Literature update week 26 (2018)

[1] *Bai X, Zhang B, Wang P et al.* **Effects of SLCO1B1 and GATM gene variants on rosuvastatin-induced myopathy are unrelated to high plasma exposure of rosuvastatin and its metabolites**. Acta pharmacologica Sinica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29950617
ABSTRACT
Myotoxicity is a significant factor contributing to the poor adherence and reduced effectiveness in the treatment of statins. Genetic variations and high drug plasma exposure are considered as critique causes for statin-induced myopathy (SIM). This study aims to explore the sequential influences of rosuvastatin (RST) pharmacokinetic and myopathy-related single-nucleotide polymorphisms (SNPs) on the plasma exposure to RST and its metabolites: rosuvastatin lactone (RSTL) and N-desmethyl rosuvastatin (DM-RST), and further on RST-induced myopathy. A total of 758 Chinese patients with coronary artery disease were enrolled and followed up SIM incidents for 2 years. The plasma concentrations of RST and its metabolites were determined through a validated ultra-performance liquid chromatography mass spectrometry method. Nine SNPs in six genes were genotyped by using the Sequenom MassArray iPlex platform. Results revealed that ABCG2 rs2231142 variations were highly associated with the plasma concentrations of RST, RSTL, and DM-RST (Padj < 0.01, FDR < 0.05). CYP2C9 rs1057910 significantly affected the DM-RST concentration (Padj < 0.01, FDR < 0.05). SLCO1B1 rs4149056 variant allele was significantly associated with high SIM risk (OR: 1.741, 95% CI: 1.180-2.568, P = 0.0052, FDR = 0.0468). Glycine amidinotransferase (GATM) rs9806699 was marginally associated with SIM incidents (OR: 0.617, 95% CI: 0.406-0.939, P = 0.0240, FDR = 0.0960). The plasma concentrations of RST and its metabolites were not significantly different between the SIM (n = 51) and control groups (n = 707) (all P > 0.05). In conclusion, SLCO1B1 and GATM genetic variants are potential biomarkers for predicting RST-induced myopathy, and their effects on SIM are unrelated to the high plasma exposure of RST and its metabolites.

[2] *McQuillan C, Gray A, Kearney A, Menown IBA*. **Advances in Clinical Cardiology 2017: A Summary of Key Clinical Trials**. Adv Ther 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29949039
ABSTRACT
INTRODUCTION: Numerous important cardiology clinical trials have been published or presented at major international meetings during 2017. This paper aims to summarize these trials and place them in clinical context. METHODS: The authors reviewed clinical trials presented at major cardiology conferences during 2017 including the American College of Cardiology, European Association for Percutaneous Cardiovascular Interventions, European Society of Cardiology, European Association for the Study of Diabetes, Transcatheter Cardiovascular Therapeutics, and the American Heart Association. Selection criteria were trials with a broad relevance to the cardiology community and those with potential to change current practice. RESULTS: A total of 75 key cardiology clinical trials were identified for inclusion. New interventional and structural cardiology data include left main bifurcation treatment strategy, multivessel disease management in cardiogenic shock, drug-eluting balloons for in-stent restenosis, instantaneous wave-free physiological assessment, new-generation stents (COMBO, Orsiro), transcatheter aortic valve implantation, and closure devices. New preventative cardiology data include trials of liraglutide, empagliflozin, PCSK9 inhibitors (evolocumab and

bococizumab), inclisiran, and anacetrapib. Antiplatelet data include the role of uninterrupted aspirin therapy during non-cardiac surgery and dual antiplatelet therapy following coronary artery bypass grafting. New data are also included from fields of heart failure (levosimendan, spironolactone), atrial fibrillation (apixaban in DC cardioversion), cardiac devices (closed loop stimulation pacing for neuromediated syncope), and electrophysiology (catheter ablation for atrial fibrillation). CONCLUSION: This paper presents a summary of key clinical cardiology trials during the past year and should be of practical value to both clinicians and cardiology researchers.

[3] *Hu G, Ito O, Rong R et al.* **Pitavastatin Upregulates Nitric Oxide Synthases in the Kidney of Spontaneously Hypertensive Rats and Wistar-Kyoto rats**. American journal of hypertension 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29955802
ABSTRACT
Background: Clinical trials show potent renoprotective effects of pitavastatin (PTV), although the precise mechanism for these renoprotective effects is not fully clarified. The aim of this study was to examine the antihypertensive and renoprotective effects of PTV, focusing on the nitric oxide (NO) system. Methods: Male, 6-week-old, spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY) were randomized to receive vehicle or PTV (2 mg/kg bodyweight) for 8 weeks. Blood pressure and urinary albumin excretion were measured every 2 weeks. After 8 weeks, plasma biochemical parameters and renal histology were examined. NO synthase isoform (neuronal, nNOS; inducible, iNOS; and endothelial, eNOS) expression and eNOS phosphorylation were examined by western blotting. RESULTS: PTV attenuated hypertension and albuminuria development in SHR. PTV decreased glomerular desmin expression and medullary interstitial fibrosis in SHR. PTV tended to increase plasma NO in both strains, but significantly increased urinary NO excretion only in WKY. PTV significantly increased nNOS and eNOS expression, enhanced eNOS phosphorylation at serine1177, and inhibited eNOS phosphorylation at threonine495 in the kidney of both strains. Conclusions: PTV treatment led to increased renal NOS expression and upregulated eNOS activity in both SHR and WKY. The antihypertensive and renoprotective effects of PTV may be related to upregulation of the NO system.

[4] *Sahebkar A, Simental-Mendia LE, Pirro M et al.* **Impact of fibrates on circulating cystatin C levels: a systematic review and meta-analysis of clinical trials**. Annals of medicine 2018:1-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29957074
ABSTRACT
AIMS: To assess the effect of fibrates on circulating cystatin C levels. MATERIALS AND METHODS: Clinical studies evaluating the effect of a fibrate on circulating cystatin C levels were searched in PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases. A random-effect model and generic inverse variance method were used for quantitative data synthesis, sensitivity analysis conducted using the leave-one-out method, and weighted random-effects meta-regression performed to evaluate potential confounders on cystatin C levels. RESULTS: This meta-analysis of data from 9 published studies (16 treatment arms) involved a total of 2195 subjects. In a single-arm analysis of clinical trials (without control

group; 8 studies comprising 14 treatment arms), fibrate therapy increased circulating cystatin C concentrations (WMD: 0.07 mg/dL, 95% CI: 0.04, 0.10, p <0.001; I(2) = 82.66%). When the analysis was restricted to randomized controlled trials (4 studies comprising 6 treatment arms), again elevation of circulating cystatin C levels was observed (WMD: 0.06 mg/L, 95% CI: 0.03, 0.09, p <0.001; I(2) = 42.98%). Elevated cystatin C levels were only seen with fenofibrate, not other fibrates. CONCLUSION: The results suggest that fenofibrate treatment adversely affects cystatin C levels and might partially explain the limited efficacy of fenofibrate in reducing cardiovascular events.

[5] *Kosmas CE, Sourlas A, Bouza KV et al.* **Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition with evolocumab: powerful low-density lipoprotein cholesterol (LDL-C) lowering and improved cardiovascular outcomes without an increase in the risk of diabetes mellitus**. Annals of translational medicine 2018; 6:130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29955590
ABSTRACT

[6] *Fuentes-Orozco C, Garcia-Salazar SJ, Gomez-Navarro B et al.* **Anti-Inflammatory Effect of Atorvastatin on the Kidney Graft of Living Donor Transplants**. Annals of transplantation 2018; 23:442-449.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29955032
ABSTRACT
BACKGROUND Recent studies have demonstrated that statins have anti-inflammatory and immunomodulatory properties, which could be considered beneficial in kidney transplantations. This study assesses the anti-inflammatory effect of atorvastatin on the kidney grafts of living donor transplants. MATERIAL AND METHODS In a randomized clinical trial, kidney donors were divided into 2 groups. The study group constituted 24 donors who received 40 mg atorvastatin, and 24 donors who received a placebo control, 4 weeks prior to transplantation. Serum C-reactive protein (CRP) levels were measured before and after atorvastatin administration. CRP and renal function of kidney recipients were measured at baseline and 1, 6, and 24 hours after transplantation. RESULTS After 4 weeks of treatment, the CRP level was 5.62+/-3.82 mg/dL in the control group and 3.27+/-0.62 mg/dL in the study group (P=0.007). Upon reperfusion, CRP levels in recipients at 1 hour were, 5.8+/-3.9 and 3.8+/-1.0 mg/dL, respectively (P=0.04). Twenty-four hours after the kidney transplantations, serum creatinine levels were 2.5+/-1.5 mg/dL in the study group and 3.7+/-2.4 mg/dL in the control group (P=0.04). CONCLUSIONS Our study suggests that the use of atorvastatin prior to allograft procurement of kidney transplant, reduces the acute kidney inflammatory burden profile, and promotes an improved kidney function recovery following transplantation.

[7] *Stock JK*. **Navigating the highlights of EAS Congress Lisbon**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29945722
ABSTRACT

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[8] *Usategui-Martin R, Vega G, Abad-Manteca L et al.* **Role of Bone Morphogenetic Protein 2 (BMP-2) Polymorphisms in Bone Mineral Density after the Start of Treatment with Atorvastatin**. Basic & clinical pharmacology & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29956474
ABSTRACT
One of the pleiotropic effects of statins is their capacity to increase bone formation. This is due to, among other things, they modify BMP-2 pathway. Several experimental studies have confirmed that statins have bone anabolic properties but the consequences in bone metabolism in the clinical practice are very variable. Our hypothesis is that the clinical variability in bone metabolism response could be attributed, among other causes, to genetic factors. Therefore, we analysed polymorphisms in BMP-2 gene (rs235768, rs1980499, rs2273073 and rs1005464) in order to evaluate the role of these variants in modulating bone metabolism response to statins treatment in patients with acute coronary syndrome. Our results showed that being a carrier of the variant allele T of BMP2 rs2273073 polymorphism was associated with an increased in the total hip BMD following atorvastatin therapy. This is the first report showing an association between a polymorphism in BMP-2 gene and bone changes in response to atorvastatin treatment. This report reinforces the hypothesis that genetic factors are crucial in the clinical variability of bone metabolism changes in response to statin treatment.

[9] *Sarangi B, Jana U, Sahoo J et al.* **Systematic approach for the formulation and optimization of atorvastatin loaded solid lipid NANOAPARTICLES using response surface methodology**. Biomedical microdevices 2018; 20:53.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29946758
ABSTRACT
Atorvastatin is a lipid lowering agent with poor oral bioavailability (12%) because of poor solubility and extensive first pass hepatic metabolism. In order to overcome these issues, atorvastatin loaded solid lipid nanoparticles (ATOR-SLNs) were prepared by using glyceryl tripalmitate as lipid carrier, poloxamer 407 as surfactant and soya lecithin as emulsifier. The purpose of this work was to optimize the formulation with the application of response surface methodology to improve the physicochemical properties. The central composite rotatable design consisting of three factored factorial design with three levels was used for the optimization of the formulations. The optimized formulation was composed of drug/lipid ratio of 1:3.64, surfactant concentration of 1.5% with 5 min time for sonication. Fourier transforms infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC) studies confirmed the compatibility of drug and lipid in the formulation. The optimized ATOR- SLNs showed almost spherical shape with a mean particle size of 338.5 nm, zeta potential of -24.7mV, DL of 17.7% and EE of 81.06% respectively. The in vitro drug release study showed a burst release at the initial stage followed by the prolongation of drug release from lipid matrix. Stability study revealed that ATOR-SLNs were more stable at 4+/-2 C when compared with storage at 25+/-2 C/60+/-5% RH during the six months storage period. These results indicated that the developed ATOR-SLNs is a promising approach for increment of bioavailability by improving the physicochemical properties.

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[10] *Park JG, Jeong SJ, Yu J et al.* **LJ-1888, a selective antagonist for the A3 adenosine receptor, ameliorates the development of atherosclerosis and hypercholesterolemia in apolipoprotein E knock-out mice**. BMB reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29936931
ABSTRACT
Cardiovascular diseases arising from atherosclerosis are the leading causes of mortality and morbidity worldwide. Lipid-lowering agents have been developed in order to treat hypercholesterolemia, a major risk factor for atherosclerosis. However, the prevalence of cardiovascular diseases is increasing, indicating a need to identify novel therapeutic targets and develop new treatment agents. Adenosine receptors (ARs) are emerging as therapeutic targets in asthma, rheumatoid arthritis, cancer, ischemia, and inflammatory diseases. This study assessed whether LJ-1888, a selective antagonist for A3 AR, can inhibit the development of atherosclerosis in apolipoprotein E knock-out (ApoE-/-) mice who are fed a western diet. Plaque formation was significantly lower in ApoE-/- mice administered LJ-1888 than in mice not administered LJ-1888, without any associated liver damage. LJ-1888 treatment of ApoE-/- mice prevented western diet-induced hypercholesterolemia by markedly reducing low-density lipoprotein cholesterol levels and significantly increasing high-density lipoprotein cholesterol concentrations. Reduced hypercholesterolemia in ApoE-/- mice administered LJ-1888 was associated with the enhanced expression of genes involved in bile acid biosynthesis. These findings indicate that LJ-1888, a selective antagonist for A3 AR, may be a novel candidate for the treatment of atherosclerosis and hypercholesterolemia.

[11] *Zagelbaum NK, Yandrapalli S, Nabors C, Frishman WH*. **Bempedoic Acid (ETC-1002): ATP Citrate Lyase Inhibitor: Review Of A First In Class Medication With Potential Benefit In Statin-Refractory Cases**. Cardiology in review 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29939848
ABSTRACT
Bempedoic acid (ETC-1002) is a new agent that reduces cholesterol synthesis through inhibition of adenosine triphosphate citrate lyase (ACL), an enzyme upstream from 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA). In animal models, bempedoic acid also influences fatty acid synthesis but in humans its role is limited primarily to lowering low-density lipoprotein cholesterol (LDL-C). In early clinical trials, bempedoic acid has been well tolerated and without major side effects. Alone or in various combinations with Atorvastatin and/or Ezetimibe, LDL-C lowering has ranged from 17% to 64%. In addition, it lowers levels of non high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), and apolipoprotein B (apoB). Statins are first line agents for primary and secondary prevention of cardiovascular disease. However, muscle related side effects and other problems such as elevated liver enzymes may limit their use. In addition, LDL-C lowering beyond that provided by statin therapy alone may be needed. Bempedoic acid may be useful in either of these scenarios, as it is relatively free of muscle related side effects and appears to enhance LDL-C lowering beyond that achieved with statin monotherapy. Phase 3 trials and one outcomes study are currently under way to better define this agent's potential clinical role.

[12] *Tumurkhuu G, Dagvadorj J, Porritt RA et al.* **Chlamydia pneumoniae Hijacks a Host Autoregulatory IL-1beta Loop to Drive Foam Cell Formation and Accelerate Atherosclerosis**. Cell Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29937375
ABSTRACT
Pathogen burden accelerates atherosclerosis, but the mechanisms remain unresolved. Activation of the NLRP3 inflammasome is linked to atherogenesis. Here we investigated whether Chlamydia pneumoniae (C.pn) infection engages NLRP3 in promoting atherosclerosis. C.pn potentiated hyperlipidemia-induced inflammasome activity in cultured macrophages and in foam cells in atherosclerotic lesions of Ldlr(-/-) mice. C.pn-induced acceleration of atherosclerosis was significantly dependent on NLRP3 and caspase-1. We discovered that C.pn-induced extracellular IL-1beta triggers a negative feedback loop to inhibit GPR109a and ABCA1 expression and cholesterol efflux, leading to accumulation of intracellular cholesterol and foam cell formation. Gpr109a and Abca1 were both upregulated in plaque lesions in Nlrp3(-/-) mice in both hyperlipidemic and C.pn infection models. Mature IL-1beta and cholesterol may compete for access to the ABCA1 transporter to be exported from macrophages. C.pn exploits this metabolic-immune crosstalk, which can be modulated by NLRP3 inhibitors to alleviate atherosclerosis.

[13] *Kraus D, Reckenbeil J, Veit N et al.* **Targeting glucose transport and the NAD pathway in tumor cells with STF-31: a re-evaluation**. Cellular oncology (Dordrecht) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29949049
ABSTRACT
BACKGROUND: Targeting glucose metabolism is a promising way to interfere with tumor cell proliferation and survival. However, controversy exists about the specificity of some glucose metabolism targeting anticancer drugs. Especially the potency of STF-31 has been debated. Here, we aimed to assess the impact of the glucose transporter (GLUT) inhibitors fasentin and WZB117, and the nicotinamide phosphoribosyltransferase (NAMPT) inhibitors GMX1778 and STF-31 on tumor cell proliferation and survival, as well as on glucose uptake. METHODS: Tumor-derived A172 (glioblastoma), BHY (oral squamous cell carcinoma), HeLa (cervix adenocarcinoma), HN (head neck cancer), HT-29 (colon carcinoma) and MG-63 (osteosarcoma) cells were treated with fasentin, WZB117, GMX1778 and STF-31. Proliferation rates and cell viabilities were assessed using XTT, crystal violet and LDH assays. mRNA and protein expression of GLUT1 and NAPRT were assessed using qPCR and Western blotting, respectively. The effects of inhibiting compounds on glucose uptake were measured using [(18)F]-fluoro-deoxyglucose uptake experiments. RESULTS: Stimulation of tumor-derived cells with the different inhibitors tested revealed a complex pattern, whereby proliferation inhibiting and survival reducing concentrations varied in [(18)F]-fluoro-deoxyglucose uptake experiments more than one order of magnitude among the different cells tested. We found that the effects of GMX1778 and STF-31 could be partially abolished by (i) nicotinic acid (NA) only in nicotinic acid phosphoribosyltransferase (NAPRT) expressing cells and (ii) nicotinamide mononucleotide (NMN) in all cells tested, supporting the classification of these compounds as NAMPT inhibitors. In short-time [(18)F]-fluoro-deoxyglucose uptake experiments the application of WZB-117 was found to lead to an almost complete uptake inhibition in all cells tested, whereas the effect of

fasentin was found to be cell type dependent with a maximum value of ~35% in A172, BHY, HeLa and HT-29 cells. We also found that STF-31 inhibited glucose uptake in all cells tested in a range of 25-50%. These data support the classification of STF-31 as a GLUT inhibitor. CONCLUSIONS: Our data reveal a dual mode of action of STF-31, serving either as a NAMPT or as a GLUT inhibitor, whereby the latter seems to be apparent only at higher STF-31 concentrations. The molecular basis of such a dual function and its appearance in compounds previously designated as NAMPT-specific inhibitors requires further investigation.

[14] *Hsiao CC, Lin HC, Chang YJ et al.* **Intravenous fish oil containing lipid emulsion attenuates inflammatory cytokines and the development of bronchopulmonary dysplasia in very premature infants: A double-blind, randomized controlled trial**. Clinical nutrition (Edinburgh, Scotland) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29941233
ABSTRACT
BACKGROUND & AIMS: Preterm infants have lower levels of long-chain polyunsaturated fatty acids (LCPUFAs). Supplementing very premature infants with intravenous lipid emulsions that fish oil, which is rich in n-3 LC-PUFAs, may decrease bronchopulmonary dysplasia (BPD) by modulating inflammation and neonatal immune function. METHODS: Sixty very low birth weight (VLBW) premature infants requiring ventilator support were randomized in a double-blind manner to 2 groups and received total parenteral nutrition with fish oil containing LE (intervention group, n = 30) or soybean oil containing LE (control group, n = 30) for 7 days. Blood samples and bronchoalveolar lavage fluid (BALF) were obtained for assay on day 1 and 7 days after LE. The primary outcome was to compare the levels of interleukin (IL)-1beta and IL-6 in serum and BALF. Secondary outcomes were to compare mortality and co-morbidities. RESULTS: The levels of IL-1beta and IL-6 in serum and BALF were significantly lower in the intervention group at day 8 ($p < 0.05$). The incidence of BPD in the intervention group compared to the control group was 13.3% versus 36.7% ($p = 0.04$; odds ratio [OR], 0.36; 95% confidence interval [CI], 0.21-0.86). The duration of ventilator support and oxygen use was significantly less in the intervention group than in the control group ($p < 0.05$). The level of alanine aminotransferase was significantly lower in the intervention group on day 8 ($p = 0.031$). CONCLUSIONS: In very premature infants, early administration of fish oil containing LE significantly decreased IL-1beta and IL-6 levels in serum and BALF and was associated with shorter duration of ventilator support and less bronchopulmonary dysplasia (BPD). TRIAL REGISTRATION NUMBER: ISRCTN 11427103.

[15] *Ference BA*. **Using Genetic Variants in the Targets of Lipid Lowering Therapies to Inform Drug Discovery and Development: Current and Future Treatment Options**. Clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29953581
ABSTRACT
Mendelian randomization studies and "human knock-out" studies of rare loss-of-function coding variants suggest that plasma levels of LDL-C, triglycerides and Lp(a) are causally associated with the risk of cardiovascular disease, and therefore therapies directed against these targets should reduce the risk of cardiovascular events. However, several therapies

directed against these targets have failed to reduce the risk of cardiovascular events in large-scale randomized trials, thus suggesting that causality is not sufficient evidence to establish genetic target validation. Instead, the critical question that needs to be answered to improve drug discovery and development is how much a causal biomarker needs to be changed to produce a clinically meaningful benefit in a short-term trial. This review describes how to use naturally randomized genetic evidence to accurately anticipate the results of randomized trials evaluating current and future lipid lowering therapies, inform the design of randomized trials, and transform the drug discovery and development process.

[16] *Hellberg S, Liljenback H, Eskola O et al.* **Positron Emission Tomography Imaging of Macrophages in Atherosclerosis with (18)F-GE-180, a Radiotracer for Translocator Protein (TSPO)**. Contrast media & molecular imaging 2018; 2018:9186902.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29950954
ABSTRACT
Intraplaque inflammation plays an important role in the progression of atherosclerosis. The 18 kDa translocator protein (TSPO) expression is upregulated in activated macrophages, representing a potential target to identify inflamed atherosclerotic plaques. We preclinically evaluated (18)F-GE-180, a novel third-generation TSPO radioligand, in a mouse model of atherosclerosis. Methods. Nine hypercholesterolemic mice deficient in low density lipoprotein receptor and apolipoprotein B48 (LDLR(-/-)ApoB(100/100)) and six healthy C57BL/6N mice were injected with 10 MBq of (18)F-GE-180. Specificity of binding was demonstrated in three LDLR(-/-)ApoB(100/100) mice by injection of nonradioactive reference compound of (18)F-GE-180 before (18)F-GE-180. Dynamic 30-minute PET was performed followed by contrast-enhanced CT, and the mice were sacrificed at 60 minutes after injection. Tissue samples were obtained for ex vivo biodistribution measurements, and aortas were cut into serial cryosections for digital autoradiography. The presence of macrophages and TSPO was studied by immunohistochemistry. The (18)F-GE-180 retention in plaque areas with different macrophage densities and lesion-free vessel wall were compared. Results. The LDLR(-/-)ApoB(100/100) mice showed large, inflamed plaques in the aorta. Autoradiography revealed significantly higher (18)F-GE-180 retention in macrophage-rich plaque areas than in noninflamed areas (count densities 150 +/- 45 PSL/mm(2) versus 51 +/- 12 PSL/mm(2), $p < 0.001$). Prominent retention in the vessel wall without plaque was also observed (220 +/- 41 PSL/mm(2)). Blocking with nonradioactive GE-180 diminished the difference in count densities between macrophage-rich and noninflamed areas in atherosclerotic plaques and lowered the count density in vessel wall without plaque. Conclusion. (18)F-GE-180 shows specific uptake in macrophage-rich areas of atherosclerotic plaques in mice. However, retention in atherosclerotic lesions does not exceed that in lesion-free vessel wall. The third-generation TSPO radioligand (18)F-GE-180 did not show improved characteristics for imaging atherosclerotic plaque inflammation compared to previously studied TSPO-targeting tracers.

[17] *Torchon ET, Das S, Beckford RC, Voy BH*. **Enriching the Starter Diet in n-3 Polyunsaturated Fatty Acids Reduces Adipocyte Size in Broiler Chicks**. Current developments in nutrition 2017; 1:e001644.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29955687
ABSTRACT
Epidemiologic studies associate perinatal intake of eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) with reduced adiposity in children, suggesting that these fatty acids may alter adipose tissue development. The objective of this study was to determine whether enriching the perinatal diet in EPA and DHA reduces fat deposition in young chicks. Cobb 500 broiler chicks were fed isocaloric diets containing fat (8% wt:wt) from fish oil (FO), lard, canola oil, or flaxseed oil from 7 to 30 d of age. Adiposity (abdominal fat pad weight/body weight) at 30 d was not significantly affected by diet, but FO significantly reduced adipocyte size, increasing the abundance of small adipocytes. Plasma nonesterified fatty acid concentrations suggest that reduced adipocyte size was due, in part, to enhanced mobilization of fatty acids from adipose tissue. Our work indicates that dietary EPA and DHA effectively reduce the size of developing adipocytes in juveniles, which may limit adipose deposition and provide metabolic benefits.

[18] *Mirnejad R, Jahromi IR, Sepehrimanesh M et al.* **A proteomics analysis of the virulence factors of three common bacterial species involved in periodontitis and consequent possible atherosclerosis: A narrative review**. Current protein & peptide science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29938619
ABSTRACT
The incidence of cardiovascular disorders, especially coronary artery disease and atherosclerosis, is increasing alarmingly. Clarifying the underlying causes is of the utmost importance and should be elucidated in order to reduce this growing trend. Periodontitis is known as a chronic destructive disease with sophisticated pathophysiological mechanisms that slowly impose negative effects not only on the oral tissues but also on distant organs. Additionally, it has been shown in many studies that atherosclerosis and periodontitis utilized common inflammatory signaling pathways and mediators. Several lines of evidence have demonstrated the signatures of periodontitis-related bacteria in atherosclerotic plaque specimens. It is proposed that virulent proteins of these bacteria probably accelerate the initiation or development of plaque formation on the inner walls of the coronary arteries. Proteomics techniques are very sensitive and have a global point of view. They can help to discover host factors and pathogen-related biomarkers. This review summarizes the studies focused on the three most important bacterial species involved in both diseases and presents recent findings about the proteomic evaluation of virulence factors of these bacteria. The known mechanisms of action of the virulence factors are also described.

[19] *Gambhire VM, Salunkhe SM, Gambhire MS*. **Atorvastatin loaded lipid nanoparticles: Antitumor activity studies on MCF-7 breast cancer cells**. Drug development and industrial pharmacy 2018:1-37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29936872
ABSTRACT
Atorvastatin is a synthetic statin commonly used in treatment of hypercholesterolemia. Apart from this, statins appear to have pleiotropic effects, including modulation of cell growth, apoptosis. Through modulation of these pathways, statins have the potential to influence a

wide range of disease processes, including cancer. However, poor aqueous solubility (0.1mg/mL) and poor oral bioavailability has limited therapeutic application of atorvastatin. Present work is an attempt to improve tumor targeting of atorvastatin by incorporating in nanostructured lipid carriers (NLCs) and studying its anticancer activity on MCF-7 cell lines. NLCs of atorvastatin were formulated by high speed homogenization followed by probe sonication method. The optimized batch of NLCs had a mean size of 130.02 +/-3.1 nm and entrapment efficiency of 90.42 +/-3.7%. The in vitro drug release study by dialysis method indicated that drug entrapped in the NLCs remains entrapped at acidic pH as well as in phosphate buffer of pH 7.4 for a prolonged period of time as compared to plain drug. In vitro cytotoxicity studies on MCF- 7 (Mammary adenocarcinoma human cell lines) cell lines showed that concentration of drug required for total growth inhibition (TGI) and 50% growth inhibition (GI50) of MCF-7 cells was found to be 27.4 microg/mL and <10 microg/mL respectively, in case of atorvastatin- NLCs which is less than that required in case of plain atorvastatin and almost similar to that of adriamycin. All these findings reinforce the fact that atorvastatin loaded NLCs are promising novel delivery system for treating breast cancer.

[20] *Hansen D, Verboven K, Van Dijk JW et al.* **Adipose tissue lipolytic inhibition enhances the glucoregulatory properties of exercise in type 2 diabetes patients**. European journal of sport science 2018:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29938604
ABSTRACT
AIMS: Exercise combined with adipose tissue lipolytic inhibition augments intramuscular lipid and glycogen use in type 2 diabetes patients. The present study investigates the impact of adipose tissue lipolytic inhibition during exercise on subsequent postprandial glycemic control in type 2 diabetes patients. METHODS: Fourteen male type 2 diabetes patients (age 65 +/- 2 years, HbA1c 6.7 +/- 0.1% (50 +/- 2 mmol/mol)) participated in a double-blind placebo-controlled randomized cross-over study in which subjects performed endurance-type exercise after being administered 250 mg of a nicotinic acid analogue (acipimox; ACP) or a placebo (PLA). A control experiment was included in which no exercise was performed (CON). RESULTS: Sixty minutes of endurance-type exercise (at 45% Wpeak) did not significantly lower circulating plasma glucose and insulin excursions in PLA when compared with CON (P = .300). Acipimox administration strongly reduced circulating plasma FFA concentrations during exercise (P < .001). Circulating plasma glucose and insulin excursions were substantially lower during 7.5 h of recovery from exercise (i.e. postprandial) in ACP when compared with either CON (P = .041 and P = .002, respectively) or PLA (P = .009 and P = .001, respectively). CONCLUSIONS: Collectively, exercise with adipose tissue lipolytic inhibition reduces postprandial blood glucose and insulin excursions and, as such, further improves glycemic control in male type 2 diabetes patients.

[21] *Stechovsky C, Hajek P, Horvath M, Veselka J*. **Effect of Stenting on the Near-Infrared Spectroscopy-Derived Lipid Core Burden Index of Carotid Artery Plaque**. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29957596
ABSTRACT

AIMS: Catheter-based intravascular near-infrared spectroscopy (NIRS) detects a lipid signal from atherosclerotic plaque. The aim of this study was to describe the effect of carotid artery stenting (CAS) on the lipid signal in a carotid stenosis. METHODS AND RESULTS: We performed NIRS combined with intravascular ultrasound (IVUS) during 120 CAS procedures. Minimal luminal area (MLA) and plaque burden (PB) at the site of MLA were measured with IVUS and lipid core burden index (LCBI), maximal LCBI in a 4-mm segment of the artery (LCBImax) and LCBI in a 4-mm segment at the site of MLA (LCBImla) with NIRS-derived chemograms. NIRS-IVUS imaging was performed at baseline, after stent implantation and after balloon postdilatation. The most common lesion type was the fibrocalcific plaque (76%). Lipid-rich plaque (LCBImax >/=400) was present in 33% of carotid stenoses and in 20% at the site of MLA. Median MLA increased significantly from baseline to stent implantation (3.63 mm2 to 5.56 mm2, P<0.001) and to postdilatation (5.56 mm2 to 12.03 mm2, P<0.001). Median LCBI, LCBImax and LCBImla significantly decreased from baseline to stent implantation: LCBI (60 to 8, P<0.001), LCBImax (294 to 60, P<0.001) and LCBImla (124 to 0, P<0.001). Postdilatation of the stent had no further significant effect on median LCBI (8 to 5, P=0.890), LCBImax (60 to 50, P=0.690) and LCBImla (0 to 0, P=0.438). CONCLUSIONS: Carotid artery stenting significantly reduced the NIRS-derived lipid core burden index at the stented segment.

[22] *Pouwer MG, Pieterman EJ, Verschuren L et al.* **The BCR-ABL1 Inhibitors Imatinib and Ponatinib Decrease Plasma Cholesterol and Atherosclerosis, and Nilotinib and Ponatinib Activate Coagulation in a Translational Mouse Model**. Frontiers in cardiovascular medicine 2018; 5:55.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29946549
ABSTRACT
Treatment with the second and third generation BCR-ABL1 tyrosine kinase inhibitors (TKIs) increases cardiovascular risk in chronic myeloid leukemia (CML) patients. We investigated the vascular adverse effects of three generations of TKIs in a translational model for atherosclerosis, the APOE*3Leiden.CETP mouse. Mice were treated for sixteen weeks with imatinib (150 mg/kg BID), nilotinib (10 and 30 mg/kg QD) or ponatinib (3 and 10 mg/kg QD), giving similar drug exposures as in CML-patients. Cardiovascular risk factors were analyzed longitudinally, and histopathological analysis of atherosclerosis and transcriptome analysis of the liver was performed. Imatinib and ponatinib decreased plasma cholesterol (imatinib, -69%, $p < 0.001$; ponatinib 3 mg/kg, -37%, $p < 0.001$; ponatinib 10 mg/kg-44%, $p < 0.001$) and atherosclerotic lesion area (imatinib, -78%, $p < 0.001$; ponatinib 3 mg/kg, -52%, $p = 0.002$; ponatinib 10 mg/kg, -48%, $p = 0.006$), which were not affected by nilotinib. In addition, imatinib increased plaque stability. Gene expression and pathway analysis demonstrated that ponatinib enhanced the mRNA expression of coagulation factors of both the contact activation (intrinsic) and tissue factor (extrinsic) pathways. In line with this, ponatinib enhanced plasma levels of FVII, whereas nilotinib increased plasma FVIIa activity. While imatinib showed a beneficial cardiovascular risk profile, nilotinib and ponatinib increased the cardiovascular risk through induction of a pro-thrombotic state.

Literature update week 26 (2018)

[23] *Park YJ, Park J, Huh JY et al.* **Regulatory Roles of Invariant Natural Killer T Cells in Adipose Tissue Inflammation: Defenders Against Obesity-Induced Metabolic Complications**. Frontiers in immunology 2018; 9:1311.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29951059
ABSTRACT
Adipose tissue is a metabolic organ that plays a central role in controlling systemic energy homeostasis. Compelling evidence indicates that immune system is closely linked to healthy physiologic functions and pathologic dysfunction of adipose tissue. In obesity, the accumulation of pro-inflammatory responses in adipose tissue subsequently leads to dysfunction of adipose tissue as well as whole body energy homeostasis. Simultaneously, adipose tissue also activates anti-inflammatory responses in an effort to reduce the unfavorable effects of pro-inflammation. Notably, the interplay between adipocytes and resident invariant natural killer T (iNKT) cells is a major component of defensive mechanisms of adipose tissue. iNKT cells are leukocytes that recognize lipids loaded on CD1d as antigens, whereas most other immune cells are activated by peptide antigens. In adipose tissue, adipocytes directly interact with iNKT cells by presenting lipid antigens and stimulate iNKT cell activation to alleviate pro-inflammation. In this review, we provide an overview of the molecular and cellular determinants of obesity-induced adipose tissue inflammation. Specifically, we focus on the roles of iNKT cell-adipocyte interaction in maintaining adipose tissue homeostasis as well as the consequent modulation in systemic energy metabolism. We also briefly discuss future research directions regarding the interplay between adipocytes and adipose iNKT cells in adipose tissue inflammation.

[24] *Chen YA, Shih HW, Lin YC et al.* **Simvastatin Sensitizes Radioresistant Prostate Cancer Cells by Compromising DNA Double-Strand Break Repair**. Frontiers in pharmacology 2018; 9:600.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29950990
ABSTRACT
Prostate cancer (PCa) is one of the most prevalent male cancers in western world. Radiation therapy (RT) is commonly used to treat PCa patients. However, a certain proportion of patients develop radioresistant PCa cells, which results in metastatic disease. Statins, which inhibit 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, are commonly used to treat hypercholesterolemia, exhibiting beneficial effects on cardiovascular diseases and on several types of cancers, including PCa. However, the mechanistic details and crosstalk between statins and RT in PCa cells remain unknown. In this study, radioresistant DOC-2/DAB2 interactive protein (DAB2IP)-deficient PCa cells were used to evaluate whether simvastatin could enhance the effect of ionizing radiation (IR). The crucial molecules that associated with simvastatin elevated radiosensitivity in PCa cells were explored. Our results demonstrated that a combination treatment with simvastatin and IR synergistically induced apoptosis of radioresistant PCa cells. In addition, simvastatin appeared to compromise DNA double-strand breaks repair by activating the expressions of histone 2A family member X (gamma-H2AX) and phospho-checkpoint kinase 1 (p-CHK1), suggesting an underlying mechanism for this radiosensitization of PCa cells. These findings reveal that simvastatin may be a potent therapeutic agent for co-treatment with radiation to overcome radioresistance in PCa cells.

Literature update week 26 (2018)

[25] *Farahnak Z, Chapados N, Lavoie JM*. **Exercise training increased gene expression of LDL-R and PCSK9 in intestine: link to transintestinal cholesterol excretion**. General physiology and biophysics 2018; 37:309-317.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29938676
ABSTRACT
Transintestinal cholesterol excretion (TICE) is known as an alternate non-biliary route of cholesterol excretion from the body. The aim of this study was to determine whether exercise training has effects on intestinal membrane receptors involved in TICE in intact and ovariectomized (Ovx) rats. Sprague-Dawley rats were first divided into 4 groups: Sham operated and Ovx rats fed a standard diet (Sham-SD; Ovx-SD), or a high cholesterol diet (Sham-Chol; Ovx-Chol). These 4 groups were subsequently subdivided into either sedentary or voluntary wheel running groups for 6 weeks. The cholesterol diet resulted in increased hepatic cholesterol accumulation ($p< 0.001$) in both Sham and Ovx rats. Exercise training increased ($p < 0.01$) transcripts of intestinal low density lipoprotein receptor (LDL-R) and proprotein convertase subtilisin/kexin type 9 (PCSK9), which are involved in trans-intestinal cholesterol uptake from circulation, in both Sham and Ovx rats compared to rats remaining sedentary in all diet conditions. The up-regulation of intestinal gene expression of LDL-R and PCSK9 following voluntary wheel running in intact and Ovx rats suggests that exercise training may contribute to elimination of cholesterol through the TICE pathway.

[26] *Turk Veselic M, Zorz N, Erzen B et al.* **Improvement of arterial wall phenotype in subjects at moderate cardiovascular risk induced by very low-dose fluvastatin/valsartan combination: a pilot study**. International angiology : a journal of the International Union of Angiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29952159
ABSTRACT
BACKGROUND: The largest population that suffers from cardiovascular events are subjects at moderate cardiovascular risk. However, no effective and safe preventive treatment is available for this population. We investigated whether their arterial wall phenotype could be turned to a lower risk direction by low-dose fluvastatin/valsartan combination (low-flu/val). METHODS: Twenty males at moderate cardiovascular risk (as classified by SCORE) were blindly randomised into the intervention group (n=10, low-flu/val: 10 mg/20mg) or control group (n=10, placebo). At inclusion and after 30 days of treatment, brachial flow-mediated dilatation (FMD), beta-stiffness coefficient, carotid pulse wave velocity (c-PWV), carotid- femoral PWV, reactive hyperaemia index, high-sensitivity C-reactive protein (hs-CRP), interleukin 6, vascular cell adhesion molecule 1, total antioxidant status and expression of several protective genes (SIRT1, mTOR, NF-kappaB1, NFE2L2, PRKAA1) were followed. RESULTS: Treatment resulted in improved FMD (from 3% to 4.2%, p=0.008), c-PWV (from 6.7 to 6.2 m/s, p=0.006), hs-CRP (from 5.39 to 3.35 mg/L, p=0.041) and SIRT1 expression (3.34-fold difference, p=0.047). No other vascular, inflammation and genetic parameters changed. The hs-CRP values after intervention correlated significantly with SIRT1 expression. The improved FMD persisted even 10 weeks after treatment discontinuation. The obtained changes were not followed by changes of lipids or blood pressure. Overall, the results revealed improvement in three different, although interrelated preventive arterial wall characteristics. CONCLUSIONS: This pilot study revealed that intervention with low-flu/val importantly shifts the arterial wall phenotype in a lower risk

direction. This improvement could be interpolated into clinical benefits that remain to be further studied.

[27] *Banach M, Patti AM, Giglio RV et al.* **The Role of Nutraceuticals in Statin Intolerant Patients**. Journal of the American College of Cardiology 2018; 72:96-118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29957236
ABSTRACT
Statins are the most common drugs administered for patients with cardiovascular disease. However, due to statin-associated muscle symptoms, adherence to statin therapy is challenging in clinical practice. Certain nutraceuticals, such as red yeast rice, bergamot, berberine, artichoke, soluble fiber, and plant sterols and stanols alone or in combination with each other, as well as with ezetimibe, might be considered as an alternative or add-on therapy to statins, although there is still insufficient evidence available with respect to long-term safety and effectiveness on cardiovascular disease prevention and treatment. These nutraceuticals could exert significant lipid-lowering activity and might present multiple non-lipid-lowering actions, including improvement of endothelial dysfunction and arterial stiffness, as well as anti-inflammatory and antioxidative properties. The aim of this expert opinion paper is to provide the first attempt at recommendation on the management of statin intolerance through the use of nutraceuticals with particular attention on those with effective low-density lipoprotein cholesterol reduction.

[28] *Huang S, Li J, Wu Y et al.* **Tea Consumption and Longitudinal Change in High-Density Lipoprotein Cholesterol Concentration in Chinese Adults**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29941658
ABSTRACT
BACKGROUND: The relation between tea consumption and age-related changes in high-density lipoprotein cholesterol (HDL-C) concentrations remains unclear, and longitudinal human data are limited. The aim of current study was to examine the relation between tea intake and longitudinal change in HDL-C concentrations. METHODS AND RESULTS: Baseline (2006) tea consumption was assessed via a questionnaire, and plasma HDL-C concentrations were measured in 2006, 2008, 2010, and 2012 among 80 182 individuals (49+/-12 years of age) who did not have cardiovascular diseases or cancer, or did not use cholesterol-lowering agents both at baseline (2006) and during the follow-up period (2006-2012). The associations between baseline tea consumption and rate of change in HDL-C concentrations were examined using generalized estimating equation models. Tea consumption was inversely associated with a decreased rate of HDL-C concentrations (P-trend <0.0001) in the fully adjusted model. The adjusted mean difference in the HDL-C decreased rate was 0.010 (95% confidence interval, 0.008, 0.012) mmol/L per year for tea consumers versus nonconsumers (never or less than once/month group). Interactions between tea consumption and age, sex, lifestyle scores, and metabolic syndrome (all P-interaction <0.0001) were identified. The associations between greater tea consumption and slower decrease in HDL-C concentrations were more pronounced in men, individuals aged 60 or older, individuals with a lower lifestyle score, and individuals with metabolic syndrome (all P-trend <0.0001). CONCLUSIONS: Tea consumption was

associated with slower age-related decreases in HDL-C concentrations during 6 years of follow-up. CLINICAL TRIAL REGISTRATION: URL: www.chictr.org. Unique identifier: ChiCTR-TNRC-11001489.

[29] *Durham SH, Covington EW, Clemmons KJ*. **Hepatotoxicity upon using niacin to pass a drug test: A case report**. Journal of the American Pharmacists Association : JAPhA 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29941333
ABSTRACT
OBJECTIVES: To report a case of hepatotoxicity when niacin was used by a patient with HIV to pass a drug test. METHODS: Niacin is a soluble pyridine derivative widely used in the management of dyslipidemia. Common adverse effects include flushing, nausea, gastrointestinal discomfort, and hepatotoxicity. The use of niacin for nonmedical purposes has been increasing in prevalence in recent years, particularly in attempts to alter or mask results of urine drug tests. Although there is no scientific evidence that niacin can alter a urine drug screen result, easily retrievable information exists on the Internet touting niacin as a potential way to prevent detection of tetrahydrocannabinol (THC). The following report describes a case of hepatotoxicity in an HIV-infected adult who reported using niacin to mask THC in urine drug screen results. RESULTS: The patient developed marked elevations in his liver enzymes (aspartate aminotransferase greater than 25 times the upper limit of normal and alanine aminotransferase greater than 3 times the upper limit of normal) that resolved after discontinuation of the drug. Because of the patient's self-reported use and discontinuation of niacin, the Naranjo Adverse Drug Reaction Probability Scale demonstrated a "definite" relationship between the development of hepatotoxicity and the ingestion of over-the-counter sustained-release niacin. The patient did not develop further clinical abnormalities proposed to be secondary to niacin toxicity in previously published case reports, including glucose abnormalities, coagulopathies, metabolic acidosis, QTc prolongation, and myalgias. CONCLUSION: Health care providers should be aware of this nonmedical use of niacin to alter or mask a drug test, especially when discerning the cause of hepatotoxicity. In addition, pharmacists in the community setting should be aware of this use of niacin when encountering patients purchasing over-the-counter niacin, particularly in patients who may be more likely to use illicit substances.

[30] *Brandt EJ, Benes LB, Lee L et al.* **The Effect of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition on Sterol Absorption Markers in a Cohort of Real-World Patients**. Journal of cardiovascular pharmacology and therapeutics 2018:1074248418780733.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29940784
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is expressed in multiple tissues, including the small intestine. The effect of PCSK9 inhibition on cholesterol absorption is not known. OBJECTIVES: Measure serum cholesterol absorption markers before and after initiation of PCSK9 inhibitors. METHODS: Single-center retrospective cohort of patients administered evolocumab and alirocumab between July 2015 and January 2017. Paired t tests were used to compare mean serum cholesterol marker concentrations, and ratios to total cholesterol, before and after PCSK9 inhibitor initiation. Analyses were repeated for those taking

and not taking statins and taking or not taking ezetimibe at both initiation and follow-up, for each PCSK9 inhibitor, and based on follow-up time (<60, 60-120, and >120 days). RESULTS: There were 62 possible participants, 34 were excluded for lack of data or unknown PCSK9 inhibitor initiation date. Average follow-up was 92.5 days. Mean campesterol (before 3.14 mug/mL, 95% CI: 2.79-4.38 mug/mL; after 2.09 mug/mL, 95% CI: 1.87-2.31 mug/mL; P < .0001), sitosterol (before 2.46 mug/mL, 95% CI: 2.23-2.70 mug/mL; after 1.62 mug/mL, 95% CI: 1.48-1.75 mug/mL; P < .0001), and cholestanol (before 3.25 mug/mL, 95% CI: 3.04-3.47 mug/mL; after 2.08 mug/mL, 95% CI: 1.96-2.21 mug/mL; P < .0001) all significantly decreased at follow-up. There was no significant change in absorption marker to total cholesterol ratios. Findings were not influenced by statin or ezetimibe use or nonuse, which PCSK9 inhibitor was prescribed, or time to follow-up. CONCLUSION: Proprotein convertase subtilisin/kexin type 9 inhibition was associated with decreased cholesterol absorption markers.

[31] *Generoso G, Bensenor IM, Santos RD et al.* **Association between high-density lipoprotein subfractions and low-grade inflammation, insulin resistance, and metabolic syndrome components: The ELSA-Brasil study**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29941395
ABSTRACT
BACKGROUND: High-density lipoprotein cholesterol (HDL-C) can be divided into subfractions, which may have variable effects in atherogenesis. The results about the association between HDL-C subfractions and risk factors for cardiovascular disease are mixed. OBJECTIVE: The objective of this study was to analyze the association between HDL-C subfractions and each metabolic syndrome component, homeostasis model assessment-estimated insulin resistance (HOMA-IR) and C-reactive protein (CRP). METHODS: Four thousand five hundred thirty-two individuals between 35 and 74 years old without previous manifest cardiovascular disease not using fibrates were enrolled. HDL-C subfractions were separated by vertical ultracentrifugation (vertical auto profile-in mg/dL) into HDL2-C and HDL3-C. HDL2-C/HDL3-C ratio, HOMA-IR, and high-sensitivity CRP were also included in the analysis. RESULTS: Mean age of participants was 51 +/- 9 years, and 54.8% were women. In univariate analysis, HDL-C, HDL2-C, and HDL3-C were all inversely associated with each of the metabolic syndrome defining factors, HOMA-IR values, and serum CRP. We also observed a negative association between HDL2-C/HDL3-C ratio with the variables aforementioned even after adjusting for smoking, alcohol use, physical activity, and HDL-C levels (P < .01). CONCLUSION: HDL-C and its subfractions (HDL2-C and HDL3-C) are inversely associated with the defining features of metabolic syndrome, insulin resistance, and systemic inflammation. In addition, the HDL2-C/HDL3-C ratio measured by vertical auto profile is significantly associated with the former factors even after comprehensive adjustment for HDL-C and other confounding variables.

[32] *Maki KC*. **The ODYSSEY Outcomes trial: Clinical implications and exploration of the limits of what can be achieved through lipid lowering**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29941396
ABSTRACT

[33] *Taylor BA, Panza G, Ballard KD et al.* **Creatine supplementation does not alter the creatine kinase response to eccentric exercise in healthy adults on atorvastatin**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29945780
ABSTRACT
BACKGROUND: Serum creatine kinase (CK) levels are higher after eccentric, muscle-damaging exercise in statin-treated patients. This could contribute to the increased statin-associated muscle symptoms reported in physically active individuals. OBJECTIVE: We tested the hypothesis in this pilot study that creatine (Cr) monohydrate supplementation would reduce the CK response to eccentric exercise in patients using statins to determine if Cr supplementation could be a strategy to mitigate statin-associated muscle symptoms in physically active individuals. METHODS: Healthy, nonsmoking men (n = 5) and women (n = 14) were randomized to Cr monohydrate = atorvastatin 80 mg + 10 g Cr monohydrate (n = 10, age = 60 +/- 7 years) or to placebo (PL) = atorvastatin 80 mg + PL (n = 9, age = 52 +/- 6 years). After 4 weeks of treatment, subjects performed 45 minutes of eccentric exercise (downhill walking at a -15% grade). Serum CK levels, muscle soreness (visual analog scale after two squats), and muscle pain severity and interference (using the brief pain inventory) were measured before and after 4 weeks of treatment, and then for 4 consecutive days after downhill walking. Vitamin D, or serum 25(OH)D, was also measured at baseline. RESULTS: The PL group was younger (P = .01) but not otherwise different in blood lipids, vitamin D, CK, muscle visual analog scale, and pain scores before (all P > .21) or after (all P > .12) treatment. CK increased in all subjects after downhill walking (P < .01), but neither the relative peak change (expressed as group mean difference with 95% confidence intervals: 43.52% [-196.41, 283.45]) nor the absolute peak change (67.38 U/L [-121.55, 256.31]) relative to baseline was different between groups (P = .46 and .71, respectively). A similar lack of treatment effect was observed for muscle soreness (11.03 mm [-9.49, 31.55]), pain severity (0.77 pts [-0.95, 2.50]), and pain interference (1.02 pts [-1.25, 3.29]) with P-values for group comparisons = 0.27, 0.36, and 0.35, respectively. However, subjects with "insufficient" Vitamin D < 30 ng/mL (n = 10) had an approximately 2-fold greater CK increase with eccentric exercise (nominal P-value = .04) than subjects with higher vitamin D levels. CONCLUSION: Cr monohydrate did not reduce CK increases after exercise in statin-treated subjects. We did observe that low vitamin D levels are associated with a greater CK response to eccentric exercise in statin-treated subjects.

[34] *Ward NC, Watts GF*. **PCSK9 monoclonal antibody on a knife-edge: An article of faith in FH?** Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29945779
ABSTRACT

[35] *Wojcik C, Fazio S, McIntyre AD, Hegele RA*. **Co-occurrence of heterozygous CREB3L3 and APOA5 nonsense variants and polygenic risk in a patient with severe hypertriglyceridemia exacerbated by estrogen administration**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29954705
ABSTRACT

We describe a case of a 36-year-old woman with severe hypertriglyceridemia likely caused by double heterozygosity of a known pathogenic APOA5 nonsense variant (p.Q275X) and a novel CREB3L3 nonsense variant (p.C296X) on a background of very strong polygenic susceptibility. Her clinical course worsened with development of eruptive xanthomata after oral administration of 2 mg estradiol twice daily for 2 weeks as part of a medical protocol for intrauterine embryo transfer following in vitro fertilization. Her triglyceride levels decreased to baseline and xanthomata resolved without treatment after discontinuation of hormonal therapy, which also resulted in termination of pregnancy. Before undergoing a second embryo transfer using her natural cycle and no exogenous hormones, the patient started combination therapy with eicosapentaenoic acid ethyl ester and gemfibrozil, leading to an approximately 80% decrease in triglyceride levels. She continued treatment throughout pregnancy, which progressed to term with the delivery of healthy twins.

[36] *Suraweera D, Fanous C, Jimenez M et al.* **Risk of Cardiovascular Events in Patients with Primary Biliary Cholangitis - Systematic Review**. Journal of clinical and translational hepatology 2018; 6:119-126.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29951355
ABSTRACT
Background and Aims: Hypercholesterolemia is a common finding in patients with primary biliary cholangitis (PBC) and is a well-defined risk factor for cardiovascular disease. However, studies have been mixed on whether PBC patients do, in fact, have higher cardiovascular risk. The aim of this study is to review the current literature and provide an evidence-based assessment of cardiovascular risk in PBC patients. Methods: We performed a systematic literature search on PubMed regarding patients with PBC and cardiovascular events from the database inception to July 1, 2017. A total of 33 articles fulfilling our inclusion criteria were found. Results: The majority of the studies evaluated yielded no statistically significant difference in cardiovascular disease in the PBC population compared to the general public. However, some reports found a statistically significantly increase in coronary artery disease. Several studies have looked at the specific lipid profile of patients with PBC with hypocholesteremia. While these lipid abnormalities differ by stage of disease, there is evidence to suggest that the specific lipid profile in PBC may have lower atherogenicity than in patients with hypercholesterolemia without PBC. Studies looking at patients with PBC with other risk factors for cardiovascular disease, such as hypertension and metabolic syndrome, have consistently found a higher risk for cardiovascular disease in these patients. Statin treatment is effective in reducing lipid levels and possibly improving endothelial inflammation in patients with PBC with hypercholesterolemia. Conclusions: There is not enough evidence to suggest an increased risk of cardiovascular disease in patients with PBC with hypercholesterolemia, except for those individuals with concomitant features of metabolic syndrome. In patients with PBC with no additional cardiovascular risk factors, individual risk/benefit discussion on lipid-lowering treatment should be considered.

[37] *Drouin-Chartier JP, Tremblay AJ, Hogue JC et al.* **Plasma PCSK9 correlates with apoB-48-containing TG-rich lipoprotein production in men with insulin resistance**. Journal of lipid research 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29946054

ABSTRACT

Intestinal TG-rich lipoproteins (TRLs) are important in the pathogenesis of atherosclerosis in insulin resistance (IR). We investigated the association of plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations with apoB-48-containing TRL metabolism in 148 men displaying various degrees of IR by measuring in vivo kinetics of TRL apoB-48 during a constant-fed state after a primed-constant infusion of L-[5,5,5-D3]leucine. Plasma PCSK9 concentrations positively correlated with TRL apoB-48 pool size ($r = 0.31$, $p = 0.0002$) and production rate ($r = 0.24$, $p = 0.008$) but not fractional catabolic rate ($r = -0.04$, $p = 0.6$). Backward stepwise multiple linear regression analysis identified PCSK9 concentrations as a positive predictor of TRL apoB-48 production rate (standard beta = +0.20, $p = 0.007$) independent of BMI, age, type 2 diabetes/metformin use, dietary fat intake during the kinetic study, and fasting concentrations of TGs, insulin, glucose, LDL cholesterol, or C reactive protein. We also assessed intestinal expression of key genes involved in chylomicron processing from duodenal samples of 71 men. Expression of PCSK9 and HMG-CoAR genes was positively associated ($r = 0.43$, $p = 0.002$). These results support PCSK9 association with intestinal secretion and plasma overaccumulation of TRL apoB-48 in men with IR.

[38] *Yu D, Cai Y, Qin R et al.* **Total / high-density lipoprotein cholesterol and cardiovascular disease (re)hospitalisation nadir in type 2 diabetes**. Journal of lipid research 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29959181

ABSTRACT

Total cholesterol to high density lipoprotein cholesterol ratio (TC/HDL) is an important prognostic factor for cardiovascular disease (CVD). This study used restricted cubic spline modelling to investigate the dose-response associations between TC/HDL and both CVD hospitalisation and CVD re-hospitalisation in two independent prospective cohorts. The East Cambridgeshire and Fenland (ECF) cohort includes 4,704 patients with type 2 diabetes from 18 general practices in Cambridgeshire. The RAndomised controlled trial of Peer Support In type 2 Diabetes (RAPSID) cohort comprises 1,121 patients with type 2 diabetes with post-trial follow-up data. TC/HDL and other demographic and clinical measurements were measured at baseline. Outcomes were CVD hospitalisation over 2 years, and CVD re-hospitalisation after 90 days of the prior CVD hospitalisation. Modelling showed nonlinear relationships between TC/HDL and risks of CVD hospitalisation and re-hospitalisation consistently in both cohorts (all $P < 0.001$ for linear tests). The lowest risks of CVD hospitalisation and re-hospitalisation were consistently found for TC/HDL at 2.8 (95% confidence interval: 2.6 to 3.0) in both cohorts and both overall and by gender. This is lower than the current lipid control target, 4.0 of TC/HDL. Reducing the TC/HDL target to 2.8 would include a further 33-44% patients with TC/HDL in the 2.8-4.0 range. Studies are required to assess the effectiveness and cost effectiveness of the earlier introduction of, and more intensive, lipid lowering treatment needed to achieve this new lower TC/HDL target.

[39] *Naidoo P, Mothilal R, Blom DJ*. **Therapeutic Management of Dyslipidemia Patients at Very High Cardiovascular Risk (CARDIO TRACK): Protocol for the Observational Registry Study**. JMIR research protocols 2018; 7:e163.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29959115
ABSTRACT
BACKGROUND: Dyslipidemia is a major modifiable risk factor for atherosclerotic cardiovascular disease. Current South African guidelines recommend titrating lipid-lowering therapy (LLT) to low-density lipoprotein cholesterol (LDL-C) targets stratified by cardiovascular risk. The LDL-C goal for very high-risk patients is <1.8 mmol/L. In international studies, approximately 30% of patients do not achieve this goal despite receiving maximally tolerated statin doses. There is, however, a paucity of data on LDL-C goal achievement in very high-risk South African patients receiving maximal statin doses. OBJECTIVE: The goal of the research it to assess LDL-C goal achievement in, and clinical characteristics of, very high cardiovascular risk dyslipidemic patients receiving maximal tolerated statin doses with or without ezetimibe. METHODS: This is an observational, cross-sectional South African registry study that plans to include up to 30 sites and 500 study participants. Adult patients with very high cardiovascular risk status receiving stable, maximally tolerated statin doses (with or without ezetimibe) will be eligible for inclusion. RESULTS: Funding has been awarded and enrollment began on November 15, 2017, and was completed on April 13, 2018, with 507 participants. Database lock was done on June 21, 2018. The statistical analysis has commenced and we expect the final clinical study report to be completed by October 2018. CONCLUSIONS: This study will document the adequacy of LLT in those at highest risk and will thus fill an important data gap in South Africa. This data may be useful in assessing the need for novel LLTs like proprotein convertase subtilisin/kexin 9 inhibitors that substantially lower cholesterol levels in addition to optimal statin therapy. REGISTERED REPORT IDENTIFIER: RR1-10.2196/9248.

[40] *Brinchmann MF, Patel DM, Iversen MH*. **The Role of Galectins as Modulators of Metabolism and Inflammation**. Mediators of inflammation 2018; 2018:9186940.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29950926
ABSTRACT
Galectins are beta-galcotosid-binding lectins. The function of galectins varies with their tissue-specific and subcellular location, and their binding to carbohydrates makes them key players in several intra- and extracellular processes where they bind to glycosylated proteins and lipids. In humans, there are 12 identified galectins, some with tissue-specific distribution. Galectins are found inside cells and in the nucleus, cytosol, and organelles, as well as extracellularly. Galectin-1, -2, -3, -4, -7, -8, -9, and -12 can all induce T-cell apoptosis and modulate inflammation. In the context of metabolic control and loss of the same in, for example, diabetes, galectin-1, -2, -3, -9, and -12 are especially interesting. This review presents information on galectins relevant to the control of inflammation and metabolism and the potential to target galectins for therapeutic purposes.

[41] *Antonopoulos N, Machairas G, Migias G et al.* **Hydrophilic Interaction Liquid Chromatography-Electrospray Ionization Mass Spectrometry for Therapeutic Drug Monitoring of Metformin and Rosuvastatin in Human Plasma**. Molecules (Basel, Switzerland) 2018; 23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29954074
ABSTRACT

In this work a hydrophilic interaction liquid chromatography/positive ion electrospray mass spectrometric assay (HILIC/ESI-MS) has been developed and fully validated for the quantitation of metformin and rosuvastatin in human plasma. Sample preparation involved the use of 100 μL of human plasma, following protein precipitation and filtration. Metformin, rosuvastatin and 4-[2-(propylamino) ethyl] indoline 2 one hydrochloride (internal standard) were separated by using an X-Bridge-HILIC BEH analytical column (150.0 × 2.1 mm i.d., particle size 3.5 μm) with isocratic elution. A mobile phase consisting of 12% (v/v) 15 mM ammonium formate water solution in acetonitrile was used for the separation and pumped at a flow rate of 0.25 mL min(−1). The linear range of the assay was 100 to 5000 ng mL(−1) and 2 to 100 ng mL(−1) for metformin and rosuvastatin, respectively. The current HILIC-ESI/MS method allows for the accurate and precise quantitation of metformin and rosuvastatin in human plasma with a simple sample preparation and a short a chromatographic run time (less than 15 min). Plasma samples from eight patients were further analysed proving the capability of the proposed method to support a wide range of clinical studies.

[42] *Hoyles L, Fernandez-Real JM, Federici M et al.* **Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women**. Nat Med 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29942096
ABSTRACT
Hepatic steatosis is a multifactorial condition that is often observed in obese patients and is a prelude to non-alcoholic fatty liver disease. Here, we combine shotgun sequencing of fecal metagenomes with molecular phenomics (hepatic transcriptome and plasma and urine metabolomes) in two well-characterized cohorts of morbidly obese women recruited to the FLORINASH study. We reveal molecular networks linking the gut microbiome and the host phenome to hepatic steatosis. Patients with steatosis have low microbial gene richness and increased genetic potential for the processing of dietary lipids and endotoxin biosynthesis (notably from Proteobacteria), hepatic inflammation and dysregulation of aromatic and branched-chain amino acid metabolism. We demonstrated that fecal microbiota transplants and chronic treatment with phenylacetic acid, a microbial product of aromatic amino acid metabolism, successfully trigger steatosis and branched-chain amino acid metabolism. Molecular phenomic signatures were predictive (area under the curve = 87%) and consistent with the gut microbiome having an effect on the steatosis phenome (>75% shared variation) and, therefore, actionable via microbiome-based therapies.

[43] *Lopes LAR, Martins M, Farias LM et al.* **Cholesterol-Lowering and Liver-Protective Effects of Cooked and Germinated Mung Beans (Vigna radiata L.)**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29949855
ABSTRACT
We investigated the hypocholesterolemic and liver-protective effects of cooked and germinated whole mung beans. Hamsters were fed for 28 days on diets rich in saturated fatty acids and cholesterol, differing only in protein source (20%): casein, cooked whole mung bean, and germinated mung bean. After 28 days, we found reduced plasma concentrations of total cholesterol and non-HDL cholesterol, increased faecal cholesterol excretion, and reduced levels of asparagine aminotransferase and alanine aminotransferase enzymes in the liver. Reduction

in hepatic lipid deposition was observed between each of the mung bean groups relative to the casein group. In addition, the animals of the geminated mung bean group showed a lack of inflammatory infiltrate and better vascularisation of the hepatic tissue. Results from this study show significant hypocholesterolemic and liver-protective properties of the mung bean, which are further enhanced after germination.

[44] *Jaskiewicz A, Pajak B, Litwiniuk A et al.* **Geranylgeraniol Prevents Statin-Dependent Myotoxicity in C2C12 Muscle Cells through RAP1 GTPase Prenylation and Cytoprotective Autophagy**. Oxidative medicine and cellular longevity 2018; 2018:6463807.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29951166
ABSTRACT
The present study investigated the cytotoxic effects of statins (atorvastatin (ATR) and simvastatin (SIM), resp.) and methyl-beta-cyclodextrin (MbetaCD), at their respective IC50 concentrations, on muscle regeneration in the in vitro model of murine C2C12 myoblasts. Cotreatment with mevalonate (MEV), farnesol (FOH), geranylgeraniol (GGOH), or water-soluble cholesterol (Chol-PEG) was employed to determine whether the statin-dependent myotoxicity resulted from the lower cholesterol levels or the attenuated synthesis of intermediates of mevalonate pathway. Our findings demonstrated that while GGOH fully reverted the statin-mediated cell viability in proliferating myoblasts, Chol-PEG exclusively rescued MbetaCD-induced toxicity in myocytes. Statins caused loss of prenylated RAP1, whereas the GGOH-dependent positive effect was accompanied by loss of nonprenylated RAP1. Geranylgeranyltransferases are essential for muscle cell survival as inhibition with GGTI-286 could not be reversed by GGOH cotreatment. The increase in cell viability correlated with elevated AKT 1(S463) and GSK-3beta(S9) phosphorylations. Slight increase in the levels of autophagy markers (Beclin 1, MAP LC-3IIb) was found in response to GGOH cotreatment. Autophagy rose time-dependently during myogenesis and was inhibited by statins and MbetaCD. Statins and MbetaCD also suppressed myogenesis and neither nonsterol isoprenoids nor Chol-PEG could reverse this effect. These results point to GGOH as the principal target of statin-dependent myotoxicity, whereas plasma membrane cholesterol deposit is ultimately essential to restore viability of MbetaCD-treated myocytes. Overall, this study unveils for the first time a link found between the GGOH- and Chol-PEG-dependent reversal of statin- or MbetaCD-mediated myotoxicity and cytoprotective autophagy, respectively.

[45] *Wang X, Jia Z, Almoshari Y et al.* **Local Application of Pyrophosphorylated Simvastatin Prevents Experimental Periodontitis**. Pharm Res 2018; 35:164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29943090
ABSTRACT
PURPOSE: Simvastatin (SIM), a HMG-CoA reductase inhibitor widely prescribed for hypercholesterolemia, has been reported to ameliorate inflammation and promote osteogenesis. Its clinical applications on these potential secondary indications, however, have been hampered by its lack of osteotropicity and poor water solubility. To address this challenge, we propose to design and evaluate the therapeutic efficacy of a novel simvastatin prodrug with better water solubility and bone affinity. METHOD: The prodrug (SIM-PPi) was synthesized by directly conjugating a SIM trimer to a pyrophosphate (PPi). It was characterized and evaluated

in vitro for its water solubility, osteotropicity, toxicity, anti-inflammatory and osteoinductive properties. It was then tested for anti-inflammatory and osteoinductive properties in vivo by three weekly injections into gingiva of a ligature-induced experimental periodontitis rat model. RESULTS: In vitro studies showed that SIM-PPi has greatly improved water-solubility of SIM and shows strong binding to hydroxyapatite (HA). In macrophage culture, SIM-PPi inhibited LPS-induced pro-inflammatory cytokines (IL-1beta, IL-6). In osteoblast culture, it was found to significantly increase alkaline phosphatase (ALP) activity with accelerated mineral deposition, confirming the osteogenic potential of SIM-PPi. When tested in vivo on an experimental periodontal bone-loss model, SIM-PPi exhibited a superior prophylactic effect compared to dose equivalent SIM in reducing inflammatory cells and in preserving alveolar bone structure, as shown in the histological and micro-CT data. CONCLUSION: SIM-PPi may have the potential to be further developed for better clinical management of bone loss associated with periodontitis.

[46] *Gage MC, Becares N, Louie R et al.* **Disrupting LXRalpha phosphorylation promotes FoxM1 expression and modulates atherosclerosis by inducing macrophage proliferation**. Proceedings of the National Academy of Sciences of the United States of America 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29950315

ABSTRACT

Macrophages are key immune cells for the initiation and development of atherosclerotic lesions. However, the macrophage regulatory nodes that determine how lesions progress in response to dietary challenges are not fully understood. Liver X receptors (LXRs) are sterol-regulated transcription factors that play a central role in atherosclerosis by integrating cholesterol homeostasis and immunity. LXR pharmacological activation elicits a robust antiatherosclerotic transcriptional program in macrophages that can be affected by LXRalpha S196 phosphorylation in vitro. To investigate the impact of these transcriptional changes in atherosclerosis development, we have generated mice carrying a Ser-to-Ala mutation in myeloid cells in the LDL receptor (LDLR)-deficient atherosclerotic background (M-S196A(Ldlr-KO)). M-S196A(Ldlr-KO) mice fed a high-fat diet exhibit increased atherosclerotic plaque burden and lesions with smaller necrotic cores and thinner fibrous caps. These diet-induced phenotypic changes are consistent with a reprogramed macrophage transcriptome promoted by LXRalpha-S196A during atherosclerosis development. Remarkably, expression of several proliferation-promoting factors, including the protooncogene FoxM1 and its targets, is induced by LXRalpha-S196A. This is consistent with increased proliferation of plaque-resident cells in M-S196A(Ldlr-KO) mice. Moreover, disrupted LXRalpha phosphorylation increases expression of phagocytic molecules, resulting in increased apoptotic cell removal by macrophages, explaining the reduced necrotic cores. Finally, the macrophage transcriptome promoted by LXRalpha-S196A under dietary perturbation is markedly distinct from that revealed by LXR ligand activation, highlighting the singularity of this posttranslational modification. Overall, our findings demonstrate that LXRalpha phosphorylation at S196 is an important determinant of atherosclerotic plaque development through selective changes in gene transcription that affect multiple pathways.

[47] *Olry de Labry Lima A, Gimeno Ballester V, Sierra Sanchez JF et al.* **Cost-effectiveness and Budget Impact of Treatment with Evolocumab Versus Statins and Ezetimibe for Hypercholesterolemia in Spain**. Revista espanola de cardiologia (English ed.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29937273
ABSTRACT
INTRODUCTION AND OBJECTIVES: To analyze the cost-effectiveness ratio and budget impact of treatment with evolocumab (PCSK9 inhibitor) for patients in secondary prevention in the Spanish National Health System. METHODS: A budget impact analysis, decision tree and Markov models were designed under the public health system perspective, based on the only study with morbidity and mortality data (FOURIER). The alternatives compared were evolocumab vs statins, and dual therapy with ezetimibe in 5% of the population. The measure of effectiveness used was the number of cardiovascular events avoided. Univariate and probabilistic sensitivity analyses were performed. RESULTS: The average annual cost of patients receiving evolocumab was 11 134.78euro and 393.83euro for standard treatment (statins plus ezetimibe). The incremental cost-effectiveness ratio was > 600 000 euro per avoided cardiovascular event for both assessed outcomes (first: cardiovascular death, myocardial infarction, stroke, and hospitalization due to unstable angina or coronary revascularization; second: includes the first 3 events). To perform the 10-year Markov model, the average cost of standard treatment was 13 948.45euro vs 471 417.37euro with evolocumab. Treatment with evolocumab for patients with familial hypercholesterolemia would cost between 3 and 6.1 million euros, assuming a difference of 2.5 and 5.1 million euros with the standard treatment (2017). This difference would be between 204.3 and 1364.7 million euros (2021) for those with nonfamiliar hypercholesterolemia (secondary prevention). CONCLUSIONS: Treatment with evolocumab is associated with a lower frequency of cardiovascular events, but is inefficient for patients suitable to receive this drug in the Spanish National Health System.

[48] *Silvola JMU, Li XG, Virta J et al.* **Aluminum fluoride-18 labeled folate enables in vivo detection of atherosclerotic plaque inflammation by positron emission tomography**. Scientific reports 2018; 8:9720.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29946129
ABSTRACT
Inflammation plays an important role in the development of atherosclerosis and its complications. Because the folate receptor beta (FR-beta) is selectively expressed on macrophages, an FR targeted imaging agent could be useful for assessment of atherosclerotic inflammation. We investigated aluminum fluoride-18-labeled 1,4,7-triazacyclononane-1,4,7-triacetic acid conjugated folate ((18)F-FOL) for the detection of atherosclerotic plaque inflammation. We studied atherosclerotic plaques in mice, rabbits, and human tissue samples using (18)F-FOL positron emission tomography/computed tomography (PET/CT). Compound 2-deoxy-2-[(18)F]fluoro-D-glucose ((18)F-FDG) was used as a comparison. Firstly, we found that the in vitro binding of (18)F-FOL co-localized with FR-beta-positive macrophages in carotid endarterectomy samples from patients with recent ischemic symptoms. We then demonstrated specific accumulation of intravenously administered (18)F-FOL in atherosclerotic plaques in mice and rabbits using PET/CT. We noticed that the (18)F-FOL uptake correlated with the density of macrophages in plaques and provided a target-to-background ratio as high as (18)F-

FDG, but with considerably lower myocardial uptake. Thus, (18)F-FOL PET/CT targeting of FR-beta-positive macrophages presents a promising new tool for the in vivo imaging of atherosclerotic inflammation.

[49] Zain MA, Siddiqui WJ. Coronary Stents. In: StatPearls. Treasure Island (FL): StatPearls Publishing
StatPearls Publishing LLC.; 2018.
[50] *Climent E, David B, Flores-Le Roux JA et al.* **Changes in the lipid profile 5 years after bariatric surgery: laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy**. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29941302
ABSTRACT
BACKGROUND: Few studies have compared mid-term results of laparoscopic Roux-en-Y gastric bypass (LRYGB) versus laparoscopic sleeve gastrectomy (LSG), and none have focused on lipid profile. OBJECTIVES: To compare LRYGB versus LSG with respect to lipid disturbance evolution and remission at mid-term after bariatric surgery (BS) and to assess associated factors with the remission of lipid disturbances at 5 years. SETTING: Hospital del Mar, Barcelona, from January 2005 to January 2012. METHODS: A retrospective analysis of a nonrandomized, prospective cohort was conducted on patients undergoing BS at Hospital del Mar, Barcelona, from January 2005 to January 2012 with >/=5 years' follow-up. RESULTS: Of 259 patients, 151 (58.3%) completed the 5-year follow-up. The proportion of patients who achieved normal low-density lipoprotein cholesterol levels at 5 years post-LRYGB was greater than after LSG (30/49 [61.2%] versus 6/23 [26.1%]; P=.005), being male sex, absence of statins treatment, and type of BS technique (LRYGB) the associated factors with remission. Hypertriglyceridemia remission was also higher after LRYGB (23/25 [92.0%] versus 10/15 [66.7%]; P=.041), although type of surgery was not an associated factor. No differences were found in remission rates of low high-density lipoprotein cholesterol between groups. Absence of fibrates treatment and 5-year percentage of excess weight loss were independently associated with hypertriglyceridemia remission, and only the latter was independently associated with low high-density lipoprotein cholesterol remission 5 years after surgery. CONCLUSIONS: Five-year outcome data showed that, among patients with severe obesity undergoing BS, LRYGB was associated with a higher total and low-density lipoprotein cholesterol reduction and remission in comparison to LSG, with no differences in hypertriglyceridemia and high-density lipoprotein cholesterol normalization.