Literature update week 13 (2018)

[1] *Maixent JM, Gerbi A, Barbey O et al.* **Dietary fish oil promotes positive inotropy of ouabain in the rat heart**. American journal of physiology. Heart and circulatory physiology 1999; 277:H2290-h2297.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29592273
ABSTRACT
We tested the hypothesis that a fish oil (FO) diet promotes positive inotropy of ouabain without increased toxicity. For 2 mo, two groups of adult male rats were fed 1) a regular food diet supplemented with dietary long-chain polyunsaturated fatty acid from FO or 2) a regular food diet (control). The responsiveness to ouabain was evaluated for the two groups in Langendorff-perfused hearts, by(31)P nuclear magnetic resonance spectroscopy, and on purified membrane-bound Na-K-ATPase. The maximum positive inotropy achieved with ouabain was nearly two times higher in the FO than in the control group and was not associated with significant changes in energetics. Alteration of function and energetic metabolism and inhibition of Na-K-ATPase in response to 3 x 10(-4) M ouabain were delayed in the FO group. This study demonstrates that dietary FO, by a cardiac membrane incorporation of n-3 polyunsaturated fatty acid, promotes positive inotropy of ouabain without toxicity and changes in cardiac metabolism.

[2] *Ahangari N, Ghayour Mobarhan M, Sahebkar AH, Pasdar A*. **Molecular Aspects of Hypercholesterolemia Treatment; Current Perspectives and Hopes**. Annals of medicine 2018:1-16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29578362
ABSTRACT
BACKGROUND: Hypercholesterolemia is a pathological condition which has been reported in 39% of the worlds' adult population. We aimed to review molecular aspects of current and novel therapeutic approaches based on low-density lipoprotein cholesterol lowering strategies. METHODS: Searching through PubMed and Scopus databases for relative articles using the following keywords have been done: Hypercholesterolemia, Therapy, lipid-lowering drugs, low-density lipoprotein cholesterol. RESULTS: Pathogenic mutations in the LDLR, ApoB, PCSK9 and LDLRAP genes cause deficient clearance of circulating low-density lipoprotein cholesterol particles via hepatic LDL receptor leading to increased plasma LDL cholesterol levels from birth and deposition in the arterial wall, hence leading to atherosclerosis and increased risk of premature cardiovascular diseases. CONCLUSION: Currently, statins, Ezetimibe, Bile acid sequestrants and PCSK9 inhibitors are the main therapeutic agents for the treatment of hypercholesterolemia. Moreover, novel RNA-based therapy had a strong impact on therapeutic strategies in recent decades. Additional development in understanding of the molecular basis of hypercholesterolemia will provide opportunities for development of targeted therapy in the near future.

[3] *Munkboel CH, Baake MLK, Styrishave B*. **Atorvastatin decreases steroid production in H295R cells and in major endocrine tissues of male rats**. Archives of toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574565
ABSTRACT

Obesity is increasing worldwide, and since obesity is associated with dyslipidemia, the consumption of cholesterol-lowering pharmaceuticals has increased. The aim of this study was therefore to study potential endocrine disrupting effects of one of the world's most frequently prescribed drugs, the cholesterol-lowering drug, atorvastatin (ATO) in vitro using the H295R steroidogenesis assay and in vivo using male Sprague-Dawley rats. We analyzed all major steroids in the mammalian steroidogenesis using liquid chromatography-tandem mass spectrometry (LC-MS/MS). In vitro, ATO significantly decreased all steroids in the H295R steroidogenesis at concentrations close to human plasma Cmax values, with an IC50 value for testosterone of 0.093 +/- 0.033 microM. Additionally, we determined steroid hormone levels in testis, adrenals, brain and plasma from rats after 14 days of exposure to three therapeutically relevant doses of ATO and observed pronounced decreasing steroid levels in particular in testis and adrenals but also in brain and plasma. In testis, all major steroidogenic enzymes were up-regulated, indicating autocrine and/or paracrine compensation for the decrease in steroid production by this tissue. In adrenals, StAR and CYP11A1 gene expression were decreased, whereas little effects were observed in the brain. Furthermore, we analyzed plasma LH and ACTH levels to investigate feedback via the PT and HPA axes. No effects were observed on LH levels, indicating little compensation via the PT axis. In contrast, ACTH levels increased during ATO exposure, indicating that the HPA axis to some extend compensated for the decrease in adrenal steroid production. Overall, ATO exerted pronounced effects on steroid production both in vitro and in vivo at therapeutically relevant doses. This clearly demonstrates the high potency of ATO to affect steroid homeostasis during therapeutic treatment. Further clinical and epidemiological studies should be conducted to investigate the relevance of these observations in patients treated with cholesterol-lowering pharmaceuticals.

[4] *Andrews JPM, Fayad ZA, Dweck MR*. **New methods to image unstable atherosclerotic plaques**. Atherosclerosis 2018; 272:118-128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29602139
ABSTRACT
Atherosclerotic plaque rupture is the primary mechanism responsible for myocardial infarction and stroke, the top two killers worldwide. Despite being potentially fatal, the ubiquitous prevalence of atherosclerosis amongst the middle aged and elderly renders individual events relatively rare. This makes the accurate prediction of MI and stroke challenging. Advances in imaging techniques now allow detailed assessments of plaque morphology and disease activity. Both CT and MR can identify certain unstable plaque characteristics thought to be associated with an increased risk of rupture and events. PET imaging allows the activity of distinct pathological processes associated with atherosclerosis to be measured, differentiating patients with inactive and active disease states. Hybrid integration of PET with CT or MR now allows for an accurate assessment of not only plaque burden and morphology but plaque biology too. In this review, we discuss how these advanced imaging techniques hold promise in redefining our understanding of stable and unstable coronary artery disease beyond symptomatic status, and how they may refine patient risk-prediction and the rationing of expensive novel therapies.

[5] *Hodges GW, Bang CN, Forman JL et al.* **Effect of simvastatin and ezetimibe on suPAR levels and outcomes**. Atherosclerosis 2018; 272:129-136.

Literature update week 13 (2018)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29602140
ABSTRACT
BACKGROUND AND AIMS: Soluble urokinase plasminogen activator receptor (suPAR) is an inflammatory marker associated with cardiovascular disease. Statins lower both low-density lipoprotein (LDL)-cholesterol and C-reactive protein (CRP), resulting in improved outcomes. However, whether lipid-lowering therapy also lowers suPAR levels is unknown. METHODS: We investigated whether treatment with Simvastatin 40mg and Ezetimibe 10mg lowered plasma suPAR levels in 1838 patients with mild-moderate, asymptomatic aortic stenosis, included in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, using a pattern mixture model. A 1-year Cox analysis, adjusted for established cardiovascular risk factors, allocation to study treatment, peak aortic valve velocity and baseline suPAR, was performed to evaluate relationships between change in suPAR with all-cause mortality and the composite endpoint of major cardiovascular events (MCE) composed of ischemic cardiovascular events (ICE) and aortic valve related events (AVE). RESULTS: After 4.3 years of follow-up, suPAR levels had increased by 9.2% (95% confidence interval [CI]: 7.0%-11.5%) in the placebo group, but only by 4.1% (1.9%-6.2%) in the group with lipid-lowering treatment (p<0.001). In a multivariate 1-year analysis, 1-year suPAR was strongly associated with all-cause mortality, hazard ratio (HR)=2.05 (1.17-3.61); MCE 1.40 (1.01-1.92); and AVE 1.42 (1.02-1.99) (all p<0.042) for each doubling of suPAR; but was not associated with ICE. CONCLUSIONS: Simvastatin and Ezetimibe treatment impeded the progression of the time-related increase in plasma suPAR levels. Year-1 suPAR was associated with all-cause mortality, MCE, and AVE irrespective of baseline levels (SEAS study: NCT00092677).

[6] *Stock J*. **The highs and lows of cardiovascular disease prevention**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29602514
ABSTRACT

[7] *Qi W, Cao D, Li Y et al.* **Atorvastatin ameliorates early brain injury through inhibition of apoptosis and ER stress in a rat model of subarachnoid hemorrhage**. Bioscience reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29592873
ABSTRACT
Objective: Aneurysmal subarachnoid hemorrhage (SAH) is a severe cerebrovascular disease with very poor prognosis. The aim of this study was to evaluate the protective effects of atorvastatin on early brain injury (EBI) after SAH using a perforation SAH model. Methods: Male Sprague-Dawley rats were randomly divided into four groups: the sham group, the SAH group (model group), SAH + 10 mg.kg(-1).d(-1) atorvastatin (low atorvastatin group), and SAH + 20 mg.kg(-1).d(-1) atorvastatin (high atorvastatin group). Atorvastatin was administered orally by gastric gavage for 15 days before operation. At 24 h after SAH, we evaluated the effects of atorvastatin on brain water content, apoptosis by TUNEL assay and scanning electron microscope, and the expression of apoptosis-related proteins by immunofluorescence and western blotting analysis. Results: Compared with the sham group, we observed increased brain water content, significant apoptosis and elevated levels of apoptosis-related proteins including caspase-3, CCAAT enhancer-binding protein homologous protein (CHOP), the 78 kDa glucose-regulated protein (GRP78), and aquaporin-4 (AQP4) in the SAH group. Atorvastatin

administration under all doses could significantly reduce brain water content, apoptosis, and the expression levels of caspase-3, CHOP, GRP78, and AQP4 at 24 h after SAH. Conclusion: Our data show that early treatment with atorvastatin effectively ameliorates EBI after SAH through anti-apoptotic effects and the effects might be associated inhibition of caspase-3 and endoplasmic reticulum stress related proteins CHOP and GRP78.

[8] *Karlsson SA, Hero C, Svensson AM et al.* **Association between refill adherence to lipid-lowering medications and the risk of cardiovascular disease and mortality in Swedish patients with type 2 diabetes mellitus: a nationwide cohort study**. BMJ open 2018; 8:e020309.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29602853

ABSTRACT

OBJECTIVES: To analyse the association between refill adherence to lipid-lowering medications, and the risk of cardiovascular disease (CVD) and mortality in patients with type 2 diabetes mellitus. DESIGN: Cohort study. SETTING: National population-based cohort of Swedish patients with type 2 diabetes mellitus. PARTICIPANTS: 86 568 patients aged >/=18 years, registered with type 2 diabetes mellitus in the Swedish National Diabetes Register, who filled at least one prescription for lipid-lowering medication use during 2007-2010, 87% for primary prevention. EXPOSURE AND OUTCOME MEASURES: Refill adherence of implementation was assessed using the medication possession ratio (MPR), representing the proportion of days with medications on hand during an 18-month exposure period. MPR was categorised by five levels (</=20%, 21%-40%, 41%-60%, 61%-80% and >80%). Patients without medications on hand for >/=180 days were defined as non-persistent. Risk of CVD (myocardial infarction, ischaemic heart disease, stroke and unstable angina) and mortality by level of MPR and persistence was analysed after the exposure period using Cox proportional hazards regression and Kaplan-Meier, adjusted for demographics, socioeconomic status, concurrent medications and clinical characteristics. RESULTS: The hazard ratios for CVD ranged 1.33-2.36 in primary prevention patients and 1.19-1.58 in secondary prevention patients, for those with MPR </=80% (p<0.0001). The mortality risk was similar regardless of MPR level. The CVD risk was 74% higher in primary prevention patients and 33% higher in secondary prevention patients, for those who were non-persistent (p<0.0001). The mortality risk was 6% higher in primary prevention patients and 18% higher in secondary prevention patients, for non-persistent patients (p<0.0001). CONCLUSIONS: Higher refill adherence to lipid-lowering medications was associated with lower risk of CVD in primary and secondary prevention patients with type 2 diabetes mellitus.

[9] *de Mello AH, Uberti MF, de Farias BX et al.* **n-3 PUFA and obesity: from peripheral tissues to the central nervous system**. The British journal of nutrition 2018:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29580307

ABSTRACT

The current paradigms of prevention and treatment are unable to curb obesity rates, which indicates the need to explore alternative therapeutic approaches. Obesity leads to several damages to the body and is an important risk factor for a number of other chronic diseases. Furthermore, despite the first alterations in obesity being observed and reported in peripheral tissues, studies indicate that obesity can also cause brain damage. Obesity leads to a chronic

low-grade inflammatory state, and the therapeutic manipulation of inflammation can be explored. In this context, the use of n-3 PUFA (especially in the form of fish oil, rich in EPA and DHA) may be an interesting strategy, as this substance is known by its anti-inflammatory effect and numerous benefits to the body, such as reduction of TAG, cardiac arrhythmias, blood pressure and platelet aggregation, and has shown potential to help treat obesity. Thereby, the aim of this narrative review was to summarise the literature related to n-3 PUFA use in obesity treatment. First, the review provides a brief description of the obesity pathophysiology, including alterations that occur in peripheral tissues and at the central nervous system. In the sequence, we describe what are n-3 PUFA, their sources and their general effects. Finally, we explore the main topic linking obesity and n-3 PUFA. Animal and human studies were included and alterations on the whole organism were described (peripheral tissues and brain).

[10] *Cesena FHY, Laurinavicius AG, Valente VA et al.* **Low-density lipoprotein-cholesterol lowering in individuals at intermediate cardiovascular risk: Percent reduction or target level?** Clinical cardiology 2018; 41:333-338.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574925
ABSTRACT
BACKGROUND: Recommendations for blood cholesterol management differ across different guidelines. HYPOTHESIS: Lipid-lowering strategies based on low-density lipoprotein-cholesterol (LDL-c) percent reduction or target concentration may have different effects on the expected cardiovascular benefit in intermediate-risk individuals. METHODS: We selected individuals between 40 and 75 years of age with 10-year risk for atherosclerotic cardiovascular disease (ASCVD) between 5.0% and <7.5% who underwent a routine health screening. For every subject, we simulated a strategy based on a 40% LDL-c reduction (S40%) and another strategy based on achieving LDL-c target </=100 mg/dL (Starget-100). The cardiovascular benefit was estimated assuming a 22% relative risk reduction in major cardiovascular events for each 39 mg/dL of LDL-c lowered. RESULTS: The study comprised 1756 individuals (94% men, 52 +/- 5 years old). LDL-c and predicted 10-year ASCVD risk would be slightly lower in S40% compared to Starget-100 . The number needed to treat to prevent 1 major cardiovascular event in 10 years (NNT10) would be 56 with S40% and 66 with Starget-100 . S40% would prevent more events in individuals with lower baseline LDL-c, whereas Starget-100 would be more protective in those with higher LDL-c. A dual-target strategy (40% minimum LDL-c reduction and achievement of LDL-c </=100 mg/dL) would be associated with outcomes similar to those expected with the S40% (NNT10 = 55). CONCLUSIONS: In an intermediate-risk population, cardiovascular benefit from LDL-c lowering may be optimized by tailoring the treatment according to the baseline LDL-c or by setting a dual-target strategy (fixed dose statin plus achievement of target LDL-c concentration).

[11] *Li X, Gao L, Wang Z et al.* **Lipid profile and incidence of atrial fibrillation: A prospective cohort study in China**. Clinical cardiology 2018; 41:314-320.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29575115
ABSTRACT
BACKGROUND: The association between dyslipidemia, a major risk factor for cardiovascular diseases, and atrial fibrillation (AF) is not clear because of limited evidence. HYPOTHESIS:

Dyslipidemia may be associated with increased risk of AF in a Chinese population. METHODS: A total of 88 785 participants free from AF at baseline (2006-2007) were identified from the Kailuan Study. Fasting levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured at baseline using standard procedures. The study population was stratified based on quartiles of lipid profile. Incident AF was ascertained from electrocardiograms at biennial follow-up visits (2008-2015). The associations between incident AF and the different lipid parameters (TC, LDL-C, HDL-C, and TG) were assessed by Cox proportional hazards regression analysis. RESULTS: Over a mean follow-up period of 7.12 years, 328 subjects developed AF. Higher TC (hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.43-0.84) and LDL-C (HR: 0.60, 95% CI: 0.43-0.83) levels were inversely associated with incident AF after multivariable adjustment. HDL-C and TG levels showed no association with newly developed AF. The results remained consistent after exclusion of individuals with myocardial infarction or cerebral infarction, or those on lipid-lowering therapy. Both TC/HDL-C and LDL-C/HDL-C ratios were inversely associated with risk of AF (per unit increment, HR: 0.88, 95% CI: 0.79-0.98 and HR: 0.77, 95% CI: 0.66-0.91, respectively). CONCLUSIONS: TC and LDL-C levels were inversely associated with incident AF, whereas no significant association of AF with HDL-C or TG levels was observed.

[12] *Kotyla P*. **Low dose of simvastatin reduces disease activity and improves endothelial function in patients with SLE**. Clinical and experimental rheumatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29600937
ABSTRACT

[13] *Tacconelli S, Dovizio M, Di Francesco L et al.* **Reduced variability to aspirin antiplatelet effect by the coadministration of statins in high-risk patients for cardiovascular disease**. Clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574792
ABSTRACT
We studied the influence of cardiovascular(CV) risk factors, previous CV events, and co-treatments with preventive medicines, on residual platelet thromboxane(TX)B2 production in 182 patients chronically treated with enteric coated(EC)-aspirin(100mg/day). The response to aspirin was also verified by assessing arachidonic acid-induced platelet aggregation and urinary 11-dehydro-TXB2 levels. Residual serum TXB2 levels exceeded the upper limit value for an adequate aspirin response in 14% of individuals. This phenomenon was detected at 12h after dosing with aspirin. The co-administration of statins(atorvastatin, used mostly) was an independent predictor of residual serum TXB2 levels, and the percentage of patients with enhanced values was significantly lower in statin users vs. nonusers. We provide evidence in vitro that atorvastatin reduced residual TXB2 generation by increasing the extent of acetylation of platelet COX-1 by aspirin. In conclusion, the coadministration of statins may counter the mechanisms associated with reduced bioavailability of aspirin detected in some individuals with CV disease.

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[14] *Apostolopoulou M, Gordillo R, Koliaki C et al.* **Specific Hepatic Sphingolipids Relate to Insulin Resistance, Oxidative Stress, and Inflammation in Nonalcoholic Steatohepatitis**. Diabetes Care 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29602794
ABSTRACT
OBJECTIVE: Insulin resistance and nonalcoholic fatty liver (NAFL) disease have been linked to several lipid metabolites in animals, but their role in humans remains unclear. This study examined the relationship of sphingolipids with hepatic and peripheral metabolism in 21 insulin-resistant obese patients without (NAFL-) or with (NAFL+) and nonalcoholic steatohepatitis (NASH), and 7 healthy lean individuals undergoing tissue biopsies during bariatric or elective abdominal surgery. RESEARCH DESIGN AND METHODS: Hyperinsulinemic-euglycemic clamps with d-[6,6-(2)H2]glucose were performed to quantify tissue-specific insulin sensitivity. Hepatic oxidative capacity, lipid peroxidation, and the phosphorylated-to-total c-Jun N-terminal kinase (pJNK-to-tJNK) ratio was measured to assess mitochondrial function, oxidative stress, and inflammatory activity. RESULTS: Hepatic total ceramides were higher by 50% and 33% in NASH compared with NAFL+ and NAFL-, respectively. Only in NASH were hepatic dihydroceramides (16:0, 22:0, and 24:1) and lactosylceramides increased. Serum total ceramides and dihydroceramides (hepatic dihydroceramides 22:0 and 24:1) correlated negatively with whole-body but not with hepatic insulin sensitivity. Hepatic maximal respiration related positively to serum lactosylceramides subspecies, hepatic sphinganine, and lactosylceramide 14:0. Liver lipid peroxides (total ceramides, sphingomyelin 22:0) and the pJNK-to-tJNK ratio (ceramide 24:0; hexosylceramides 22:0, 24:0, and 24:1) all positively correlated with the respective hepatic sphingolipids. CONCLUSIONS: Sphingolipid species are not only increased in insulin-resistant humans with NASH but also correlate with hepatic oxidative stress and inflammation, suggesting that these lipids may play a role during progression of simple steatosis to NASH in humans.

[15] *Landmesser U, Chapman MJ, Stock JK et al.* **New prospects for PCSK9 inhibition?** European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29579192
ABSTRACT

[16] *Milner J, Cunha A, Gamboa-Cruz C et al.* **Recent major advances in cardiovascular pharmacotherapy**. Eur J Clin Pharmacol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29589064
ABSTRACT
The field of cardiovascular pharmacotherapy remains extremely active. The aim of this review is to summarize the recent major advances in cardiovascular pharmacotherapy, with a focus on (1) the new approved drug for treatment of heart failure with reduced ejection fraction-sacubitril/valsartan; (2) proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors; (3) the novel reversal agents for non-vitamin K oral anticoagulants (NOACs); and finally, (4) new evidence on pharmacological treatment of coronary artery disease.

[17] *Liu H, Cai M*. **Effect of probucol on hemodynamics, rheology and blood lipid of diabetic retinopathy**. Experimental and therapeutic medicine 2018; 15:3809-3814.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29581738
ABSTRACT
The effect of probucol in the treatment of diabetic retinopathy was investigated to analyze its impact on its hemodynamics, rheology and blood lipid. A total of 80 patients with diabetic retinopathy who were treated in the Ninth People's Hospital of Chongqing (Chongqing, China) from January 2015 to August 2016 were selected and divided into two groups by random number table, with 40 patients in each group. Control group was treated by conventional and intensive glycemic control and antihypertensive therapy, while observation group was orally administered with 0.375 g probucol twice a day on the basis of intensive therapy. Outpatient follow-up was performed to all the patients for 6 months, then, among the blood rheology, the changes in blood viscosity and erythrocyte aggregation indexes at different time points before and after intervention in the two groups were compared, mean blood flow velocities in renal artery, renal artery pulse indexes and renal artery resistance indexes at different time points were recorded, changes in blood lipid of the two groups before and after intervention were compared, and complication rates during the treatment were calculated. After intervention, the whole blood viscosity at high shear rate, whole blood viscosity at low shear rate and plasma viscosity in observation group were lower than those before intervention and lower than those in control group after intervention (P<0.05); The erythrocyte aggregation indexes in observation group were obviously increased compared with those in control group at 1 week, 1 month and 6 months after intervention (P<0.05). The mean blood flow velocities in renal artery in observation group were remarkably higher than those in control group at 1 week, 1 month and 6 months after intervention (P<0.05), while the renal artery pulse indexes and resistance indexes in observation group were lower than those in control group in the same period (P<0.05). In observation group, the levels of total cholesterol (TC), triglyeride (TG) and low density lipoprotein cholesterol (LDL-C) after intervention were decreased compared with those before intervention, while the level of high-density lipoprotein cholesterol (HDL-C) was increased. The levels of TC, TG and LDL-C in observation group were lower than those in control group after intervention, while the HDL-C level was higher (P<0.05). During the treatment, the total incidence of phlebitis, chills, fever, rash and maculopapule in observation group was obviously lower than that in control group. Probucol can significantly improve the hemodynamic and rheological indexes and lower blood lipid in the body, and is an effective medicine for diabetic retinopathy.

[18] *Zeki AA, Elbadawi-Sidhu M*. **Innovations in asthma therapy: is there a role for inhaled statins?** Expert review of respiratory medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29575963
ABSTRACT
INTRODUCTION: Asthma manifests as chronic airflow obstruction with persistent inflammation and airway hyperresponsiveness. The immunomodulatory and anti-inflammatory properties of the HMG-CoA reductase (HMGCR) inhibitors (a.k.a. statins), suggest a therapeutic role in chronic inflammatory lung diseases. However, despite positive laboratory investigations and promising epidemiological data, clinical trials using statins for the treatment of asthma have

yielded conflicting results. Inadequate statin levels in the airway compartment could explain these findings. Areas covered: HMGCR is in the mevalonate (MA) pathway and MA signaling is fundamental to lung biology and asthma. This article will discuss clinical trials of oral statins in asthma, review lab investigations relevant to the systemic versus inhaled administration of statins, address the advantages and disadvantages of inhaled statins, and answer the question: is there a role for delivering inhaled statins for the treatment of asthma? Expert commentary: If ongoing investigations show that oral administration of statins has no clear clinical benefits, then repurposing statins for delivery via inhalation is a logical next step. Inhalation of statins bypasses first-pass metabolism by the liver, and therefore, allows for delivery of significantly lower doses to the airways at greater potency. Statins could become the next major class of novel inhalers for the treatment of asthma.

[19] *Younis A, Younis A, Goldkorn R et al.* **The Association of Body Mass Index and 20-Year All-Cause Mortality Among Patients With Stable Coronary Artery Disease**. Heart, lung & circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29581037
ABSTRACT
BACKGROUND: Limited data exist regarding the long-term association of body mass index (BMI) and all-cause mortality among patients with stable coronary artery disease (CAD). Accordingly, the aim of this study is to explore the association between BMI and long-term all-cause mortality among patients with stable CAD. METHODS: Our study included 15,357 patients with stable CAD who were enrolled in the Bezafibrate Infarction Prevention (BIP) registry between February, 1990 and October1992, and subsequently followed-up through December 2014. RESULTS: 5051 (33%) patients were classified as normal weight (BMI 18.5-24.99kg/m(2)), while 7841 (51%) patients classified as overweight (BMI 25-29.99kg/m(2)), and 2465 (16%) as obese (BMI>/=30). Kaplan-Meier survival analysis showed that at 20 years of follow-up the rate of all-cause mortality was significantly higher among obese patients (67%) compared to overweight (61%) and normal weight (61%); log rank p-value for the overall difference <0.001. Multivariable analysis showed that obese patients had an independently 12% greater mortality risk compared to normal weight patients (HR=1.12; 95% CI 1.02-1.23; p=0.02), whereas, overweight patients experienced a similar mortality risk as normal weight patients (HR=0.99; 95% CI 0.92-1.06; p=0.76). The mortality risk associated with obesity was pronounced among patients younger than 65 years (p-value for interaction<0.05). CONCLUSIONS: Our findings indicate that obesity is independently associated with increased risk for long-term mortality among patients with stable coronary artery disease, whereas overweight does not appear to confer an additional risk in this population.

[20] *Caprio S, Pierpont B, Kursawe R*. **The "adipose tissue expandability" hypothesis: a potential mechanism for insulin resistance in obese youth**. Hormone molecular biology and clinical investigation 2018; 33.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29596053
ABSTRACT
Obesity has become a major global health challenge of the 21st century, as it is associated with the onset of type 2 diabetes (T2D) and cardiovascular complications, even at a very early age in

life. The root causes of pediatric obesity remain incompletely understood. The obesity epidemic together with the relationship of obesity to the growing population burden of chronic disease presents unprecedented research opportunities and challenges. Decades of obesity-related research funded by governments around the world have yielded many important discoveries about both etiological pathways and preventive or therapeutic interventions. Yet, there is a sense that the problem is outpacing these research efforts. Obesity poses a significant risk for the development of cardiovascular disease (CVD) , diabetes and certain cancers thereby shortening life expectancy. Nevertheless, many obese individuals do not develop any of these comorbidities. One hypothesis explaining this dilemma is that total body fat is not the culprit of adverse health in obesity rather the relative proportion of lipids in various fat depots is what determines the metabolic risk. In this review, we describe the role of altered fat partitioning in youth onset obesity and its relation to fatty liver and T2D during adolescence.

[21] *Dias S, Paredes S, Ribeiro L*. **Drugs Involved in Dyslipidemia and Obesity Treatment: Focus on Adipose Tissue**. Int J Endocrinol 2018; 2018:2637418.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29593789
ABSTRACT
Metabolic syndrome can be defined as a state of disturbed metabolic homeostasis characterized by visceral obesity, atherogenic dyslipidemia, arterial hypertension, and insulin resistance. The growing prevalence of metabolic syndrome will certainly contribute to the burden of cardiovascular disease. Obesity and dyslipidemia are main features of metabolic syndrome, and both can present with adipose tissue dysfunction, involved in the pathogenic mechanisms underlying this syndrome. We revised the effects, and underlying mechanisms, of the current approved drugs for dyslipidemia and obesity (fibrates, statins, niacin, resins, ezetimibe, and orlistat; sibutramine; and diethylpropion, phentermine/topiramate, bupropion and naltrexone, and liraglutide) on adipose tissue. Specifically, we explored how these drugs can modulate the complex pathways involved in metabolism, inflammation, atherogenesis, insulin sensitivity, and adipogenesis. The clinical outcomes of adipose tissue modulation by these drugs, as well as differences of major importance for clinical practice between drugs of the same class, were identified. Whether solutions to these issues will be found in further adjustments and combinations between drugs already in use or necessarily in new advances in pharmacology is not known. To better understand the effect of drugs used in dyslipidemia and obesity on adipose tissue not only is challenging for physicians but could also be the next step to tackle cardiovascular disease.

[22] *Pesarini G, Ariotti S, Ribichini F*. **Current Antithrombotic Therapy in Patients with Acute Coronary Syndromes Undergoing Percutaneous Coronary Interventions**. Interventional cardiology (London, England) 2014; 9:94-101.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29588785
ABSTRACT
Acute coronary syndromes (ACS) represent a life-threatening complication of the systemic atherosclerotic process, affecting the coronary circulation. Thrombosis, defined as an uncontrolled activation of the endogenous thrombogenetic reparative process, often follows atherosclerotic plaque damage and is mainly engaged by two main pathways: platelet

aggregation and coagulation. Therefore, antithrombotic therapy to modulate either pathway plays an important role for the reduction of ischaemic adverse events in ACS patients. Since the advent of aspirin and warfarin, numerous antiaggregant and anticoagulant molecules have been developed to achieve this goal, but their anti-ischaemic efficacy is often obtained at the price of augmented bleedings, which are known to be strong predictors of adverse outcome. This article briefly reviews the physiopathological mechanisms of thrombosis and presents an overview of the available literature supporting the use of these major drugs, as well as the European Society of Cardiology recommendations for their utilisation in the setting of non-ST and ST-elevation myocardial infarction undergoing invasive treatment.

[23] *Vasquez A, Mistry N, Singh J*. **Impact of Intravascular Ultrasound in Clinical Practice**. Interventional cardiology (London, England) 2014; 9:156-163.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29588795
ABSTRACT
Intravascular ultrasound (IVUS) has expanded our understanding of atherosclerotic plaque morphology, and provides an opportunity to guide cardiovascular interventions and evaluate results. Use of this technique requires understanding of ultrasound physics, catheter differences, skills in vessel, plaque and stent quantification and knowledge of artifacts and various physiologic and pathologic findings. Optimal cardiovascular interventions should result in absence of inflow or outflow obstruction, precise geographic landing, while attaining the largest feasible luminal gain without plaque protrusion, vessel dissection or perforation and, if deployed, with complete stent expansion and apposition to the vessel wall. IVUS is safe, cost efficient and effectively optimises cardiovascular interventions. In addition, IVUS improves outcomes when used to guide coronary interventions using bare metal stents (BMS) and drug eluting stents (DES). The role of IVUS in endovascular therapy is rapidly expanding. This review will focus on the impact of IVUS in clinical practice.

[24] *Wu M, Fw van der Steen A, Regar E, van Soest G*. **Emerging Technology Update Intravascular Photoacoustic Imaging of Vulnerable Atherosclerotic Plaque**. Interventional cardiology (London, England) 2016; 11:120-123.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29588718
ABSTRACT
The identification of vulnerable atherosclerotic plaques in the coronary arteries is emerging as an important tool for guiding atherosclerosis diagnosis and interventions. Assessment of plaque vulnerability requires knowledge of both the structure and composition of the plaque. Intravascular photoacoustic (IVPA) imaging is able to show the morphology and composition of atherosclerotic plaque. With imminent improvements in IVPA imaging, it is becoming possible to assess human coronary artery disease in vivo. Although some challenges remain, IVPA imaging is on its way to being a powerful tool for visualising coronary atherosclerotic features that have been specifically associated with plaque vulnerability and clinical syndromes, and thus such imaging might become valuable for clinical risk assessment in the catheterisation laboratory.

[25] *Foldyna B, Fourman LT, Lu MT et al.* **Sex Differences in Subclinical Coronary Atherosclerotic Plaque Among Individuals with HIV on Antiretroviral Therapy**. Journal of acquired immune deficiency syndromes (1999) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29601406
ABSTRACT
BACKGROUND: In high-resource settings, the HIV-attributable risk of myocardial infarction (MI) is higher among women than among men. The extent to which unique mechanisms contribute to MI risk among women vs. men with HIV remains unclear. METHODS: Subclinical coronary atherosclerotic plaque characteristics - including high-risk morphology plaque features - were compared among 48 HIV-infected women (48 [41, 54] years) and 97 HIV-infected men (48 [42, 52] years) on stable antiretroviral therapy (ART) without known cardiovascular disease. These individuals had previously completed coronary computed tomography angiography and metabolic/immune phenotyping as part of a prospective study. RESULTS: Extending prior analyses, now focusing exclusively on ART-treated participants, we found that HIV-infected women had a lower prevalence of any subclinical coronary atherosclerotic plaque (35% vs. 62%, P=0.003) and a lower number of segments with plaque (P=0.01), compared to HIV-infected men. We also report for the first time that ART-treated HIV-infected women had a lower prevalence of high-risk positively remodeled plaque (25% vs. 51%, P=0.003) and a lower number of positively remodeled plaque segments (P=0.002). In models adjusting for cardiovascular risk factors, we further showed that male sex remained associated with any coronary plaque (OR 3.8, 95%CI [1.4, 11.4]) and with positively remodeled plaque (OR 3.7, 95%CI [1.4, 10.9]). CONCLUSIONS: ART-treated HIV-infected women (vs. HIV-infected men) had a lower prevalence and burden of subclinical coronary plaque and high-risk morphology plaque. Thus, unique sex-specific mechanisms beyond subclinical plaque may drive the higher HIV-attributable risk of MI among women vs. men.

[26] *Ghalwash M, Elmasry A, El-Adeeb N*. **Effect of L-carnitine on the skeletal muscle contractility in simvastatin-induced myopathy in rats**. Journal of basic and clinical physiology and pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29584613
ABSTRACT
BACKGROUND: Statins therapy is effective in the prevention of cardiovascular events. However, its use is associated with skeletal muscle myopathy, which may be severe enough to discontinue statin therapy, thus exposing patients to more morbidity and mortality. This study was conducted to assess the effect of L-carnitine on the skeletal muscle contractility in a rat model of statin-induced myopathy and to clarify its possible mechanisms. METHODS: Twenty-one female Sprague Dawley rats were used throughout this study. The rats were divided into the normal control group, statin-induced myopathy group and statin/L-carnitine-treated group. The assessment of gastrocnemius muscle contractility, plasma creatine kinase (CK) levels and oxidative stress markers (malondialdehyde, reduced glutathione) was also carried out done. RESULTS: The results of the current study suggest that simvastatin decreased the skeletal muscle mass and altered the muscle contractile properties. It also significantly increased plasma CK level and induced a state of oxidative stress state (high MDA, low GSH). Meanwhile, concurrent L-carnitine significantly reduced statin-induced myopathy and improved the

oxidative stress markers and skeletal muscle contractile parameters. CONCLUSIONS: Statin myopathy is postulated to be due to mitochondrial dysfunction, cellular oxidative stress, induction of apoptosis, reduction in the expression of chloride channel and its related conductance, in addition to the alteration of Ca2+ homeostasis. L-carnitine has an antioxidant effect, reduces skeletal muscle atrophy and improves the skeletal muscle contractility in simvastatin-induced myopathy.

[27] *Lebeau P, Platko K, Al-Hashimi AA et al.* **Loss-of-function PCSK9 mutants evade the unfolded protein response sensor, GRP78, and fail to induce endoplasmic reticulum stress when retained**. The Journal of biological chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29593095
ABSTRACT
The proprotein convertase subtilisin/kexin type-9 (PCSK9) plays a central role in cardiovascular disease (CVD) by degrading hepatic low-density lipoprotein receptor (LDLR). As such, loss-of-function (LOF) PCSK9 variants that fail to exit the endoplasmic reticulum (ER) increase hepatic LDLR levels and lower the risk of developing CVD. The retention of misfolded protein in the ER can cause ER stress and activate the unfolded protein response (UPR); in this study, we investigated whether a variety of LOF PCSK9 variants that are retained in the ER can cause ER stress and hepatic cytotoxicity. Although overexpression of these PCSK9 variants caused an accumulation in the ER of hepatocytes, UPR activation or apoptosis were not observed. Further, ER-retention of endogenous PCSK9 via splice-switching also failed to induce the UPR. Consistent with these in vitro studies, overexpression of PCSK9 in the livers of mice had no impact on UPR activation. To elucidate the cellular mechanism to explain these surprising findings, we observed that the 94-kDa glucose regulated protein (GRP94) sequesters PCSK9 away from the 78-kDa glucose regulated protein (GRP78), the major activator of the UPR. As a result, GRP94 knockdown increased the stability of GRP78-PCSK9 complex and resulted in UPR activation following overexpression of ER-retained PCSK9 variants relative to wild-type secreted controls. Given that overexpression of these LOF PCSK9 variants does not cause UPR activation under normal homeostatic conditions, therapeutic strategies aimed at blocking the autocatalytic cleavage of PCSK9 in the ER represent a viable strategy for reducing circulating PCSK9.

[28] *Chapman MJ, Orsoni A, Robillard P et al.* **Duality of statin action on lipoprotein subpopulations in the mixed dyslipidemia of metabolic syndrome: Quantity vs quality over time and implication of CETP**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574070
ABSTRACT
BACKGROUND: Statins impact the metabolism, concentrations, composition, and function of circulating lipoproteins. OBJECTIVE: We evaluated time course relationships between statin-mediated reduction in atherogenic apolipoprotein B (ApoB)-containing particles and dynamic intravascular remodeling of ApoAI-containing lipoprotein subpopulations in the mixed dyslipidemia of metabolic syndrome. METHODS: Insulin-resistant, hypertriglyceridemic, hypercholesterolemic, obese males (n = 12) were treated with pitavastatin (4 mg/d) and response evaluated at 6, 42, and 180 days. RESULTS: Reduction in low-density lipoprotein (LDL) cholesterol, ApoB, and triglycerides (TGs) was essentially complete at 42 days (-38%, -32%, and

-35%, respectively); rapid reduction equally occurred in remnant cholesterol, ApoCII, CIII, and E levels (day 6; -35%, -50%, -23%, and -26%, respectively). Small dense LDLs (LDL4 and LDL5 subpopulations) predominated at baseline and were markedly reduced on treatment (-29% vs total LDL mass). Cholesteryl ester (CE) transfer protein activity and mass decreased progressively (-18% and -16%, respectively); concomitantly, TG depletion (up to -49%) and CE enrichment occurred in all high-density lipoprotein (HDL) particle subpopulations with normalization of CE/TG mass ratio at 180 days. ApoAI was redistributed from LpAI to LpAI:AII particles in HDL2a and HDL3a subpopulations; ApoCIII was preferentially depleted from LpAI:AII-rich particles on treatment. CONCLUSION: Overall, statin action exhibits duality in mixed dyslipidemia, as CE transfer protein-mediated normalization of the HDL CE/TG core lags markedly behind subacute reduction in elevated levels of atherogenic ApoB-containing lipoproteins. Normalization of the HDL neutral lipid core is consistent with enhanced atheroprotective function. The HDL CE/TG ratio constitutes a metabolomic marker of perturbed HDL metabolism in insulin-resistant states, equally allowing monitoring of statin impact on HDL metabolism, structure, and function.

[29] *Dopheide JF, Papac L, Schindewolf M et al.* **Poor attainment of lipid targets in patients with symptomatic peripheral artery disease**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574071
ABSTRACT
BACKGROUND: Patients with peripheral artery disease (PAD) are at very high risk of future cardiovascular (CV) events. Strict lipid-lowering therapy is recommended. However, data on target level attainment are scarce. OBJECTIVE: The objective of the study was to investigate guideline equitable lipid lowering in a large observational study of symptomatic PAD patients. METHODS: Single-center observational study including 1109 patients with symptomatic PAD planned for revascularization at a tertiary university center. Between 2010 and 2017, guideline target level attainment trends over time and the association of statin therapy with CV mortality were analyzed. RESULTS: Atorvastatin (52.3%) and rosuvastatin (23.5%) were the most frequently prescribed statins and amounted to an average simvastatin equivalent of 52 mg/d. Attainment rates of low-density lipoprotein cholesterol (LDL-C) and of non-high-density lipoprotein cholesterol goals were as low as 27% and 33%, respectively. Although there was a significant improvement of LDL-C from 2010 to 2017 (mean LDL-C 110 vs 80 mg/dL, $P < .0001$ for trend), attainment remained poor, that is, only 42% in 2016 and 45% in 2017 achieved the <70 mg/dL goal. CV mortality was significantly lower (4% vs 11%, $P < .01$) in statin-treated patients over a median follow-up period of 50 +/- 26 months. CONCLUSION: There is a remarkable undertreatment of LDL-C and non-high-density lipoprotein cholesterol in patients with symptomatic PAD, although LDL-C decreased significantly from 2010 to 2017. As statin treatment was associated with a reduced CV mortality rate, our findings call for an increased awareness in clinical lipidology regarding symptomatic PAD patients.

[30] *Sahebkar A, Simental-Mendia LE, Mikhailidis DP et al.* **Effect of statin therapy on plasma apolipoprotein CIII concentrations: A systematic review and meta-analysis of randomized controlled trials**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29580713

ABSTRACT
BACKGROUND: Statins are well-established low-density lipoprotein cholesterol-lowering drugs. Elevated apolipoprotein CIII (Apo CIII) levels are associated with elevated triglyceride-rich particles, which are also considered to be a possible risk factor for cardiovascular disease. OBJECTIVE: The aim of this meta-analysis of randomized placebo-controlled clinical trials was to assess the effect of statins on Apo CIII concentrations. METHODS: Randomized placebo-controlled trials investigating the impact of statin treatment on cholesterol lowering that include lipoprotein measurement were searched in PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar databases (up to July 31, 2017). A random-effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. A weighted random-effects meta-regression was performed to evaluate the impact of potential confounders on Apo CIII concentrations. RESULTS: This meta-analysis of data from 6 randomized placebo-controlled clinical trials (10 statin arms) involving 802 subjects showed that statin therapy significantly decreased circulating Apo CIII concentrations (weighted mean difference [WMD]: -2.71, 95% confidence interval [CI]: -3.74 to -1.68, P < .001; I(2): 73.83%). The effect size was robust in the leave-one-out sensitivity analysis and not driven by any single study. Subgroup analysis showed a reduction of Apo CIII concentrations by atorvastatin (WMD: -4.74, 95% CI: -3.74 to -1.68, P = .002; I(2): 84.02%), rosuvastatin (WMD: -2.68, 95% CI: -4.52 to -0.84, P = .004; I(2): 0%), and lovastatin (WMD: -1.64, 95% CI: -2.22 to -1.07, P < .001; I(2): 0%). CONCLUSION: This meta-analysis suggests that statin treatment significantly reduces plasma Apo CIII levels.

[31] *Viney NJ, Yeang C, Yang X et al.* **Relationship between "LDL-C", estimated true LDL-C, apolipoprotein B-100, and PCSK9 levels following lipoprotein(a) lowering with an antisense oligonucleotide**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574075

ABSTRACT
BACKGROUND: The laboratory measurement of "low-density lipoprotein cholesterol (LDL-C)" includes the cholesterol content of lipoprotein(a) (Lp(a)-C). OBJECTIVE: To estimate the "true" LDL-C in relation to changes in apolipoprotein B-100 (apoB-100) and assess changes in proprotein convertase subtilisin/kexin 9 (PCSK9) levels in patients with elevated Lp(a) treated with IONIS-APO(a)Rx. METHODS: A pooled placebo group (n = 29), and cohort A (n = 24, baseline Lp(a) 50-175 mg/dL) and cohort B (n = 8, baseline Lp(a) > 175 mg/dL) treated with IONIS-APO(a)Rx were studied. Lp(a) particle number, ultracentrifugation-measured "LDL-C", apoB-100, total PCSK9, and lipoprotein-associated PCSK9 (PCSK9-Lp(a), PCSK9-apoB, PCSK9-apoAI) were measured. Lp(a)-cholesterol (Lp(a)-C) and LDL-C corrected for Lp(a)-C (LDL-Ccorr) were calculated. RESULTS: Baseline mean (standard deviation) "LDL-C" was 120 (42), 128 (45), and 112 (39) mg/dL in placebo, cohorts A and B, respectively, whereas LDL-Ccorr was 86 (48), 96 (43), and 57 (37) mg/dL (P < .001 compared with placebo), representing 28%, 25%, and 50% lower levels than "LDL-C". Following IONIS-APO(a)Rx treatment at day 85/99, Lp(a) particle number and Lp(a)-C decreased -66.8% and -71.6%, apoB-100 -10.3% and -17.5%, "LDL-C" -11.8% and -22.7%, (P < .001 for all vs placebo), whereas LDL-Ccorr increased +10.4% (P = .66) and +49.9% (P < .001) in cohorts A and B, respectively. Total PCSK9 did not change but PCSK9-Lp(a) decreased with IONIS-APO(a)Rx vs placebo (-39.0% vs +8.4%, P < .001). CONCLUSION: LDL-

Ccorr is lower than laboratory "LDL-C" in patients with elevated Lp(a). Following apolipoprotein(a) inhibition and decline in Lp(a) and Lp(a)-C, the decline in apoB-100 is consistent with the notion that LDL devoid of apo(a) is cleared faster than Lp(a). These types of analyses may provide insights into the mechanisms of drugs affecting Lp(a) levels in clinical trials.

[32] *Kaewboonlert N, Thitisopee W, Sirintronsopon W et al.* **Lack of association between SLCO1B1 polymorphisms and lipid-lowering response to simvastatin therapy in Thai hypercholesterolaemic patients**. Journal of clinical pharmacy and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29575099
ABSTRACT
WHAT IS KNOWN: SLCO1B1 polymorphisms have been reported to affect the responses to statin therapy. However, the association of these polymorphisms and lipid-lowering responses has been inconsistent. OBJECTIVE: To investigate the effect of SLCO1B1 c.388A>G, c.521T>C and g.89595T>C polymorphisms on the lipid-lowering response to simvastatin therapy in Thai hypercholesterolaemic patients. METHODS: Three hundred and 91 hypercholesterolaemic patients in Southern Thailand were enrolled and treated with simvastatin 20 or 40 mg per day. Among them, 191 and 200 patients were treated for 3 and 12 months, respectively. Serum lipids were measured before and after the treatment. SLCO1B1 c.388A>G, c.521T>C and g.89595T>C polymorphisms were analysed using polymerase chain reaction-high-resolution melting (PCR-HRM). RESULTS: The allele frequencies of the SLCO1B1 c.388A>G, c.521T>C and g.89595T>C polymorphisms in Thai hypercholesterolaemic patients were 74.9%, 11.8% and 37.2%, respectively. After treatment with 20-40 mg simvastatin daily for 3 and 12 months, TC, TG and LDL-C concentrations were significantly lower than at baseline ($P < .05$). However, there was no a significant change in serum HDL-C after simvastatin treatment for 3 and 12 months ($P > .05$). Moreover, there was no association between SLCO1B1 c.388A>G, c.521T>C and g.89595T>C polymorphisms and lipid-lowering response to 3 and 12 months of either 20 or 40 mg/day simvastatin treatment. WHAT IS NEW AND CONCLUSION: SLCO1B1 c.388A>G, c.521T>C and g.89595T>C polymorphisms may not be useful as genetic markers of lipid-lowering response to simvastatin therapy in Thai hypercholesterolaemic patients.

[33] *Gremmels H, Joles JA*. **Fibrates in hypertension: where do we stand?** Journal of hypertension 2018; 36:1024-1028.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29578959
ABSTRACT

[34] *Kotzbeck P, Giordano A, Mondini E et al.* **Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29599420
ABSTRACT
In mammals, white adipose tissue (WAT) stores and releases lipids, whereas brown adipose tissue (BAT) oxidizes lipids to fuel thermogenesis. In obese individuals WAT undergoes profound changes; it expands, becomes dysfunctional, and develops a low-grade inflammatory state. Importantly, BAT content and activity decline in obese subjects, mainly as a result of the

conversion of brown adipocytes to white-like unilocular cells. Here, we show that BAT ''whitening'' is induced by multiple factors, including high ambient temperature, leptin receptor deficiency, beta-adrenergic signaling impairment, and lipase deficiency, each of which is capable of inducing macrophage infiltration, brown adipocyte death, and crown-like structure (CLS) formation. Brown-to-white conversion and increased CLS formation were most marked in BAT from adipose triglyceride lipase (Atgl)-deficient mice, where according to transmission electron microscopy whitened brown adipocytes contained enlarged endoplasmic reticulum, cholesterol crystals and some degenerating mitochondria, and were surrounded by an increased number of collagen fibrils. Gene expression analysis showed that BAT whitening in Atgl-deficient mice was associated to a strong inflammatory response and NLRP3 inflammasome activation. Altogether the present findings suggest that converted, enlarged brown adipocytes are highly prone to death which, by promoting inflammation in whitened BAT, may contribute to the typical inflammatory state seen in obesity.

[35] *Khadge S, Thiele GM, Sharp JG et al.* **Long-Chain Omega-3 Polyunsaturated Fatty Acids Modulate Mammary Gland Composition and Inflammation**. Journal of mammary gland biology and neoplasia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29574638
ABSTRACT
Studies in rodents have shown that dietary modifications as mammary glands (MG) develop, regulates susceptibility to mammary tumor initiation. However, the effects of dietary PUFA composition on MGs in adult life, remains poorly understood. This study investigated morphological alterations and inflammatory microenvironments in the MGs of adult mice fed isocaloric and isolipidic liquid diets with varying compositions of omega (omega)-6 and long-chain (Lc)-omega3FA that were pair-fed. Despite similar consumption levels of the diets, mice fed the omega-3 diet had significantly lower body-weight gains, and abdominal-fat and mammary fat pad (MFP) weights. Fatty acid analysis showed significantly higher levels of Lc-omega-3FAs in the MFPs of mice on the omega-3 diet, while in the MFPs from the omega-6 group, Lc-omega-3FAs were undetectable. Our study revealed that MGs from omega-3 group had a significantly lower ductal end-point density, branching density, an absence of ductal sprouts, a thinner ductal stroma, fewer proliferating epithelial cells and a lower transcription levels of estrogen receptor 1 and amphiregulin. An analysis of the MFP and abdominal-fat showed significantly smaller adipocytes in the omega-3 group, which was accompanied by lower transcription levels of leptin, IGF1, and IGF1R. Further, MFPs from the omega-3 group had significantly decreased numbers and sizes of crown-like-structures (CLS), F4/80+ macrophages and decreased expression of proinflammatory mediators including Ptgs2, IL6, CCL2, TNFalpha, NFkappaB, and IFNgamma. Together, these results support dietary Lc-omega-3FA regulation of MG structure and density and adipose tissue inflammation with the potential for dietary Lc-omega-3FA to decrease the risk of mammary gland tumor formation.

[36] *Ramirez-Lopez G, Moran-Villota S, Mendoza-Carrera F et al.* **Metabolic and genetic markers' associations with elevated levels of alanine aminotransferase in adolescents**. J Pediatr Endocrinol Metab 2018; 31:407-414.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29584615

ABSTRACT
BACKGROUND: Non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease in adolescents, is a feature of metabolic syndrome (MetS). Obesity and insulin resistance (IR) are risk factors for NAFLD, as well as inflammation-related genetic markers. The relationship between metabolic or inflammation-related genetic markers and alanine aminotransferase (ALT) is not fully understood. We examined the relationship of MetS, metabolic and inflammation-related genetic markers with elevated ALT in adolescents. METHODS: A total of 674 adolescents participated in a cross-sectional study in Guadalajara, Mexico. Elevated ALT (>40 IU/L), a surrogate marker of NAFLD, and MetS (International Diabetes Federation definition) were evaluated. Obesity, IR, lipids, C-reactive protein (CRP) and genetic markers (TNFA-308G>A, CRP+1444C>T, IL1RN and IL6-597/-572/-174 haplotype) were evaluated. Multivariate logistic regression was performed. RESULTS: Elevated ALT was observed in 3% and 14.1% (total and obese, respectively) of the adolescents. Obesity (odds ratio [OR], 5.86; 95% confidence interval [95% CI], 1.16-25.89), insulin (OR, 8.51; 95% CI, 2.61-27.71), IR (OR, 9.10; 95% CI, 2.82-29.38), total cholesterol (TC) (OR, 3.67; 95% CI, 1.25-10.72), low-density lipoprotein-cholesterol (LDL-C) (OR, 3.06; 95% CI, 1.06-8.33), non-high-density lipoprotein-cholesterol (HDL-C) (OR, 3.88; 95% CI, 1.27-11.90) and IL1RN (OR, 4.64; 95% CI, 1.10-19.53) were associated with elevated ALT. Among males, >/=2 MetS criteria were associated with elevated ALT (OR, 4.22; 95% CI, 1.14-15.71). CONCLUSIONS: Obesity, insulin, IR, high TC, high LDL-C, high non-HDL-C and IL1RN polymorphism were associated with elevated ALT. Among males, >/=2 MetS criteria were associated with elevated ALT. There is an urgent need to reduce obesity and IR in adolescents to prevent NAFLD.

[37] *Khokhar B, Simoni-Wastila L, Slejko JF et al.* **Patterns of Statin Use in Older Medicare Beneficiaries With Traumatic Brain Injury**. The Journal of pharmacy technology : jPT : official publication of the Association of Pharmacy Technicians 2017; 33:156-166.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29577114

ABSTRACT
Background: In addition to lowering lipids, statins also may be beneficial for older adults sustaining a traumatic brain injury (TBI), as statin use prior to and following trauma may decrease mortality following injury. However, despite statins' potential to reduce mortality, there is limited research regarding statin use among older adults. Objective: To characterize and investigate factors associated with statin use among older adults with TBI. Methods: A retrospective drug utilization study was used to characterize statin use among Medicare beneficiaries 65 and older hospitalized with a TBI during 2006 to 2010 and with continuous Medicare Parts A, B, and D coverage 6 months prior and 12 months following TBI. Logistic regression was used to investigate the factors associated with statin use. The exposure of interest was statin use prior to and following TBI. Results: Of the 75 698 beneficiaries included in the study, 37 874 (~50%) of beneficiaries used a statin at least once during the study period. The most common statin used was simvastatin, while fluvastatin was the least used statin. Statin users were more likely to have cardiovascular diseases when compared to nonusers. Hyperlipidemia was a major factor associated with statin use and had the greatest impact on statin use compared to nonuse (odds ratio = 9.54; 95% confidence interval = 9.07, 10.03). Conclusions: This national sample of older adults with TBI suggests that statins are commonly

used. Future studies must next examine the impact of statin use on mortality and secondary injury in order to shape pharmacological therapy guidelines following TBI.

[38] *Cheng F, Lin P, Wang Y et al.* **Type D personality and coronary atherosclerotic plaque vulnerability: The potential mediating effect of health behavior**. Journal of psychosomatic research 2018; 108:54-60.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29602326
ABSTRACT
OBJECTIVE: The association between type D personality and coronary plaque vulnerability has been suggested. The objective of the study was to evaluate the potential mediating effects of health behavior on the association between type D personality and plaque vulnerability in coronary artery disease (CAD) patients. METHODS: A total of 319 CAD patients were assessed for type D personality and health behavior via self-administered questionnaires. The plaque vulnerability, evaluated according to characteristics, accompaniment, and outcomes of plaque, was assessed by optical coherence tomography. RESULTS: Regression analysis showed that type D personality was independently associated with lipid plaque (odds ratio [OR]=2.387, p=0.001), thin cap fibroatheroma (TCFA) (OR=2.366, p=0.001), rupture (OR=2.153, p=0.002), and lipid arc (beta=-0.291, p<0.001). Mediation analyses showed that aspects of health behavior were significant mediators of the relationship between type D personality and plaque vulnerability. Psychological stress mediated the relationship between type D and lipid plaque (p=0.030), TCFA (p=0.034), and rupture (p=0.013). Living habits significantly mediated the relationship between type D and lipid plaque (p=0.028), TCFA (p=0.036), but not rupture (p=0.066). Participating in activities was not a significant mediator of the relationship between type D personality and lipid plaque (p=0.115), TCFA (p=0.115), or rupture (p=0.077). CONCLUSIONS: Health behaviors (psychological stress and living habits) may be mediators of the association between type D personality and plaque vulnerability.

[39] *Ades S, Douce D, Holmes CE et al.* **Effect of rosuvastatin on risk markers for venous thromboembolism in cancer**. Journal of thrombosis and haemostasis : JTH 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29575637
ABSTRACT
BACKGROUND: Statin therapy is associated with lower risk of venous thromboembolism (VTE), but has not been prospectively evaluated in patients with advanced cancer. OBJECTIVES: We determined if statin administration in this high-risk population reduces VTE risk, based on established and emerging biomarkers. PATIENTS/METHODS: This double-blind crossover randomized controlled trial among patients with advanced cancer receiving systemic therapy allocated participants to rosuvastatin 20mg daily, or placebo for 3-4 weeks prior to crossover to the alternative therapy with a 3-5 week washout. D-dimer, C-reactive protein (CRP), soluble (s)P-Selectin, factor VIII (FVIII), thrombin generation, and exploratory biomarkers focusing on endogenous thrombin potential including tissue factor (TF), activated factor IX (FIXa), and activated factor XI (FXIa) were measured at start and end of both treatment periods. The primary outcome was change in D-dimer with rosuvastatin compared to placebo. RESULTS: Of 38 enrolled participants, 24 (63%) completed the study. Rosuvastatin did not cause statistically significant changes in D-dimer levels or any other biomarker. CRP levels decreased by 40%; 4.3

mg/L (95% CI -11.0 to +2.5 mg/L) compared to placebo. In post-hoc analysis, participants who received rosuvastatin initially on their first line of treatment had a 13% decrease in D-dimer. Circulating TF, FIXa and FXIa were detected in 26%, 68% and 71% of cancer patients despite not being found in healthy individuals. CONCLUSIONS: Rosuvastatin did not cause favorable changes in biomarkers of VTE risk in advanced cancer patients receiving chemotherapy. The role of statin therapy as thromboprophylaxis in the cancer population remains uncertain.

[40] *Brinton EA, Ballantyne CM, Guyton JR et al.* **Lipid Effects of Icosapent Ethyl in Women with Diabetes Mellitus and Persistent High Triglycerides on Statin Treatment: ANCHOR Trial Subanalysis**. Journal of women's health (2002) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29583081
ABSTRACT
BACKGROUND: High triglycerides (TG) and diabetes mellitus type 2 (DM2) are stronger predictors of cardiovascular disease (CVD) in women than in men, but few randomized, controlled clinical trials have investigated lipid-lowering interventions in women and none have reported results specifically in women with high TG and DM2. Icosapent ethyl (Vascepa) is pure prescription eicosapentaenoic acid (EPA) ethyl ester approved at 4 g/day as an adjunct to diet to reduce TG >/=500 mg/dL. METHODS: The 12-week ANCHOR trial randomized 702 statin-treated patients (73% with DM; 39% women) at increased CVD risk with TG 200-499 mg/dL despite controlled low-density lipoprotein cholesterol (LDL-C; 40-99 mg/dL) to receive icosapent ethyl 2 g/day, 4 g/day, or placebo. This post hoc analysis included 146 women with DM2 (97% white, mean age 62 years) randomized to icosapent ethyl 4 g/day (n = 74) or placebo (n = 72). RESULTS: Icosapent ethyl significantly reduced TG (-21.5%; $p < 0.0001$) without increasing LDL-C and lowered other potentially atherogenic lipid/lipoprotein, apolipoprotein, and inflammatory parameters versus placebo. Icosapent ethyl increased EPA levels in plasma (+639%; $p < 0.0001$; n = 49) and red blood cells (+599%; $p < 0.0001$; n = 47) versus placebo. Safety and tolerability of icosapent ethyl were generally similar to placebo. CONCLUSION: In women with DM2 at high CVD risk with persistently high TG on statins, icosapent ethyl 4 g/day reduced potentially atherogenic parameters with safety and tolerability comparable to placebo. Potential CVD benefits of icosapent ethyl are being tested in approximately 8000 men and women at high CVD risk with high TG on statins in the ongoing Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial (REDUCE-IT) cardiovascular (CV) outcome trial.

[41] *Mao Z, Wu F, Shan Y*. **Identification of key genes and miRNAs associated with carotid atherosclerosis based on mRNA-seq data**. Medicine (Baltimore) 2018; 97:e9832.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29595698
ABSTRACT
This study was aimed to explore the crucial genes and microRNAs (miRNAs) associated with the carotid atherosclerosis (CA).Two public datasets GSE28829 and GSE43292 were obtained from Gene Expression Omnibus databases to analyze the differentially expressed genes (DEGs) between primary and advanced atherosclerotic plaque tissues. The Gene Ontology (GO) terms, pathways, and protein-protein interactions (PPIs) of these DEGs were analyzed. miRNAs and transcription factor (TF) were predicted.A total of 112 upregulated and 179 downregulated

intersection DEGs were identified between 2 datasets. In the PPI network, HSP90AB1 (degree = 19), RAP1A (degree = 14), and integrin subunit beta 1 (ITGB1) had higher degrees. A total of 23 miRNAs were predicted, such as miR-126, miR-155, miR-19A, and miR-19B. Four TFs were associated with upregulated DEGs, while 10 TFs were identified to be associated with downregulated genes.Our study suggests the important roles of HSP90AB1, RAP1A, and integrins proteins of ITGB1, ITGA11, ITGA9, and ITGB2 in the progression of CA plaque. Additionally, miR-126, miR-155, miR-19B, and miR-19A may be considered as biomarkers of CA.

[42] *Blesso CN, Fernandez ML*. **Dietary Cholesterol, Serum Lipids, and Heart Disease: Are Eggs Working for or Against You?** Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29596318
ABSTRACT
The relationship between blood cholesterol and heart disease is well-established, with the lowering of serum low-density lipoprotein (LDL)-cholesterol being the primary target of preventive therapy. Furthermore, epidemiological studies report lower risk for heart disease with higher concentrations of high-density lipoprotein (HDL)-cholesterol. There has also been considerable interest in studying the relationship between dietary cholesterol intake and heart disease risk. Eggs are one of the richest sources of cholesterol in the diet. However, large-scale epidemiological studies have found only tenuous associations between the intake of eggs and cardiovascular disease risk. Well-controlled, clinical studies show the impact of dietary cholesterol challenges via egg intake on serum lipids is highly variable, with the majority of individuals (~2/3 of the population) having only minimal responses, while those with a significant response increase both LDL and HDL-cholesterol, typically with a maintenance of the LDL/HDL cholesterol ratio. Recent drug trials targeting HDL-cholesterol have been unsuccessful in reducing cardiovascular events, and thus it is unclear if raising HDL-cholesterol with chronic egg intake is beneficial. Other important changes with egg intake include potentially favorable effects on lipoprotein particle profiles and enhancing HDL function. Overall, the increased HDL-cholesterol commonly observed with dietary cholesterol feeding in humans appears to also coincide with improvements in other markers of HDL function. However, more investigation into the effects of dietary cholesterol on HDL functionality in humans is warranted. There are other factors found in eggs that may influence risk for heart disease by reducing serum lipids, such as phospholipids, and these may also modify the response to dietary cholesterol found in eggs. In this review, we discuss how eggs and dietary cholesterol affect serum cholesterol concentrations, as well as more advanced lipoprotein measures, such as lipoprotein particle profiles and HDL metabolism.

[43] *Ezad S, Cheema H, Collins N*. **Statin-induced rhabdomyolysis: a complication of a commonly overlooked drug interaction**. Oxford medical case reports 2018; 2018:omx104.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29593874
ABSTRACT
Rhabdomyolysis is a well-documented side effect of statin therapy. This risk is increased with concurrent use of medications that inhibit cytochrome p450-3A4 (CYP3A4), such as macrolide antibiotics. We present the case of a 67-year-old patient who was commenced on clarithromycin on a background of simvastatin therapy, resulting in rhabdomyolysis. This case

highlights the need for awareness of common drug interactions associated with statins. It also emphasizes the significance of commencing statins at a lower dose in new patients, and lastly, the importance of early recognition and management of rhabdomyolysis to prevent the development of complications.