Literature update week 17 (2018)

[1] *Wu Z, Camargo CA, Jr., Khaw KT et al.* **Effects of vitamin D supplementation on adherence to and persistence with long-term statin therapy: Secondary analysis from the randomized, double-blind, placebo-controlled ViDA study**. Atherosclerosis 2018; 273:59-66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29684661

ABSTRACT

BACKGROUND AND AIMS: Long-term statin use increases survival. However, the adherence to and persistence with statin use are challenging and this influences the success of statin treatment. Our aim was to explore if monthly vitamin D supplementation (100,000-IU) improves the adherence to and persistence with long-term statin use in older adults. METHODS: We conducted a secondary analysis of a trial comparing data on dispensed statin prescriptions, between participants allocated to vitamin D supplementation or placebo, for those taking statin therapy. Primary outcomes were defined as adherence to (proportion of days covered by prescriptions >/=80%) and persistence (non-discontinuation of the statin therapy following an allowed 30 days gap between refills) with all statins over a 24-month measurement period of statin therapy. Secondary outcomes were defined as adherence and persistence at other measurement periods for all types of statins and for individual statins. RESULTS: Overall, 2494 participants were on long-term statins at follow-up (vitamin D=1243, placebo=1251). Compared with placebo, monthly vitamin D supplementation did not improve the proportion with adherence (risk ratio: 1.01, p=0.62), but improved the persistence probability of taking all statins after 24 months (hazard ratio: 1.15, p=0.02). In further analyses, significant differences were observed in the adherence to simvastatin, the first-line statin therapy. CONCLUSIONS: Monthly vitamin D supplementation improved persistence with statins use over a 24-month measurement period in older adults on long-term statin therapy, especially for participants on simvastatin. The role of vitamin D supplementation as an adjunct therapy for patients on long-term statins merits further investigation.

[2] *Liang X, He Q, Zhao Q*. **Effect of Stains on LDL Reduction and Liver Safety: A Systematic Review and Meta-Analysis**. BioMed research international 2018; 2018:7092414.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29693013

ABSTRACT

Background and Aim: Statin is a class of medications used to decrease low-density lipoprotein cholesterol level to prevent cardiovascular disease. However, the risk of hepatic damage caused by statin therapy is still controversial. We conducted a systematic review and meta-analysis summarizing the existing evidence of the effect of statin therapy on incidence of liver injury to clarify whether statin therapy could lead to liver function test abnormalities. Methods: We searched the Cochrane Library, PubMed, and Embase database for the relevant studies update till Jan. 2017 regarding statin therapy and liver injury. Two researchers screened the literature independently by the selection and exclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled using random effects models, and subgroup analyses were performed by study characteristics. This meta-analysis was performed by STATA 13.1 software. Results: Analyses were based on 74,078 individuals from 16 studies. The summary OR of statin therapy was 1.18 (95% CI: 1.01-1.39, p = 0.04; I(2) = 0.0%) for liver injury. Subgroup analysis indicated that fluvastatin increased the risk of liver injury significantly (OR, 3.50; 95% CI: 1.07-11.53, p = 0.039; I(2) = 0.0%) and dose over 40 mg/daily had an unfavorable effect on the liver

damage (OR, 3.62; 95% CI: 1.52-8.65, p = 0.004; I(2) = 0.0%). The sensitivity analysis indicated that the results were robust. Conclusion: Our findings confirm that statin therapy substantially increases the risk of liver injury, especially using fluvastatin over 40 mg/d.

[3] *Yu T, Wu C, Shih N et al.* **Discovery of dimethyl pent-4-ynoic acid derivatives, as potent and orally bioavailable DGAT1 inhibitors that suppress body weight in diet-induced mouse obesity model**. Bioorganic & medicinal chemistry letters 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29699923
ABSTRACT
Diacylglycerol acyltransferase (DGAT) is expressed abundantly in intestine, liver, and adipose tissues. DGAT1 is the crucial and rate-limiting enzyme that mediates the final step in triacylglycerol (TAG) resynthesis during dietary fat absorption. However, too much triacylglycerol (TAG) reserve will lead to genetic obesity (Hubert et al., 2000). DGAT1 knockout mice could survive and displayed a reduction in the postprandial rise of plasma TG, and increased sensitivity of insulin and leptin. Here we report the discovery and characterization of a novel selective DGAT1 inhibitor 29 to potentially treat obesity. Compound 29 showed lipid lowering effect in mouse lipid tolerance test (LTT) and also reduced body weight in DIO mice without observable liver damage.

[4] *Pande SD, Kum S, Safdar Husain F, Kerner V*. **Complete resolution of extensive thrombosis of atheromatous non-aneurysmal descending aorta and pulmonary embolism with warfarin therapy**. BMJ case reports 2018; 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29703832
ABSTRACT
A 54-year-old man underwent decompressive craniectomy following a stroke. He further developed right lower limb ischaemia, and CT aortography revealed extensive aortic atherosclerotic disease. Urgent embolectomy prevented him from having a major amputation. He subsequently developed pulmonary embolism. This was initially treated with heparin followed by warfarin apart from antiplatelets and statin. A follow-up aortography at 3 months interval showed near complete resolution of atheromatous disease of the aorta. This report raises the possibility that apart from antiplatelets and lipid-lowering agents, anticoagulation may be responsible for resolution of such an extensive atheromatous disease and whether this can be considered as part of regular treatment.

[5] *Kruger K, Leppkes N, Gehrke-Beck S et al.* **Improving long-term adherence to statin therapy: a qualitative study of GPs' experiences in primary care**. Br J Gen Pract 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29686133
ABSTRACT
BACKGROUND: Statins substantially reduce the risk of cardiovascular disease when taken regularly. Though statins are generally well tolerated, current studies show that one-third of patients discontinue use of statins within 2 years. A qualitative approach may improve the understanding of attitudes and behaviours towards statins, the mechanisms related to discontinuation, and how they are managed in primary care. AIM: To identify factors related to statin discontinuation and approaches for long-term statin adherence. DESIGN AND SETTING: A

qualitative study of German GPs' experiences with statin therapy in rural and urban settings in primary care. METHOD: Semi-structured interviews (n = 16) with purposefully recruited GPs were recorded, transcribed, and analysed using qualitative content analysis. RESULTS: Sociodemographic patient factors, the nocebo effect, patient attitudes towards primary prevention, and negative media coverage had significant impacts on statin therapy according to GPs. To overcome these barriers, GPs described useful strategies combining patient motivation and education with person-centred care. GPs used computer programs for individual risk-benefit analyses in the context of shared decision making. They encouraged patients with strong concerns or perceived side effects to continue therapy with a modified medication regimen combined with individual therapy goals. CONCLUSION: GPs should be aware of barriers to statin therapy and useful approaches to overcome them. They could be supported by guideline recommendations that are more closely aligned to primary care as well as comprehensible patient information about lipid-lowering therapy. Future studies, exploring patients' specific needs and involving them in improving adherence behaviour, are recommended.

[6] *Camargo A, Jimenez-Lucena R, Alcala-Diaz JF et al.* **Postprandial endotoxemia may influence the development of type 2 diabetes mellitus: From the CORDIOPREV study**. Clinical nutrition (Edinburgh, Scotland) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29685478
ABSTRACT
BACKGROUND & AIMS: Insulin resistance (IR) and impaired beta-cell function are key determinants of type 2 diabetes mellitus (T2DM). Intestinal absorption of bacterial components activates the toll-like receptors inducing inflammation, and this in turn IR. We evaluated the role of endotoxemia in promoting inflammation-induced insulin resistance (IR) in the development of T2DM, and its usefulness as predictive biomarker. METHODS: We included in this study 462 patients from the CORDIOPREV study without T2DM at baseline. Of these, 107 patients developed T2DM according to the American Diabetes Association (ADA) diagnosis criteria after a median follow-up of 60 months (Incident-DIAB group), whereas 355 patients did not developed it during this period of time (Non-DIAB group). RESULTS: We observed a postprandial increase in lipopolysaccharides (LPS) levels in the Incident-DIAB at baseline ($P < 0.001$), whereas LPS levels were not modified in the Non-DIAB. Disease-free survival curves based on the LPS postprandial fold change improved T2DM Risk Assessment as compared with the previously described FINDRISC score (hazard ratio of 2.076, 95% CI 1.149-3.750 vs. 1.384, 95% CI 0.740-2.589). Moreover, disease-free survival curves combining the LPS postprandial fold change and FINDRISC score together showed a hazard ratio of 3.835 (95% CI 1.323-11.114), linked to high values of both parameters. CONCLUSION: Our results suggest that a high postprandial endotoxemia precedes the development of T2DM. Our results also showed the potential use of LPS plasma levels as a biomarker predictor of T2DM development. CLINICAL TRIALS.GOV. IDENTIFIER: NCT00924937.

[7] *McKeand W, Baird-Bellaire S, Ermer J, Patat A*. **A Study of the Potential Interaction Between Bazedoxifene and Atorvastatin in Healthy Postmenopausal Women**. Clinical pharmacology in drug development 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29683561

ABSTRACT

An open-label, 3-period study was conducted in 30 healthy postmenopausal women (mean age, 58.4 years) who received a single oral dose of atorvastatin 20 mg on day 1 (period 1), multiple daily dosing of bazedoxifene 40 mg on days 4-11 (period 2), and coadministration of atorvastatin 20 mg + bazedoxifene 40 mg on day 12 (period 3). Serial blood samples were collected (24 hours after bazedoxifene and 72 hours after atorvastatin) and assayed for bazedoxifene, atorvastatin, and its ortho-hydroxy and para-hydroxy metabolites. Pharmacokinetic parameters were calculated using noncompartmental methods. Bazedoxifene exposure was not altered with coadministration of atorvastatin 20 mg (Cmax and AUCss were within bioequivalence limits). Similarly, atorvastatin and ortho-hydroxyatorvastatin exposure was equivalent with or without coadministration with bazedoxifene. Para-hydroxyatorvastatin concentrations were below the limit of quantitation under both conditions. Cmax for atorvastatin and ortho-hydroxyatorvastatin was 14% and 18% lower, respectively, and Tmax was 20% and 34% longer, respectively, with the combination compared with atorvastatin alone. There were no serious adverse events, and no subjects discontinued the study because of safety. No clinically significant pharmacokinetic interaction was observed between bazedoxifene and atorvastatin or its active metabolites, indicating they may be safely coadministered without dosage adjustment.

[8] *Wang EQ, Plotka A, Salageanu J et al.* **Comparative Pharmacokinetics and Pharmacodynamics of Bococizumab Following a Single Subcutaneous Injection Using Drug Substance Manufactured at Two Sites or Administration via Two Different Devices**. Clinical pharmacology in drug development 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29688615

ABSTRACT

The pharmacokinetics (PK) and pharmacodynamics (PD) of bococizumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, were compared following a single 150-mg subcutaneous dose administered to healthy subjects (n = 156-158/arm) via: (1) a prefilled syringe (PFS) using drug substance (DS) manufactured by Pfizer, (2) a PFS using DS manufactured by Boehringer Ingelheim Pharma, (3) a prefilled pen using DS manufactured by Pfizer (NCT02458209). Blood samples were collected for 12 weeks postdose. Safety was monitored throughout. Mean maximum plasma concentration (Cmax) ranged between 11.0 and 11.3 mug/mL, and area under the plasma concentration-time curve (AUCinf) ranged between 177.6 and 185.0 mug.day/mL across treatments. The 90% confidence intervals for the ratios of adjusted geometric means for Cmax and AUCinf fell within the 80%-125% range for both DS and delivery device comparisons. Comparable low-density lipoprotein cholesterol profiles were observed, with nadir values of 54.3-56.1 mg/dL across treatments. Similar PCSK9 responses were also observed. Safety profiles were similar across treatments, and the majority of adverse events (AEs) were mild. Three subjects reported serious AEs. The most frequently reported AEs were headache, injection-site reaction, and upper respiratory tract infection, with no clear differences across treatments. Comparable PK, PD, and safety were observed following a single bococizumab 150-mg subcutaneous injection regardless of site of DS manufacture or delivery device used.

[9] *Zhang C, Qin JJ, Gong FH et al.* **Mindin deficiency in macrophages protects against foam cell formation and atherosclerosis by targeting LXR-beta**. Clinical science (London, England : 1979) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29695588
ABSTRACT
AbstractBackground- Mindin, which is a highly conserved ECM protein, has been documented to play pivotal roles in regulating angiogenesis, inflammatory processes and immune responses. The aim of this study was to assess whether mindin contributes to the development of atherosclerosis. Methods and Results- A significant upregulation of Mindin expression was observed in the serum, arteries and atheromatous plaques of ApoE(-/-) mice after HFD treatment. Mindin(-/-)ApoE(-/-) mice and macrophage-specific mindin overexpression in ApoE(-/-) mice (Lyz2-mindin-TG) were generated to evaluate the effect of mindin on the development of atherosclerosis. The Mindin(-/-)ApoE(-/-) mice exhibited significantly ameliorated atherosclerotic burdens in the entire aorta and aortic root and increased atherosclerotic plaque stability. Moreover, bone marrow transplantation further demonstrated that mindin deficiency in macrophages was largely responsible for the alleviated atherogenesis. The Lyz2-mindin-TG mice exhibited the opposite phenotype. Mindin deficiency enhanced foam cell formation by increasing the expression of cholesterol effectors, including ABCA1 and ABCG1. The mechanistic study indicated that mindin ablation promoted LXR-beta expression via a direct interaction. Importantly, LXR-beta inhibition largely reversed the ameliorating effect of mindin deficiency on foam cell formation and ABCA1 and ABCG1 expression. Conclusions -The present study demonstrated that mindin deficiency serves as a novel mediator that protects against foam cell formation and atherosclerosis by directly interacting with LXR-beta.

[10] *Bekkar A, Estreicher A, Niknejad A et al.* **Expert curation for building network-based dynamical models: a case study on atherosclerotic plaque formation**. Database : the journal of biological databases and curation 2018; 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29688381
ABSTRACT
Database URL: http://biomodels.caltech.edu.

[11] *Janghorbani M, Soltanian N, Amini M, Aminorroaya A*. **Low-density lipoprotein cholesterol and risk of type 2 diabetes: The Isfahan diabetes prevention study**. Diabetes & metabolic syndrome 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29699950
ABSTRACT
BACKGROUND: Studies reported that lipid-lowering treatment may increase the risk of diabetes, support the hypothesis that low-density lipoprotein cholesterol (LDLC) may be associated with type 2 diabetes (T2D). OBJECTIVE: The aim of this study was to assess the association between the LDLC levels and the incidence of T2D in an Iranian high-risk population not treated with lipid-lowering medications. METHODS: Mean 10-year follow-up data (1819) in non-diabetic first-degree relatives (FDR) of consecutive patients with T2D 30-70 years old, who were not treated with lipid-lowering drugs at baseline were examined. The diagnosis of T2D

based on serial oral glucose tolerance test was the primary outcome. Cox proportional hazard model was used to estimate the hazard ratio (HR) for the incidence of T2D within tertiles of LDLC. RESULTS: A higher LDLC concentration was significantly associated with higher risk of T2D. Compared with the first tertile, the adjusted risk of T2D increased for the second (HR 1.20, 95% CI: 1.07, 1.35, P<0.01) and third (HR 1.22, 95% CI: 1.08, 1.37, P<0.01), tertiles of LDLC. CONCLUSIONS: While these results await confirmation, a higher LDLC level was significantly associated with higher risk of T2D, independent of age, gender, fasting plasma glucose, waist circumference or blood pressure, in high-risk individuals in Iran.

[12] *Kim H, Choi HY, Kim YH et al.* **Pharmacokinetic interactions and tolerability of rosuvastatin and ezetimibe: an open-label, randomized, multiple-dose, crossover study in healthy male volunteers**. Drug design, development and therapy 2018; 12:815-821.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29692602
ABSTRACT
Purpose: Rosuvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor that effectively reduces low-density lipoprotein cholesterol levels. However, statin monotherapy does not always achieve acceptable low-density lipoprotein cholesterol levels in patients with severe hypercholesterolemia. Ezetimibe, a selective cholesterol-absorption inhibitor, is approved for use as a monotherapy or combination therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for patients with hypercholesterolemia. The aim of this study was to examine the pharmacokinetics (PKs) of drug interactions between rosuvastatin and ezetimibe, and the tolerability of combined administration in healthy Korean male volunteers. Subjects and methods: Healthy subjects (n=24) were randomly allocated to 3 treatment groups: rosuvastatin (20 mg) alone, ezetimibe (10 mg) alone, and rosuvastatin (20 mg) plus ezetimibe (10 mg). The drugs were taken once every 24 hours over a period of 10 days. Blood samples were collected to analyze steady-state PKs. Results: All adverse events observed during the study were mild, and the frequency was no higher for combined administration than for mono administration. For rosuvastatin, the steady-state mean ratios (90% CI) of the combined over the single dose were 1.076 (1.019-1.136) for AUCtau,ss and 1.099 (1.003-1.204) for concentration at steady-state, respectively. In the case of free and total ezetimibe, the steady-state ratios of AUCtau,ss and concentration at steady-state were 1.131 (1.051-1.218) and 1.182 (1.038-1.346), and 1.055 (0.969-1.148) and 0.996 (0.873-1.135), respectively. Conclusion: Combined administration of rosuvastatin and ezetimibe was well tolerated. No clinically significant PK interactions between rosuvastatin and ezetimibe were observed when the 2 drugs were administered concomitantly.

[13] *Stahli BE, Landmesser U*. **[Optimal Medical Therapy and Secondary Prevention in Patients after an Acute Coronary Syndrome]**. Deutsche medizinische Wochenschrift (1946) 2018; 143:672-679.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29684934
ABSTRACT
Antithrombotic therapy and other secondary preventive measures such as lifestyle changes, lipid lowering and blood pressure control, along with coronary revascularization strategies, can markedly improve clinical outcomes in patients after an acute coronary syndrome. Current

guideline-recommended secondary preventive measures in patients with a recent acute coronary syndrome event according to the European Society of Cardiology (ESC) are summarized in this review.

[14] *Budoff MJ, Young R, Burke G et al.* **Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA)**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29688297
ABSTRACT
Aims: While coronary artery calcium (CAC) has been extensively validated for predicting clinical events, most outcome studies of CAC have evaluated coronary heart disease (CHD) rather than atherosclerotic cardiovascular disease (ASCVD) events (including stroke). Also, virtually all CAC studies are of short- or intermediate-term follow-up, so studies across multi-ethnic cohorts with long-term follow-up are warranted prior to widespread clinical use. We sought to evaluate the contribution of CAC using the population-based MESA cohort with over 10 years of follow-up for ASCVD events, and whether the association of CAC with events varied by sex, race/ethnicity, or age category. Methods and results: We utilized MESA, a prospective multi-ethnic cohort study of 6814 participants (51% women), aged 45-84 years, free of clinical CVD at baseline. We evaluated the relationship between CAC and incident ASCVD using Cox regression models adjusted for age, race/ethnicity, sex, education, income, cigarette smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, lipid-lowering medication, systolic blood pressure, antihypertensive medication, intentional physical exercise, and body mass index. Only the first event for each individual was used in the analysis. Overall, 500 incident ASCVD (7.4%) events were observed in the total study population over a median of 11.1 years. Hard ASCVD included 217 myocardial infarction, 188 strokes (not transient ischaemic attack), 13 resuscitated cardiac arrest, and 82 CHD deaths. Event rates in those with CAC = 0 Agatston units ranged from 1.3% to 5.6%, while for those with CAC > 300, the 10-year event rates ranged from 13.1% to 25.6% across different age, gender, and racial subgroups. At 10 years of follow-up, all participants with CAC > 100 were estimated to have >7.5% risk regardless of demographic subset. Ten-year ASCVD event rates increased steadily across CAC categories regardless of age, sex, or race/ethnicity. For each doubling of CAC, we estimated a 14% relative increment in ASCVD risk, holding all other risk factors constant. This association was not significantly modified by age, sex, race/ethnicity, or baseline lipid-lowering use. Conclusions: Coronary artery calcium is associated strongly and in a graded fashion with 10-year risk of incident ASCVD as it is for CHD, independent of standard risk factors, and similarly by age, gender, and ethnicity. While 10-year event rates in those with CAC = 0 were almost exclusively below 5%, those with CAC >/= 100 were consistently above 7.5%, making these potentially valuable cutpoints for the consideration of preventive therapies. Coronary artery calcium strongly predicts risk with the same magnitude of effect in all races, age groups, and both sexes, which makes it among the most useful markers for predicting ASCVD risk.

[15] *Sabouret P, Angoulvant D, Pathak A*. **FOURIER to ODYSSEY: the end of the journey for lipid-lowering therapy trials? Lessons from recent clinical trials with anti-PCSK9 antibodies**.

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=29701178
ABSTRACT

[16] *Johnson CC, Sheffield KM, Brown RE*. **Mind-Body Therapies for African-American Women at Risk for Cardiometabolic Disease: A Systematic Review**. Evidence-based complementary and alternative medicine : eCAM 2018; 2018:5123217.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29681975
ABSTRACT
Background: A major determinant in cardiometabolic health is metabolic syndrome (MetS), a cluster of symptoms that portend the development of cardiovascular disease (CVD). As mind-body therapies are thought to help in lowering physiological and environmental CVD risk factors including blood pressure and psychological stress, they may also be beneficial for the primary prevention of CVD. Objectives: To synthesize and summarize existing knowledge on the effectiveness of mind-body therapies on MetS outcomes in African-American (AA) women, a US subpopulation at high risk for CVD. Search Methods: A systematic search of eight databases was conducted in order to identify published papers addressing the topic. We included trials involving AA adult women, ages 18-64, and we included RCTs that involved multifactorial interventions. Outcomes of interest were MetS, chronic disease, and CVD risk factors (blood pressure, blood lipids, blood glucose, BMI, waist circumference, and mental health domains). Two authors independently selected trials for inclusion, extracted data, and assessed risks of bias. Main Results: We identified five trials for inclusion in this review. One study reported outcomes associated with the full MetS symptom cluster. The included trials were small, short term, and at high risk of bias. All interventions lasted at least 6 weeks.

[17] *Hua S, Ma C, Zhang J et al.* **Influence of APOA5 Locus on the Treatment Efficacy of Three Statins: Evidence From a Randomized Pilot Study in Chinese Subjects**. Frontiers in pharmacology 2018; 9:352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29695967
ABSTRACT
Pharmacogenetics or pharmacogenomics approaches are important for addressing the individual variabilities of drug efficacy especially in the era of precision medicine. One particular interesting gene to investigate is APOA5, which has been repeatedly linked with the inter-individual variations of serum triglycerides. Here, we explored APOA5-statin interactions in 195 Chinese subjects randomized to rosuvastatin (5-10 mg/day), atorvastatin (10-20 mg/day), or simvastatin (40 mg/day) for 12 weeks by performing a targeted genotyping analysis of the APOA5 promoter SNP rs662799 (-1131T > C). There were no significant differences between the treatment arms for any of the statin-induced changes in clinical biomarkers. Reductions in LDL cholesterol were influenced by the APOA5 genotype in all three treatment groups. By contrast, changes in HDL cholesterol, and triglycerides were only affected by the APOA5 genotype in the atorvastatin and simvastatin groups and not in the rosuvastatin group. Our results suggest that future studies may need to consider stratifying subjects not only by genetic background but also by prescribed statin type.

[18] *Schafer C, Moore V, Dasgupta N et al.* **The Effects of PPAR Stimulation on Cardiac Metabolic Pathways in Barth Syndrome Mice**. Frontiers in pharmacology 2018; 9:318.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29695963

ABSTRACT
Aim: Tafazzin knockdown (TazKD) in mice is widely used to create an experimental model of Barth syndrome (BTHS) that exhibits dilated cardiomyopathy and impaired exercise capacity. Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that play essential roles as transcription factors in the regulation of carbohydrate, lipid, and protein metabolism. We hypothesized that the activation of PPAR signaling with PPAR agonist bezafibrate (BF) may ameliorate impaired cardiac and skeletal muscle function in TazKD mice. This study examined the effects of BF on cardiac function, exercise capacity, and metabolic status in the heart of TazKD mice. Additionally, we elucidated the impact of PPAR activation on molecular pathways in TazKD hearts. Methods: BF (0.05% w/w) was given to TazKD mice with rodent chow. Cardiac function in wild type-, TazKD-, and BF-treated TazKD mice was evaluated by echocardiography. Exercise capacity was evaluated by exercising mice on the treadmill until exhaustion. The impact of BF on metabolic pathways was evaluated by analyzing the total transcriptome of the heart by RNA sequencing. Results: The uptake of BF during a 4-month period at a clinically relevant dose effectively protected the cardiac left ventricular systolic function in TazKD mice. BF alone did not improve the exercise capacity however, in combination with everyday voluntary running on the running wheel BF significantly ameliorated the impaired exercise capacity in TazKD mice. Analysis of cardiac transcriptome revealed that BF upregulated PPAR downstream target genes involved in a wide spectrum of metabolic (energy and protein) pathways as well as chromatin modification and RNA processing. In addition, the Ostn gene, which encodes the metabolic hormone musclin, is highly induced in TazKD myocardium and human failing hearts, likely as a compensatory response to diminished bioenergetic homeostasis in cardiomyocytes. Conclusion: The PPAR agonist BF at a clinically relevant dose has the therapeutic potential to attenuate cardiac dysfunction, and possibly exercise intolerance in BTHS. The role of musclin in the failing heart should be further investigated.

[19] *Liao Y, Zhang P, Yuan B et al.* **Pravastatin Protects Against Avascular Necrosis of Femoral Head via Autophagy**. Front Physiol 2018; 9:307.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29686621

ABSTRACT
Autophagy serves as a stress response and may contribute to the pathogenesis of avascular necrosis of the femoral head induced by steroids. Statins promote angiogenesis and ameliorate endothelial functions through apoptosis inhibition and necrosis of endothelial progenitor cells, however the process used by statins to modulate autophagy in avascular necrosis of the femoral head remains unclear. This manuscript determines whether pravastatin protects against dexamethasone-induced avascular necrosis of the femoral head by activating endothelial progenitor cell autophagy. Pravastatin was observed to enhance the autophagy activity in endothelial progenitor cells, specifically by upregulating LC3-II/Beclin-1 (autophagy related proteins), and autophagosome formation in vivo and in vitro. An autophagy inhibitor, 3-

MA, reduced pravastatin protection in endothelial progenitor cells exposed to dexamethasone by attenuating pravastatin-induced autophagy. Adenosine monophosphate-activated protein kinase (AMPK) is a key autophagy regulator by sensing cellular energy changes, and indirectly suppressing activation of the mammalian target of rapamycin (mTOR). We found that phosphorylation of AMPK was upregulated however phosphorylation of mTOR was downregulated in pravastatin-treated endothelial progenitor cells, which was attenuated by AMPK inhibitor compound C. Furthermore, liver kinase B1 (a phosphorylase of AMPK) knockdown eliminated pravastatin regulated autophagy protein LC3-II in endothelial progenitor cells in vitro. We therefore demonstrated pravastatin rescued endothelial progenitor cells from dexamethasone-induced autophagy dysfunction through the AMPK-mTOR signaling pathway in a liver kinase B1-dependent manner. Our results provide useful information for the development of novel therapeutics for management of glucocorticoids-induced avascular necrosis of the femoral head.

[20] *Mirzaee S, Thein PM, Wong D, Nasis A*. **A Small Change Can Make a Big Difference: A Lesson from Evolocumab**. Heart, lung & circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29685715
ABSTRACT
BACKGROUND: Evolocumab is an expensive proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor which has been shown to significantly improve cardiovascular outcomes in high risk patients. METHODS: This is a case study describing a stepwise approach to "PCSK9 inhibitor non-response" in a patient with familial hypercholesterolaemia. There are a few described pathophysiological mechanisms for "PCSK9 inhibitor non-response" including homozygous LDL-C receptor-negative mutations and alteration in the binding site of PCSK9 inhibitors. RESULTS: We report the case of a 41-year-old woman with familial hypercholesterolaemia and premature cardiovascular disease, who was non-responsive to the action of PCSK9 inhibitor solely due to the incorrect subcutaneous injection technique. CONCLUSIONS: This case study highlights the importance of reviewing the accuracy of SC injection technique in patients with minimal or no response to PCSK9 inhibitors prior to proceeding to costly genetic testing.

[21] *Wang F, Chen FF, Shang YY et al.* **Insulin resistance adipocyte-derived exosomes aggravate atherosclerosis by increasing vasa vasorum angiogenesis in diabetic ApoE(-/-) mice**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29685689
ABSTRACT
BACKGROUND: Vasa vasorum (VV) angiogenesis is increased in type 2 diabetes mellitus (T2DM) and may promote atherosclerotic plaque rupture. We sought to determine whether insulin resistance adipocyte-derived exosomes (IRADEs) played a major role in modulating VV angiogenesis and the mechanisms involved. METHODS: The characterization of IRADEs was performed by electron microscopy, NTA (Nanoparticle Tracking Analysis) and western blot. The cellular effects of IRADEs on angiogenesis were explored in human umbilical vein endothelial cells (HUVECs) and murine aortic endothelial cells (MAECs) in vitro. The roles of IRADEs in angiogenesis were demonstrated with aortic ring and matrigel plug assays ex vivo and the

plaque burden, plaque stability and angiogenesis-related protein expression in vivo were evaluated by ultrasonography, immunohistochemistry and western blot. RESULTS: The IRADEs had a cup-shaped morphology, could be taken up by HUVECs and atherosclerotic plaques, and promoted tube formation by shh in vitro. In the aortic ring and matrigel plug assays, angiogenesis was significantly increased in the IRADEs group. Exogenously administered shh-containing IRADEs increased VV angiogenesis, the plaque burden, the vulnerability index and the expression of angiogenesis-related factors, whereas these effects were attenuated by silencing shh in IRADEs. CONCLUSIONS: In conclusion, IRADEs promote plaque burden and plaque vulnerability partly by inducing VV angiogenesis, which occurs partly through shh. Accordingly, the application of IRADEs may serve as a novel therapeutic approach to treat diabetic atherosclerosis.

[22] *Hashiguchi M, Hakamata J, Shimizu M et al.* **Risk factors for rhabdomyolysis with HMG-CoA reductase inhibitors identified using a postmarketing surveillance database in Japan**. International journal of clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29701171
ABSTRACT
OBJECTIVE: To investigate quantitatively the risk factors for rhabdomyolysis or related symptoms associated with HMG-CoA reductase inhibitors (statins), we used the lipid-lowering drug database (32,157 patients) developed by the RAD-AR Council, Japan, based on the postmarketing surveillance (PMS) data of pharmaceutical companies to perform a nested case-control study. MATERIALS AND METHODS: Of 26,849 patients taking statins, the case group was composed of 51 patients who experienced rhabdomyolysis or related symptoms while taking statins, and the control group was 1,020 patients randomly selected from patients who did not experience rhabdomyolysis or related symptoms while taking statins. Relevant factors that can be extracted from the database were: sex, age, body mass index (BMI), statin use duration, complications, concomitant medication, and clinical laboratory test values. RESULTS: Among those taking statins, 51 experienced rhabdomyolysis or related symptoms. Factors differing significantly between the two groups by univariate analysis were age, duration of statin intake, combination drugs (Ca antagonists, angiotensin II receptor blocker (ARB), cardiac drugs, benzodiazepines, mucoprotective drugs, insulin, alpha-glucosidase inhibitors), clinical laboratory results (high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase, alkaline phosphatase, total bilirubin), and complications (alcoholic hepatitis). Conditional multivariate logistic analysis of these factors yielded adjusted/odds ratios of 8.82 for the concomitant administration of an ARB and 3.45 for increased AST and 3.20 for increased total bilirubin levels. CONCLUSION: Risk factors for rhabdomyolysis or related symptoms associated with taking statins were combination with ARB and increases in AST or total bilirubin levels..

[23] *Vetter M, Kremer AE*. **[Primary biliary cholangitis-established and novel therapies]**. Internist (Berl) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29691599
ABSTRACT
BACKGROUND: Patients with primary biliary cholangitis (PBC, formerly primary biliary cirrhosis) and insufficient treatment response or risk factors exhibit a remarkably increased risk for

disease progression and associated complications. Furthermore, extrahepatic manifestations may considerably reduce quality of life in affected patients. OBJECTIVES: This article presents an overview on standard therapy with ursodeoxycholic acid (UDCA) and further therapeutic options in patients with insufficient treatment response. In addition, symptom-orientated therapies will be presented in a practical and compact way. METHODS: The current European and German guidelines from 2017 in addition to several research papers and expert opinions are the basis for this review. RESULTS: Every PBC patient should be treated with UDCA life-long. In case of insufficient response to UDCA, obeticholic acid (OCA) has been approved as second line therapy since 2016. Fibrates and budesonide present off-label options for certain patient subpopulations. Pruritus should initially be treated with colestyramine. In case of insufficient efficacy or intolerance, rifampicin represents the most effective off-label option. If fatigue is present, differential diagnoses shall be excluded and coping strategies combined with regular physical activity can have a positive effect. CONCLUSION: UDCA and OCA are effective and approved drugs for treating PBC. Patients with insufficient treatment response or risk factors have to be treated consequently. Due to the improved anti-cholestatic treatment options, therapies to reduce fatigue and pruritus are increasingly important.

[24] *Presta V, Figliuzzi I, Citoni B et al.* **Effects of different statin types and dosages on systolic/diastolic blood pressure: Retrospective analysis of 24-hour ambulatory blood pressure database**. Journal of clinical hypertension (Greenwich, Conn.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29683251
ABSTRACT
We previously demonstrated lower diastolic blood pressure (BP) levels under statin therapy in adult individuals who consecutively underwent 24-hour ambulatory BP monitoring and compared their levels to untreated outpatients. Here we evaluated systolic/diastolic BP levels according to different statin types and dosages. 987 patients (47.5% female, age 66.0 +/- 10.1 years, BMI 27.7 +/- 4.6 kg/m(2) , clinic BP 146.9 +/- 19.4/86.1 +/- 12.1 mm Hg, 24-hour BP 129.2 +/- 14.4/74.9 +/- 9.2 mm Hg) were stratified into 4 groups: 291 (29.5%) on simvastatin 10-80 mg/d, 341 (34.5%) on atorvastatin 10-80 mg/d, 187 (18.9%) on rosuvastatin 5-40 mg/d, and 168 (17.0%) on other statins. There were no significant BP differences among patients treated by various statin types and dosages, except in lower clinic (P = .007) and daytime (P = .013) diastolic BP in patients treated with simvastatin and atorvastatin compared to other statins. Favorable effects of statins on systolic/diastolic BP levels seem to be independent of types or dosages, thus suggesting a potential class effect of these drugs.

[25] *O'Donnell VB, Rossjohn J, Wakelam MJ*. **Phospholipid signaling in innate immune cells**. J Clin Invest 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29683435
ABSTRACT
Phospholipids comprise a large body of lipids that define cells and organelles by forming membrane structures. Importantly, their complex metabolism represents a highly controlled cellular signaling network that is essential for mounting an effective innate immune response. Phospholipids in innate cells are subject to dynamic regulation by enzymes, whose activities are highly responsive to activation status. Along with their metabolic products, they regulate

multiple aspects of innate immune cell biology, including shape change, aggregation, blood clotting, and degranulation. Phospholipid hydrolysis provides substrates for cell-cell communication, enables regulation of hemostasis, immunity, thrombosis, and vascular inflammation, and is centrally important in cardiovascular disease and associated comorbidities. Phospholipids themselves are also recognized by innate-like T cells, which are considered essential for recognition of infection or cancer, as well as self-antigens. This Review describes the major phospholipid metabolic pathways present in innate immune cells and summarizes the formation and metabolism of phospholipids as well as their emerging roles in cell biology and disease.

[26] *Gauthier MS, Awan Z, Bouchard A et al.* **Posttranslational modification of proprotein convertase subtilisin/kexin type 9 is differentially regulated in response to distinct cardiometabolic treatments as revealed by targeted proteomics**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29699916
ABSTRACT
BACKGROUND: The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein that interacts with the low-density lipoprotein (LDL) receptor at the surface of hepatocytes to regulate circulating LDL cholesterol levels. High circulating PCSK9 levels have been associated with elevated LDL cholesterol. Recently, the Food and Drug Administration of the United States approved new LDL cholesterol-lowering drugs that specifically target the inhibition of PCSK9. Similar to most human proteins, PCSK9 exists in multiple forms as it is the target of posttranslational modifications (PTMs) such as proteolytic cleavage, phosphorylation, and others, which can affect its biological activity. However, commercially available assays, such as enzyme-linked immunosorbent assays, do not discriminate between these forms. OBJECTIVE: To investigate, in 2 patient cohorts, the relationships between circulating levels of multiple forms of PCSK9 and cardiometabolic interventions or treatments known to reduce LDL cholesterol levels. METHODS: PCSK9 forms were measured in plasma: (1) in 20 patients before and 6 months after bariatric surgery and (2) in 132 patients before and 12 months after daily statin treatment. A series of specific peptides used as surrogates for various PCSK9 forms were quantified by a novel semiautomated proteomic assay termed protein affinity capture coupled to quantitative mass spectrometry. RESULTS: Bariatric surgery resulted in a decrease in the plasma level of PCSK9 prodomain ($P < .05$), but did not result in a significant change in other measured PCSK9 forms. Statin treatment resulted in an increase in all measured plasma PCSK9 peptides ($P < .001$), but a 25% decrease in the phosphorylated state of PCSK9 at S688 ($P < .05$). CONCLUSIONS: These unexpected findings indicate that measuring the circulating levels of the various domains and PTMs of PCSK9 provides more in depth information than total PCSK9 and that the prodomain and the phosphorylated state of S688 may represent novel biomarkers to explore in cardiometabolic diseases and response to treatment. In addition, our data generated new hypotheses on the function of PCSK9 PTMs in health and disease.

[27] *Ridker PM, Rose LM, Kastelein JJP et al.* **Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: Results from the SPIRE randomized trials of bococizumab**. Journal of clinical lipidology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29685591

ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH) is a dominant genetic disorder associated with elevated low-density lipoprotein cholesterol (LDL-C) and premature atherosclerotic events. Although therapeutic monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) are indicated for LDL-C reduction among adult patients with FH, placebo-controlled outcome data among FH patients are scant. OBJECTIVE: Directly compare the efficacy of PCSK9 inhibition as compared to placebo on hard cardiovascular outcomes in FH patients enrolled in the Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) program. METHODS: We estimated the efficacy of PCSK9 inhibition with bococizumab on future cardiovascular event rates among 1578 FH patients and 15,959 patients without FH who were selected for comparable lipid levels (on-statin levels of LDL-C >100 mg/dL or non-high-density lipoprotein cholesterol > 130 mg/dL). All patients were randomized by computer generated codes to bococizumab 150 mg subcutaneously every 2 weeks or to matching placebo in the SPIRE clinical trials program and were followed over a median period of 11.2 months for major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death). Analysis is by intention to treat. The SPIRE trials are closed and registered at ClinicalTrials.gov: NCT01968954, NCT01968967, NCT02100514, NCT01968980, NCT01975376, and NCT01975389. RESULTS: Compared to non-FH patients, FH patients enrolled in the SPIRE trials were on average younger (58 vs 63 years), more likely to be women (42 vs 35%), more likely to be primary prevention patients (42 vs 23%), had higher mean baseline LDL-C levels (151 vs 127 mg/dL), and lower rates of diabetes (25 vs 52%) and hypertension (59 vs 82%). FH and non-FH patients both had 55% reductions in LDL-C with bococizumab. Among FH patients, major adverse cardiovascular events occurred among 18 of 781 allocated to bococizumab and 22 of 797 allocated to placebo (hazard ratio 0.83; 95% confidence interval 0.44-1.54, P = .55). This best estimate of effect was similar in magnitude to that observed in the much larger group of patients without FH (hazard ratio 0.79, 95% confidence interval 0.64-0.97, P = .023) with no statistically significant evidence of heterogeneity between groups (P = .87). Incidence rate ratios comparing bococizumab to placebo for adverse events were similar among those with and without FH. The proportion of patients developing antidrug antibodies was higher among those with FH compared to those without FH (43% vs 36%, P < .001). CONCLUSIONS: In these randomized placebo-controlled data, the subgroup of statin-treated FH patients had a similar magnitude of risk reduction for hard cardiovascular events with the PCSK9 inhibitor bococizumab as did patients without FH, with no evidence of statistical heterogeneity between groups.

[28] *Uzhova I, Mateo-Gallego R, Moreno-Franco B et al.* **The additive effect of adherence to multiple healthy lifestyles on subclinical atherosclerosis: Insights from the AWHS**. Journal of clinical lipidology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29680699

ABSTRACT

BACKGROUND: Public health strategies targeting multiple healthy behaviors, rather than individual factors, have been proposed as more efficient strategies to promote cardiovascular health. However, the additive effect of multiple targets on primary prevention has not been

fully characterized. OBJECTIVE: To examine how adherence to multiple healthy behaviors is associated with the presence of subclinical atherosclerosis, a measure of early cardiovascular disease. METHODS: Analysis of a baseline data from 1798 middle-aged men from the Aragon Workers Health Study conducted between 2009 and 2010. Healthy behaviors were defined according to American Heart Association recommendations, aligned with Spanish Nutritional recommendations and included moderate alcohol consumption, smoking abstinence, no abdominal adiposity, decreased sedentarism, and adherence to Alternate Mediterranean Dietary Index. Presence of coronary artery calcium and plaques in femoral and carotid was quantified by a 16-slice computed tomography scanner and 2D ultrasound. RESULTS: Moderate alcohol consumption, as well as adherence to Mediterranean diet is independently associated with a 6% lower risk of having subclinical atherosclerosis. Smoking abstinence is associated with a 11% lower risk of subclinical atherosclerosis. Those who follow 3 lifestyle behaviors (Mediterranean diet, nonsmoking, and moderate alcohol intake) have 18% lower odds of presenting subclinical atherosclerosis compared with those who do not follow these protective lifestyle habits. CONCLUSION: Adoption of multiple healthy lifestyle behaviors early in life could be a key strategy to tackle the onset of atherosclerosis and reduce cardiovascular disease burden.

[29] *Fayyaz B, Rehman HJ, Upreti S*. **Beating the urine drug test - a case report on niacin toxicity**. Journal of community hospital internal medicine perspectives 2018; 8:73-75.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29686792
ABSTRACT
Niacin is a form of vitamin B3 which is used for the medical treatment of hyperlipidemia and niacin deficiency. However, within the last few years, it is being advertised on the Internet as a quick way to detoxify the human body in an attempt to evade urine drug tests. This claim is without any medical or scientific evidence and as a result, many cases have been reported where young adults have ended up with niacin toxicity. In this case report, we discuss a rare presentation of niacin toxicity and the effects Internet has had on the healthcare being practised by both the physicians and the patients themselves.

[30] *Min JJ, Shin BS, Lee JH et al.* **Effects of Pravastatin on Type 1 Diabetic Rat Heart with or without Blood Glycemic Control**. Journal of diabetes research 2018; 2018:1067853.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29682576
ABSTRACT
Although statins have been suggested to attenuate the progression of diabetic cardiomyopathy, its effect without glycemic control remains unclear. Therefore, we evaluated the effect of pravastatin on diabetic rat hearts according to glycemic control. Rats were randomly divided into five groups: control (C), diabetes (D), diabetes with insulin (I), diabetes with pravastatin (P), and diabetes with insulin and pravastatin (IP). Eight weeks after allocated treatments, the heart was extracted and analyzed following echocardiography. Cardiac fibrosis was measured using Masson's trichrome stain. Cardiac expression of collagen I/III, matrix metalloproteinase (MMP)-2, MMP-9, and angiotensin-converting enzyme (ACE)/ACE2 was evaluated by immunohistochemistry and/or Western blot. Enzyme-linked immunosorbent assay was used for measuring reactive oxygen species (ROS). Diabetic groups without glycemic control (D and P)

showed significantly impaired diastolic function and increased levels of cardiac fibrosis, collagen I/III, MMP-2, MMP-9, and ROS production. However, there were little significant differences in the outcomes among the control and two glucose-controlled diabetic groups (I and IP). Groups C and IP showed more preserved ACE2 and lower ACE expressions than the other groups did (D, I, and P). Our study suggested glycemic control would be more important to attenuate the progression of diabetic cardiomyopathy than pravastatin medication.

[31] *Parvanova A, Trillini M, Podesta MA et al.* **Blood Pressure and Metabolic Effects of Acetyl-l-Carnitine in Type 2 Diabetes: DIABASI Randomized Controlled Trial**. Journal of the Endocrine Society 2018; 2:420-436.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29696241
ABSTRACT
Context: Acetyl-l-carnitine (ALC), a mitochondrial carrier involved in lipid oxidation and glucose metabolism, decreased systolic blood pressure (SBP), and ameliorated insulin sensitivity in hypertensive nondiabetic subjects at high cardiovascular risk. Objective: To assess the effects of ALC on SBP and glycemic and lipid control in patients with hypertension, type 2 diabetes mellitus (T2D), and dyslipidemia on background statin therapy. Design: After 4-week run-in period and stratification according to previous statin therapy, patients were randomized to 6-month, double-blind treatment with ALC or placebo added-on simvastatin. Setting: Five diabetology units and one clinical research center in Italy. Patients: Two hundred twenty-nine patients with hypertension and dyslipidemic T2D >40 years with stable background antihypertensive, hypoglycemic, and statin therapy and serum creatinine <1.5 mg/dL. Interventions: Oral ALC 1000 mg or placebo twice daily on top of stable simvastatin therapy. Outcome and Measures: Primary outcome was SBP. Secondary outcomes included lipid and glycemic profiles. Total-body glucose disposal rate and glomerular filtration rate were measured in subgroups by hyperinsulinemic-euglycemic clamp and iohexol plasma clearance, respectively. Results: SBP did not significantly change after 6-month treatment with ALC compared with placebo (-2.09 mm Hg vs -3.57 mm Hg, P = 0.9539). Serum cholesterol, triglycerides, and lipoprotein(a), as well as blood glucose, glycated hemoglobin, fasting insulin levels, homeostatic model assessment of insulin resistance index, glucose disposal rate, and glomerular filtration rate did not significantly differ between treatments. Adverse events were comparable between groups. Conclusions: Six-month oral ALC supplementation did not affect blood pressure, lipid and glycemic control, insulin sensitivity and kidney function in hypertensive normoalbuminuric and microalbuminuric T2D patients on background statin therapy.

[32] *Polnak JF, Delate T, Clark NP*. **The influence of fibrate initiation on INR and warfarin dose in patients receiving chronic warfarin therapy**. Journal of thrombosis and thrombolysis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29681002
ABSTRACT
Several drug interaction compendia report a risk of warfarin potentiation after initiation of a fibrate; however, the evidence of this interaction is limited. The objective of this study was to evaluate warfarin dose and international normalized ratio (INR) response among a large sample of patients receiving chronic warfarin who initiated a fibrate. This was a retrospective, one-

sample, pre-to-post study. Adult patients who were receiving chronic warfarin therapy at the time of gemfibrozil or fenofibrate dispensing between 1/1/2000 and 3/31/2016 were included. Patients had at least one and two therapeutic INRs during the 90 days prior to (baseline) and after (follow-up), respectively, fibrate initiation. Comparison of stable warfarin dose:INR ratio between the baseline and follow-up periods and assessment of safety outcomes during follow-up were performed. There were 321 patients included. Patients were predominantly male (62.6%) with an indication of atrial fibrillation (44.2%). The mean warfarin dose:INR ratio was equivalent between the baseline and follow-up periods (13.4 mg/INR [+/- 6.9] vs. 13.5 mg/INR [+/- 7.5], respectively, p = 0.711). Rates of thromboembolism, bleeding, and all-cause mortality in the 90-day follow up were 0, 0.6, and 1.2%, respectively. Although individual patients may have labile INRs after fibrate initiation, no significant interaction between fibrate and warfarin in a large sample of real world patients was identified. The utility of additional INR monitoring after fibrate initiation in otherwise stable patients receiving chronic warfarin therapy is unclear.

[33] *Arinze N, Farber A, Sachs T et al.* **The effect of statin use and intensity on stroke and myocardial infarction after carotid endarterectomy**. Journal of vascular surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29685507

ABSTRACT

OBJECTIVE: Statin use in patients with cerebrovascular disease undergoing carotid endarterectomy (CEA) has been advocated for prevention of stroke and cardiovascular events. However, the effect of statin therapy on long-term outcomes after CEA still needs to be delineated. METHODS: OptumLabs Data Warehouse, a comprehensive, longitudinal, real-world dataset with deidentified lives across claims and clinical information, was used to analyze the rates of stroke, myocardial infarction (MI), and statin use after CEA. Both duration and intensity of statin therapy were investigated. RESULTS: There were 21,277 patients who underwent CEA from 2004 to 2014. The average age was 70 years, and 59.4% were male. The average Elixhauser index score was 4.2. Follow-up was a median of 2.4 years (range, 0.2-10.0 years). Long-term statin use was observed in 57.4%. Statin distribution included atorvastatin 35%, simvastatin 35%, pravastatin 11%, rosuvastatin 10%, and lovastatin 7%. The 30- and 90-day stroke rates were 1.3% and 2.2%, and the MI rates were 0.5% and 1.1%, respectively. Postoperative statin use was associated with a lower perioperative stroke rate at 30 days (odds ratio [OR], 0.77; 95% confidence interval [CI], 0.61-0.98; P = .036) and 90 days (OR, 0.75; 95% CI, 0.62-0.90; P = .002). Postoperative statin use did not show a protective effect on 30-day or 90-day MI rates (OR, 1.01; 95% CI, 0.69-1.46; P = .975) or 90-day MI rates (OR, 0.85; 95% CI, 0.66-1.11; P = .213). High-intensity statin use when compared with standard therapy did not affect 30-day stroke outcomes (OR, 0.96; 95% CI, 0.60-1.5; P = .847) or 90-day stroke outcomes (OR, 1.06; 95% CI, 0.74-1.5; P = .762); or 30-day MI (OR, 0.81; 95% CI, 0.39-1.68; P = .576) or 90-day MI (OR, 1.25; 95% CI, 0.79-1.96; P = .339). Statin use was independently protective against long-term stroke (hazard ratio, 0.82; 95% CI, 0.75-0.91; P < .001) and MI (hazard ratio, 0.83; 95% CI, 0.75-.92; P < .001). CONCLUSIONS: Postoperative statin use among patients undergoing CEA was associated with a decreased risk of stroke at 30 and 90 days, as well as a long-term protective effect against MI and stroke. High-intensity statin use compared with standard use did not show an effect on outcomes of stroke or MI at 30 and 90-days after CEA.

[34] *Bajawi SM, Jafarri SA, Buraik MA et al.* **Pathogenesis-based therapy: Cutaneous abnormalities of CHILD syndrome successfully treated with topical simvastatin monotherapy**. JAAD case reports 2018; 4:232-234.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29687057
ABSTRACT

[35] *Farrag SM, Hamzawy MA, El-Yamany MF et al.* **Atorvastatin in nano-particulate formulation abates muscle and liver affliction when coalesced with coenzyme Q10 and/or vitamin E in hyperlipidemic rats**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29694831
ABSTRACT
AIMS: Statins are the most widely used to lower elevated low-density lipoprotein levels and preventing cardiovascular diseases in humans. However, about 20% of patients treated with this medication suffer from statin-related myalgia. To this end, this study investigated the potential effect of nano-particulate formulation in alleviating the muscles and liver damage either alone or when co-administered with nano coenzyme Q10 and nano vitamin E. MATERIALS AND METHODS: Male Wistar rats were fed normal diet or high-fat diet for 12weeks, following which rats were treated with either (i) atorvastatin (5 or 20mg/kg/day, p.o.) or (ii) atorvastatin with CoQ10 (10mg/kg/day, p.o.) (iii) and/or vitamin E (30mg/kg/day, p.o.) in free particle or nanoparticle forms for another 4weeks. In all rats, serum total cholesterol (CH), triglycerides (TGs), low (LDL) and high (HDL) density lipoproteins, alanine (ALT) and aspartate (AST) transaminases, alkaline phosphatase (ALP), creatine kinase (CK), albumin (ALB), as well as hepatic malondialdehyde (MDA) and antioxidants "reduced glutathione (GSH) and superoxide dismutase (SOD)" were measured. Additionally quadriceps muscles and liver tissues were used for histopathological examination. KEY FINDINGS: The antihyperlipidemic effect of statins was not altered when formulated as nanoparticles; albeit the former showed a prominent reduction in the liver and muscle enzymes and histopathological alterations together with a marked decline in the oxidative stress as compared to the free particulate form. These results were augmented when atorvastatin was combined with CoQ10 and/or Vit.E. SIGNIFICANCE: Nanoparticulate formulation alleviated the statins induced liver and muscle damage especially when combined with CoQ10 and/or Vit.E.

[36] *Kotyla PJ*. **Simvastatin reduces antiphospholipid antibodies formation in patients with systemic lupus erythematosus: a preliminary study**. Lupus 2018:961203318772015.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29699441
ABSTRACT

[37] *Wang K, Chen L, Liu L et al.* **The effects of atorvastatin on IL-6, CRP, blood lipid and myocardial protection of interventional therapy in patients with acute myocardial infarction**. Minerva medica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29696937
ABSTRACT
BACKGROUND: To analyze the changes of interleukin-6 (IL-6), C-reactive protein (CRP), blood lipids and myocardial indexes after treatment of patients with acute myocardial infarction

(AMI) with intensive atorvastatin and interventional therapy, and its clinical significance. METHODS: A total of 78 patients diagnosed with AMI in our hospital from March 2016 to February 2017 were selected, and divided into treatment group (n=39) and control group (n=39). Patients in treatment group were treated with intensive atorvastatin based on conventional therapy before and after percutaneous coronary intervention (PCI), while those in control group were treated with conventional therapy before and after PCI. The levels of serum IL-6, CRP, blood lipids [total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)] and myocardial enzyme indexes [troponin T (TnT) and creatine kinase-MB (CK-MB)] at different time points were detected. The correlations among serum CRP, TC and TnT in treatment group before treatment were detected using the linear regression analysis, and changes in serum inflammatory factors, blood lipids and myocardial enzyme indexes in treatment group before and after treatment were analyzed. RESULTS: There were no statistically significant differences in general data, such as age, gender, BMI, history of hypertension, diabetes mellitus, cardiac insufficiency and smoking before treatment between treatment group and control group ($P>0.05$). There were no significant differences in levels of serum IL-6 and CRP before treatment between treatment group and control group, but they were decreased after treatment, and the curative effect in treatment group was significantly superior to that in control group. The differences were statistically significant ($P<0.05$). There were no significant differences in serum TC, TG, HDL-C and LDL-C levels before treatment between treatment group and control group. TC, TG and LDL-C were decreased but HDL-C was significantly increased after treatment compared with those before treatment. The differences were statistically significant ($P<0.05$). There were no significant differences in serum TnT and CK-MB levels before treatment between treatment group and control group. TnT and CK-MB were significantly increased at 24 h after treatment ($P>0.05$). TnT was still obviously increased, while CK MB returned to normal at 1 week after treatment. TnT and CK-MB were obviously decreased at 2 weeks after treatment. The curative effect in treatment group was superior to that in control group, and the difference was statistically significant ($P<0.05$). Correlation analyses of peripheral serum inflammatory factors, blood lipids and myocardial enzyme indexes showed that CRP ($r=0.793$, $P<0.001$) and TC ($r=0.668$, $P<0.001$) were positively correlated with TnT. The levels of serum inflammatory factors and blood lipids in treatment group before treatment, and at 24 h, 1 week and 2 weeks after treatment showed downward trends, and TnT was increased first and then decreased. CONCLUSIONS: The application of intensive atorvastatin for AMI patients, especially before PCI, has high safety, which can effectively reduce levels of serum inflammatory factors and blood lipids, protect myocardial cells after PCI and avoid injury.

[38] *Liu ZP, Wang Y*. **PCSK9 Inhibitors: Novel Therapeutic Strategies for Lowering LDL-Cholesterol**. Mini reviews in medicinal chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29692249
ABSTRACT
Statins are currently the major therapeutic strategies to lower low-density lipoprotein cholesterol (LDL-C) levels. However, a number of hypercholesterolemia patients still have a residual cardiovascular disease (CVD) risk despite taking the maximum-tolerated dose of statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low-density lipoprotein

receptor (LDLR), inducing its degradation in the lysosome and inhibiting LDLR recirculating to the cell membranes. The gain-of-function mutations in PCSK9 elevate the LDL-C levels in plasma. Therefore, PCSK9 inhibitors become novel therapeutic approaches in the treatment of hypercholesterolemia. Several PCSK9 inhibitors have been under investigation, and much progress has been made in clinical trials, especially for monoclonal antibodies (MoAbs). Two MoAbs, evolocumab and alirocumab, are now in clinical use. In this review, we summarize the development of PCSK9 inhibitors, including antisense oligonucleotides (ASOs), small interfering RNA (siRNA), small molecule inhibitor, MoAbs, mimetic peptides and adnectins, and the related safety issues.

[39] *Thakore PI, Kwon JB, Nelson CE et al.* **RNA-guided transcriptional silencing in vivo with S. aureus CRISPR-Cas9 repressors**. Nature communications 2018; 9:1674.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29700298
ABSTRACT
CRISPR-Cas9 transcriptional repressors have emerged as robust tools for disrupting gene regulation in vitro but have not yet been adapted for systemic delivery in adult animal models. Here we describe a Staphylococcus aureus Cas9-based repressor (dSaCas9(KRAB)) compatible with adeno-associated viral (AAV) delivery. To evaluate dSaCas9(KRAB) efficacy for gene silencing in vivo, we silenced transcription of Pcsk9, a regulator of cholesterol levels, in the liver of adult mice. Systemic administration of a dual-vector AAV8 system expressing dSaCas9(KRAB) and a Pcsk9-targeting guide RNA (gRNA) results in significant reductions of serum Pcsk9 and cholesterol levels. Despite a moderate host response to dSaCas9(KRAB) expression, Pcsk9 repression is maintained for 24 weeks after a single treatment, demonstrating the potential for long-term gene silencing in post-mitotic tissues with dSaCas9(KRAB). In vivo programmable gene silencing enables studies that link gene regulation to complex phenotypes and expands the CRISPR-Cas9 perturbation toolbox for basic research and gene therapy applications.

[40] *Gant CM, Binnenmars SH, Harmelink M et al.* **Real-life achievement of lipid-lowering treatment targets in the DIAbetes and LifEstyle Cohort Twente: systemic assessment of pharmacological and nutritional factors**. Nutrition & diabetes 2018; 8:24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29695715
ABSTRACT
BACKGROUND/OBJECTIVES: Lowering low-density lipoprotein cholesterol (LDLc) in type 2 diabetes mellitus is of paramount importance in preventing cardiovascular disease. However, treatment targets for LDLc are often not reached. We studied the prevalence of LDLc target achievement in a real-life population of type 2 diabetes mellitus patients in secondary care, and investigated whether in those not on target, there is room for intensifying pharmacological and lifestyle management according to current treatment guidelines. SUBJECTS/METHODS: We performed a cross-sectional analysis in the DIAbetes and LifEstyle Cohort Twente-1 (DIALECT-1; n = 450, age 63 +/- 9 years, 58% men, diabetes duration 11 (7-18) years). At baseline, we determined plasma LDLc concentration, pharmacological treatment (i.e., statin use), and lifestyle (physical activity and dietary intake). Patients were divided according to LDLc < 1.8, LDLc 1.8-2.5, and LDLc > 2.5 mmol/l. Dietary intake was collected from a validated Food Frequency Questionnaire (177 items) and we determined guideline adherence for different

food groups. Physical activity was assessed with the Short Questionnaire to ASsess Health enhancing behavior. RESULTS: LDLc data were available in 428 type 2 diabetes mellitus patients. LDLc </= 2.5 mmol/l was achieved in 317 patients (76%). In total, 76% of patients used statins, in those with LDLc > 2.5 mmol/l, this was 44%. Adherence to lifestyle guidelines was not different between the LDLc groups and was as follows: body mass index 6%, physical activity 59%, vegetables 7%, fruit 28%, legumes 59%, nuts 14%, dairy 19%, fish 36%, tea 8%, fats 66%, red meat 12%, processed meat 2%, alcohol 71%, sweetened beverages 34%, and sodium 12%. CONCLUSIONS: In type 2 diabetes mellitus patients in secondary health care, the target LDLc is achieved by three quarters of patients. Increasing statin treatment could be a first step to improve LDLc. In addition, there are ample opportunities for lifestyle management through increasing adherence to lifestyle guidelines.

[41] *Rocha B, Rodrigues AR, Tomada I et al.* **Energy restriction, exercise and atorvastatin treatment improve endothelial dysfunction and inhibit miRNA-155 in the erectile tissue of the aged rat**. Nutrition & metabolism 2018; 15:28.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29686722
ABSTRACT
Background: Endothelial dysfunction underlies cardiovascular disease that frequently affects aged individuals. Characterized by local decrease in nitric oxide, it results from down-regulation of endothelial nitric oxide synthase (eNOS) expression/activity. Aiming to elucidate the molecular mechanisms involved in age-related endothelial dysfunction and to unveil potential therapeutic targets, we tested how diet pattern, exercise and atorvastatin modulate the expression of eNOS, inducible NOS (iNOS), endothelin-1, sirtuins (SIRT) and microRNA-155 in the erectile tissue of high-fat fed aged rats. Methods: Sprague-Dawley male rats fed with high-fat diet until they completed 12 months were grouped and subjected to energy restriction (ER), ER and atorvastatin, or, ER, atorvastatin and physical exercise. Controls were fed with standard rodent chow. The blood pressure was measured using the tail-cuff method before sacrifice at 18 months. Glucose, total cholesterol, HDL, triglyceride and CRP were assessed in blood and eNOS, endothelin-1, iNOS and sirtuins were detected by immunofluorescence in the penis sections; eNOS, endothelin-1, iNOS, SIRT2-4 and SIRT6-7 were semi-quantified by western blotting in tissue homogenates. MicroRNA-155 was quantified using RT-PCR in formalin-fixed paraffin embedded sections. To compare the studied variables, two-tail student t test was used. Results: Atorvastatin promotes eNOS expression and is more efficient than ER or exercise in the control of hyperlipidemia and inflammation. Among the studied sirtuins, detected for the first time in the erectile tissue of the aged rat, SIRT2 aligns with eNOS expression. Both proteins exhibit over-expression in animals with combined exercise, atorvastatin and ER. Analysis of microRNA-155 expression also suggests its intervention in the regulation of eNOS expression. ER, particularly when combined with atorvastatin, was able to reverse the increase of iNOS and endothelin-1 in high-fat fed rats. Conclusions: The present results indicate that the association of ER, atorvastatin and exercise is more efficient than isolated interventions in the prevention of endothelial dysfunction.

[42] *Barchetta I, Cimini FA, Capoccia D et al.* **Neurotensin Is a Lipid-Induced Gastrointestinal Peptide Associated with Visceral Adipose Tissue Inflammation in Obesity**. Nutrients 2018; 10.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29690638

ABSTRACT

Neurotensin (NT) is a 13-amino acid peptide localized in the neuroendocrine cells of the small intestine, which promotes fat absorption and fatty acids translocation in response to lipid ingestion. NT-knock-out mice fed with a high-fat diet are protected from obesity, fatty liver, and the development of insulin-resistance. In humans, higher plasma levels of pro-NT, which is the stable circulating precursor of NT, predict obesity, type 2 diabetes (T2D), and cardiovascular disease. In obesity, the presence of visceral adipose tissue (VAT) inflammation leads to unfavorable metabolic outcomes and is associated with the development of T2D and non-alcoholic fatty liver disease (NAFLD). In this study, we investigated the relationship between plasma pro-NT levels and the presence of VAT inflammation in biopsies from 40 morbidly obese subjects undergoing bariatric surgery. We demonstrated that higher proNT levels are significantly associated with greater macrophages infiltration, HIF-1α, WISP-1, and UNC5B expression in VAT (all $p < 0.01$) due to the diagnosis of T2D and NAFLD. The overall results show that, in obesity, pro-NT is a biomarker of VAT inflammation and insulin-resistance. Additionally, NT may be involved in the development of dysmetabolic conditions likely mediated by increased gut fat absorption and the presence of a proinflammatory milieu in the adipose tissue.

[43] *Marzel A, Kouyos RD, Reinschmidt S et al.* **Dietary Patterns and Physical Activity Correlate With Total Cholesterol Independently of Lipid-Lowering Drugs and Antiretroviral Therapy in Aging People Living With Human Immunodeficiency Virus**. Open Forum Infect Dis 2018; 5:ofy067.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29687016

ABSTRACT

Background: Hypercholesterolemia is a well established risk factor for coronary heart disease and is highly prevalent among human immunodeficiency virus (HIV)-positive persons. Antiretroviral therapy (ART) can both directly modify total cholesterol and have drug-drug interactions with statins. This makes investigating modifiable behavioral predictors of total cholesterol a pertinent task. Methods: To explore the association between diet and physical activity with cross-sectionally measured total cholesterol, we administered a validated Food-Frequency-Questionnaire to participants of the Swiss HIV Cohort Study >/=45 years old. Linear mixed-effects models were applied to explore the associations between dietary patterns and physical activity with total cholesterol, after adjustment for clinical and demographic covariates. Results: In total, 395 patients were included. Forty percent (158 of 395) had elevated total cholesterol (>5.2 mmol/L), and 41% (164 of 395) were not regularly physically active. In multivariable analysis, 2 factors were positively associated with total cholesterol; female sex (beta = 0.562; 95% confidence interval [CI], 0.229-0.896) and the combined consumption of meat, refined/milled grains, carbonated beverages, and coffee (beta = 0.243; 95% CI, 0.047-0.439). On the other hand, regular physical activity (beta = -0.381; 95% CI, -0.626 to -0.136), lipid-lowering drugs (beta = -0.443; 95% CI -0.691 to -0.196), ART containing tenofovir (beta = -0.336; 95% CI -0.554 to -0.118), and black ethnicity (beta = -0.967; 95% CI -1.524 to -0.410) exhibited a negative association. Conclusions: We found independent associations between certain dietary patterns and physical activity with total cholesterol.

Increasing physical activity might achieve cardiovascular and other health benefits in HIV-positive individuals. The clinical relevance of the identified dietary patterns requires further investigation in prospective cohort studies and randomized controlled trials.

[44] *Grootaert MOJ, Roth L, Schrijvers DM et al.* **Defective Autophagy in Atherosclerosis: To Die or to Senesce?** Oxidative medicine and cellular longevity 2018; 2018:7687083.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29682164
ABSTRACT
Autophagy is a subcellular process that plays an important role in the degradation of proteins and damaged organelles such as mitochondria (a process termed "mitophagy") via lysosomes. It is crucial for regulating protein and mitochondrial quality control and maintaining cellular homeostasis, whereas dysregulation of autophagy has been implicated in a wide range of diseases including atherosclerosis. Recent evidence has shown that the autophagic process becomes dysfunctional during the progression of atherosclerosis, regardless of whether there are many autophagy-stimulating factors (e.g., reactive oxygen species, oxidized lipids, and cytokines) present within the atherosclerotic plaque. This review highlights the recent insights into the causes and consequences of defective autophagy in atherosclerosis, with a special focus on the role of autophagy and mitophagy in plaque macrophages, vascular smooth muscle cells (VSMCs), and endothelial cells (ECs). It has been shown that defective autophagy can promote apoptosis in macrophages but that it accelerates premature senescence in VSMCs. In the ECs, defective autophagy promotes both apoptosis and senescence. We will discuss the discrepancy between these three cell types in their response to autophagy deficiency and underline the cell type-dependent role of autophagy, which may have important implications for the efficacy of autophagy-targeted treatments for atherosclerosis.

[45] *Frankova D, Olson KM, Whyms BJ et al.* **The effect of intravenous insulin, apheresis and oral lipid-lowering agents on non-fasting hypertriglyceridemia and associated pancreatitis**. Postgraduate medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29702000
ABSTRACT
BACKGROUND: There is evidence that increasing severity of hypertriglyceridemia increases the risk of acute pancreatitis. There is a debate about superiority of treatment methods and previous works have specifically called for direct comparison between IV insulin and apheresis techniques. OBJECTIVES: Identify patient characteristics predictive of lipid-lowering therapy selection in a large community hospital for treatment of hypertriglyceridemia; evaluate for a concentration-dependent relationship between hypertriglyceridemia severity and risk of acute pancreatitis; assess for differences in clinical outcomes between patients treated with IV insulin versus apheresis. METHODS: Single center, retrospective cohort study including patients with hypertriglyceridemia between January 2007 and December 2016. Main measures included frequency of pancreatitis, choice of lipid-lowering therapy, and clinical comparisons of diet, oral lipid-lowering agents, IV insulin, and apheresis. RESULTS: Initial serum triglyceride level and disease acuity was higher among patients in insulin and apheresis groups. Neither triglyceride level, Charlson comorbidity index, age, BISAP score, nor initial CRP predicted use of IV insulin versus apheresis. Prevalence of pancreatitis increased with higher triglyceride level, reaching

48% with triglycerides >2000 md/dL (p<0.001). There was a significant decrease in serum triglycerides at each time interval (p<0.05) in patients treated with IV insulin and apheresis, but no difference in clearance rate between the two. Length of stay did not differ between IV insulin and apheresis. CONCLUSIONS: The presence of pancreatitis, hyperglycemia, and hypertriglyceridemia severity influenced selection of therapies like IV insulin and apheresis. We found no superiority of either IV insulin or apheresis in the treatment of severe hypertriglyceridemia among patients hospitalized for pancreatitis.

[46] *Domagala-Rodacka R, Cibor D, Szczeklik K et al.* **Gastrointestinal tract as a side-effect target of medications**. Przeglad lekarski 2016; 73:652-658.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29688675
ABSTRACT
World Health Organization (WHO) defines adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function". ADRs are a serious problem of contemporary pharmacotherapy. Expenditures for treatment of ADRs in the United States may cost up to 30.1 billion dollars annually. Factors affecting the development of ADRs are: age, gender, body weight, polypharmacy. About 10% of ADRs is associated with gastrointestinal tract (GIT). ADR can affect every part of GIT. Xerostomia is the most common ADR occurring in oral cavity. ADRs affecting esophagus include irritation and inflammation of the mucosa. Approximately one-third of all cases of esophageal inflammation results from administration of non-steroid anti-inflammatory drugs (NSAIDs). The main cause of ulcerations involving stomach and small intestine are NSAIDs. Drug-induced diarrheas are the most common adverse effect accounting for approximately 7% of all observed cases of ADRs. They may be triggered by antibiotics, magnesium salts, laxatives and others. On the other hand, some groups of medications may induce constipation. These drugs comprise opioids, diuretics, calcium channel blockers, cholinolytics and others. Proton pump inhibitors, metformin, orlistat and colesevelam may lead to restricted absorption of certain vitamins and minerals. Physicians' knowledge about most popular and well documented ADRs can improve patients' safety and make pharmacotherapy more comfortable for them.

[47] *Miteva K, Madonna R, De Caterina R, Van Linthout S*. **Innate and adaptive immunity in atherosclerosis**. Vascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29684642
ABSTRACT
Atherosclerosis is a chronic inflammatory disorder of the large and medium-size arteries characterized by the subendothelial accumulation of cholesterol, immune cells, and extracellular matrix. At the early onset of atherogenesis, endothelial dysfunction takes place. Atherogenesis is further triggered by the accumulation of cholesterol-carrying low-density lipoproteins, which acquire properties of damage-associated molecular patterns and thereby trigger an inflammatory response. Following activation of the innate immune response, mainly governed by monocytes and macrophages, the adaptive immune response is started which further promotes atherosclerotic plaque formation. In this review, an overview is given

describing the role of damage-associated molecular patterns, NLRP3 inflammasome activation, and innate and adaptive immune cells in the atherogenesis process.