 February 2017, were enrolled, and followed until discontinuation of PD, death, or 31 May 2017. Hemorrhagic or ischemic stroke was the primary outcome. The population was stratified by baseline serum Lp(a) tertile. The risk of each stroke subtype was analyzed using the Cox proportional hazard models. Adjustments were made for: age; gender; history of stroke and hypertension; systolic blood pressure; lipid-lowering, antiplatelet and antihypertensive medications; laboratory profiles including hemoglobin, serum albumin, calcium, triglyceride, total and low-density lipoprotein cholesterol; and apolipoprotein A1. Results: Among the 860 participants, 19.3% and 4.1% had diabetes mellitus and a history of stroke, respectively. The median baseline serum Lp(a) was 328 (172-585) mg/L. After 28 (14-41) months of follow-up, 33 (3.84%) and 12 (1.40%) patients developed hemorrhagic and ischemic stroke, respectively. Participants in the highest Lp(a) tertile had a significantly lower risk of hemorrhagic stroke compared with those in the lowest tertile (hazard ratio (HR) 0.3, 95% confidence interval (CI) 0.1-0.86; p = .026); the rates of ischemic stroke were comparable among the tertiles. Each 10 mg/L rise in serum Lp(a) was associated with a 2% (95% CI 0.96-1; p = .033) lower risk of hemorrhagic stroke. Conclusions: Among patients with incident PD, a higher serum Lp(a) level may predict a lower risk of hemorrhagic stroke.

Literature update week 37 (2019)

[50] *Hultman K, Edsfeldt A, Bjorkbacka H et al.* **Cartilage Oligomeric Matrix Protein Associates With a Vulnerable Plaque Phenotype in Human Atherosclerotic Plaques**. Stroke 2019:Strokeaha119026457.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31495329
ABSTRACT
Background and Purpose- Extracellular matrix proteins are important in atherosclerotic disease by influencing plaque stability and cellular behavior but also by regulating inflammation. COMP (cartilage oligomeric matrix protein) is present in healthy human arteries and expressed by smooth muscle cells. A recent study showed that transplantation of COMP-deficient bone marrow to apoE(-)(/-) mice increased atherosclerotic plaque formation, indicating a role for COMP also in bone marrow-derived cells. Despite the evidence of a role for COMP in murine atherosclerosis, knowledge is lacking about the role of COMP in human atherosclerotic disease. Methods- In the present study, we investigated if COMP was associated with a stable or a vulnerable human atherosclerotic plaque phenotype by analyzing 211 carotid plaques for COMP expression using immunohistochemistry. Results- Plaque area that stained positive for COMP was significantly larger in atherosclerotic plaques associated with symptoms (n=110) compared with asymptomatic plaques (n=101; 9.7% [4.7-14.3] versus 5.6% [2.8-9.8]; P=0.0002). COMP was positively associated with plaque lipids (r=0.32; P=0.000002) and CD68 cells (r=0.15; P=0.036) but was negatively associated with collagen (r=-0.16; P=0.024), elastin (r=-0.14; P=0.041), and smooth muscle cells (r=-0.25; P=0.0002). COMP was positively associated with CD163 (r=0.37; P=0.00000006), a scavenger receptor for hemoglobin/haptoglobin and a marker of Mhem macrophages, and with intraplaque hemorrhage, measured as glycophorin A staining (r=0.28; P=0.00006). Conclusions- The present study shows that COMP is associated to symptomatic carotid atherosclerosis, CD163-expressing cells, and a vulnerable atherosclerotic plaque phenotype in humans.

[51] *Zamani M, Skagen K, Scott H et al.* **Carotid Plaque Neovascularization Detected With Superb Microvascular Imaging Ultrasound Without Using Contrast Media**. Stroke 2019:Strokeaha119025496.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31510899
ABSTRACT
Background and Purpose- A significant proportion of ischemic strokes are caused by emboli from unstable carotid artery plaques with intraplaque neovascularization (IPN) as a key feature of plaque instability. IPN is not detectable with conventional Doppler ultrasound. Contrast-enhanced ultrasound (CEUS) can visualize IPN, but its use is limited in clinical practice because it requires an intravenous injection of contrast. Superb microvascular imaging (SMI) without contrast uses an algorithm to remove clutter and motion wall artifacts while preserving low-velocity blood flow signals, enabling visualization of IPN. Our aim was to assess the feasibility of SMI for the detection of IPN. Methods- Thirty-one patients with >50% carotid stenosis were included: 22 patients were symptomatic and 9 asymptomatic. All patients underwent conventional carotid ultrasound, CEUS, SMI, and blood tests. CEUS and SMI findings were compared and correlated to histological plaque assessments after endarterectomy. Results- There was significant positive correlation between an IPN visual 5-level classification of SMI and a semiquantitative analysis of CEUS (P<0.001, r=0.911). Plaques with higher SMI grades had

higher numbers of neovessels quantified at histology (P=0.041, r=0.460). Hypoechoic plaques had higher grades of IPN on both CEUS and SMI (P<0.001). Higher visual IPN counts on SMI were associated with (1) increased areas of inflammation (P=0.043, r=0.457), (2) combined rank scores of granulation tissue, inflammation and lipids (P=0.02, r=0.494) at histology, and (3) higher peak-intensity values on quantitative CEUS (P=0.042, r=0.514). Conclusions- SMI ultrasound can detect neovascularization with accuracy comparable to CEUS, suggesting SMI to be a promising noninvasive alternative to CEUS for the assessment of carotid plaque stability.

[52] *Jack Chong A, Lim SW, Lee YL et al.* **The neuroprotective effects of simvastatin on high cholesterol following traumatic brain injury in rats**. World neurosurgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31518751
ABSTRACT
BACKGROUND: High cholesterol has been correlated with a higher risk of cerebrovascular diseases. Whether pre-existing high cholesterol exacerbates traumatic brain injury (TBI), and whether treatment with the cholesterol lowering agent simvastatin has neuroprotective effects, especially anti-neuroinflammtory effects, after TBI are not well investigated. METHODS: Five-week-old male Sprague-Dawley (SD) rats were fed with a high fat diet for 8 weeks to induce hypercholesterolemia. Anesthetized male SD rats were divided into five groups, including the sham-operated control, TBI control, and TBI with simvastatin treatment (4 mg/kg, 10 mg/kg or 20 mg/kg) groups. Simvastatin was intraperitoneally injected at 0, 24, and 48 h after TBI. Motor function was measured using an inclined plane. Neuronal apoptosis (maker Neu-N, TUNEL), TNF-alpha expression in microglia (marker OX42) and astrocytes (marker GFAP), and TNFR1 and TNFR2 expression in neurons in the ischemic cortex were investigated using an immunofluorescence assay. All of the parameters were measured on the 3(rd) day after TBI. RESULTS: TBI significantly increased the serum levels of cholesterol. The TBI-induced motor deficit was significantly attenuated by 4, 10 and 20 mg/kg simvastatin therapy on the 3(rd) day after TBI. TBI-induced neuronal TNFR1 activation and apoptosis, as well as TNF-alpha expression in astrocytes in the ischemic cortex, were significantly attenuated by simvastatin, particularly when 20 mg/kg was administered. Simultaneously, the serum cholesterol remained high despite simvastatin treatment. CONCLUSIONS: The neuroprotection effects of simvastatin on the pre-existing hypercholesterolemia during TBI in rats may be related to its anti-neuroinflammatory effects but not to its cholesterol lowing effects.

[53] *Luo SH, Yang DZ, Wei XY et al.* **[Association of insulin resistance with dyslipidemia in adults with type 1 diabetes]**. Zhonghua yi xue za zhi 2019; 99:2665-2669.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31505716
ABSTRACT
Objective: To investigate the relationship between insulin resistance (IR) and dyslipidemia in adults with type 1 diabetes (T1DM) and provide more insights on diabetes-related cardiovascular disease management. Methods: A cross-sectional study recruiting patients from Guangdong T1DM Translational Study cohort was conducted between 2011 and 2017. The patients aged >/=18 years, with a diabetes duration of >/=1 year were enrolled in the study. Plasma lipid profile data of eligible patients, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)

were collected and their relationships with insulin resistance were analyzed. IR in these adults with T1DM was estimated by glucose disposal rate (eGDR) calculated by a model published previously. Patients with eGDR lower than 25 percentiles were grouped as severe IR, otherwise non-severe IR. Results: In total, 499 eligible patients were studied, among which 274 were women (54.9%). The level of eGDR was 8.43 (6.11, 10.63) mg kg(-1) min(-1) and the overall incidence of lipid disorders was 65.3% (326/499) in the study population. The result showed that eGDR was correlated with TC, TG, HDL-C and LDL-C (r=-0.163, -0.303, 0.170 and -0.150, respectively, all $P<0.05$). After adjusting for gender, age and diabetes duration, eGDR was still associated with TG, TC and LDL-C (all $P<0.05$). Stepwise multiple linear regression analysis showed that gender (female), elevated TC and declined HDL-C were independent factors associated with the severity of IR ($t=5.651$, 5.823 and 2.908, respectively, all $P<0.05$). Conclusions: IR is associated with dyslipidemiain in adults with T1DM. Elevated TC and decreased HDL-C are independent associated factors for insulin resistance.