Literature update week 16 (2018)

[1] *Jonsson AC, Delavaran H, Lovkvist H et al.* **Secondary prevention and lifestyle indices after stroke in a long-term perspective**. Acta neurologica Scandinavica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29671868
ABSTRACT
OBJECTIVES: To describe the long-term perspective regarding prevalence of risk factors, secondary stroke prevention, and lifestyle indices after stroke. METHODS: From a population-based one-year cohort (n = 416), we performed an observational study of 145 survivors at 16 months and 10 years after stroke (age 27-97 years) regarding secondary prevention including reaching acceptable treatment goals; nutritional status with focus on underweight; and the lifestyle indices: living situation, level of dependence, and self-assessed health condition. RESULTS: Ten years after stroke, 50% of the subjects with hypertension diagnosis and 55% of those without hypertension diagnosis were within the blood pressure goal <140/90 compared with 32% (P = .008) and 37% (N.S.) at 16 months. Acceptable HbA1c levels among subjects with diabetes mellitus diagnosis increased from 35% to 45% (N.S.). Among those without diabetes diagnosis, satisfactory HbA1c levels decreased from 98% to 79% (P < .001). Underweight increased from 9% to 17% (P = .019). Among patients with cerebral infarction, the prevalence of atrial fibrillation increased from 22% to 29% (P = .004), and treatment with oral anticoagulants from 75% to 78% (N.S.). Acceptable LDL cholesterol levels increased from 59% to 80% (P = .033) among subjects on lipid lowering treatment, and from 18% to 40% among untreated (P = .010). At 10 years, 90% still lived in their own home. Health condition was reported as good/very good/excellent by 65%. Age, female sex, and living situation were associated with intensity of secondary prevention measures and underweight. CONCLUSIONS: The proportion of individuals within treatment goals improved over time, but secondary prevention still needed additional consideration 10 years after stroke.

[2] *Braun MM, Stevens WA, Barstow CH*. **Stable Coronary Artery Disease: Treatment**. American family physician 2018; 97:376-384.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29671538
ABSTRACT
Stable coronary artery disease refers to a reversible supply/demand mismatch related to ischemia, a history of myocardial infarction, or the presence of plaque documented by catheterization or computed tomography angiography. Patients are considered stable if they are asymptomatic or their symptoms are controlled by medications or revascularization. Treatment involves risk factor management, antiplatelet therapy, and antianginal medications. Tobacco cessation, exercise, and weight loss are the most important lifestyle modifications. Treatment of comorbidities such as diabetes mellitus, hyperlipidemia, and hypertension should be optimized to reduce cardiovascular risk. All patients should be started on a statin unless contraindicated. No data support the routine use of monotherapy with nonstatin drugs such as bile acid sequestrants, niacin, ezetimibe, or fibrates. Studies of niacin and fibrates as adjunctive therapy found no improvement in patient outcomes. Aspirin is the mainstay of antiplatelet therapy; clopidogrel is an alternative. Antianginal medications should be added in a stepwise approach beginning with a beta blocker. Calcium channel blockers, nitrates, and ranolazine are used as adjunctive or second-line therapy when beta blockers are ineffective or

contraindicated. Select patients may benefit from coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting.

[3] *Yancey JR, Rey JB*. **Use of Niacin for Primary or Secondary Prevention of Cardiovascular or Cerebrovascular Events**. American family physician 2018; 97:436-437.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29671561
ABSTRACT

[4] *Plewes MR, Burns PD, Graham PE et al.* **Influence of omega-3 polyunsaturated fatty acids from fish oil or meal on the structure of lipid microdomains in bovine luteal cells**. Animal reproduction science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29673917
ABSTRACT
Biological membranes are composed of a lipid bilayer and proteins that form lipid microdomains. This study examined the effects of fish byproducts on lipid-protein interactions within lipid microdomains of bovine luteal cells. In Exp. 1 and 2, luteal cells were prepared from corpora lutea (CL; n=4 to 8) collected at an abattoir. Exp. 1 was conducted to optimize ultrasonication in a detergent-free protocol for isolation of lipid microdomains. A power setting of 10 to 20% was effective in isolating lipid microdomains from bulk lipid. In Exp. 2, cells were cultured in control medium or fish oil to determine influence of fish oil on distribution of lipid microdomain markers and prostaglandin F2alpha (FP) receptors. Cells treated with fish oil had a smaller percentage of microdomain markers and FP receptor in microdomains ($P<0.05$). In Exp. 3 and 4, cells were prepared from mid-cycle CL obtained from cows supplemented with corn gluten meal (n=4) or fish meal (n=4). Exp. 3 examined effects of dietary supplementation on distribution of lipid microdomain markers and FP receptor and Exp. 4 on fatty acid composition within lipid microdomains. A smaller percentage of lipid microdomain markers and FP receptor was detected in microdomains of cells collected from fish meal supplemented animals ($P<0.05$). In Exp. 4, a greater percentage of omega-3 polyunsaturated fatty acids was detected in bulk lipid from fish meal supplemented cows ($P<0.05$). Results show that fish byproducts influence lipid-protein interactions in lipid microdomains in bovine luteal cells.

[5] *Patel RS, Scopelliti EM, Olugbile O*. **The Role of PCSK9 Inhibitors in the Treatment of Hypercholesterolemia**. The Annals of pharmacotherapy 2018:1060028018771670.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29667842
ABSTRACT
OBJECTIVE: To evaluate the efficacy, safety, and cost-effectiveness of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and describe its place in therapy for the treatment of hypercholesterolemia. DATA SOURCES: A search of MEDLINE, CINAHL, and Clinicaltrials.gov was performed from January 2012 to March 2018 to identify literature pertaining to PCSK9 inhibitors using pre-specified search terms. Additional references were identified from citations of the literature. STUDY SELECTION AND DATA EXTRACTION: Only articles in English were reviewed. Phase II, phase III, pooled, post hoc, and cardiovascular (CV) trials were included. Cost-effectiveness studies and conference materials were also reviewed. DATA SYNTHESIS: All trials evaluating alirocumab and evolocumab demonstrated significant low-density lipoprotein

cholesterol (LDL-C) lowering versus comparators. Two trials revealed a decrease in the major adverse cardiovascular events (MACE) end point with PCSK9 inhibitor use; 1 of these 2 trials revealed a decrease in all-cause mortality with alirocumab use. No significant safety concerns apart from injection site reactions were noted. Despite these results, 4 cost-effectiveness analyses failed to meet acceptable thresholds. Relevance to Patient Care and Clinical Practice: This review describes the most up-to-date evidence regarding PCSK9 inhibitors. A discussion on LDL-C lowering potential, effect on CV events and mortality, safety considerations, feasibility of administration, and cost are included to guide clinicians on future use. CONCLUSION: The PCSK9 inhibitor drug class is an effective LDL-C lowering option for patients with the highest risk of CVD events and high LDL-C despite the use of statin therapy. For more widespread use, significant cost reductions are needed.

[6] *Yu Q, Liu R, Han L et al.* **Dietary restriction slightly affects glucose homeostasis and delays plasma cholesterol removal in rabbits with dietary lipid lowering**. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29658290
ABSTRACT
Dietary restriction (DR) has been reported to promote the beneficial effects on atherosclerotic progression, lipid and glucose metabolism, but little is known about these effects can be enhanced or weakened by dietary lipid lowering. After 12 weeks of the high-cholesterol diet (HCD) feeding, hypercholesterolemic rabbits were fed with either a chow diet ad libitum (AL) or a chow diet with DR for 16 weeks of dietary lipid lowering. Here, we found the DR group exhibited a loss in body weight, small internal organs and the reduced fat mass, but the AL group accumulated more subcutaneous fat than the baseline group. DR treatment slightly worsened glucose tolerance but enhanced insulin sensitivity, and a slight effect of DR on insulin secretion was also observed. After diet cholesterol withdrawal, rabbits showed persistently lowering of total cholesterol and triglyceride in plasma. The DR group had significantly higher plasma total cholesterol than the AL group at the most time points during 7 to 16 weeks of lipid lowering. Although both AL and DR groups developed more severe atherosclerosis than baseline group, DR did not improve atherosclerotic progression and the accumulation of macrophages and smooth muscle cells as well. We concluded that DR affected glucose and lipid metabolism but did not ameliorate atherosclerosis in rabbits when associated with lipid lowering by the dietary cholesterol withdrawal.

[7] *Imahori Y, Mathiesen EB, Leon DA et al.* **The contribution of obesity to carotid atherosclerotic plaque burden in a general population sample in Norway: The Tromso Study**. Atherosclerosis 2018; 273:15-20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29665456
ABSTRACT
BACKGROUND AND AIMS: Few studies have investigated the association of different measures of adiposity with carotid plaque. We aimed to investigate and compare the associations of four measures of adiposity: body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) with the presence of carotid plaque and total plaque area (TPA) in the right carotid artery. METHODS: We included 4906 individuals aged 31-88 years

who participated in a population-based study with ultrasonography of the right carotid artery. Adiposity measures were converted to sex-specific SD units to allow comparison of effect sizes. TPA was log transformed due to its skewed distribution. Logistic and linear regression models were used respectively to investigate the association of each adiposity measure with the presence of plaque and with log-transformed TPA. Estimates were adjusted for potential confounders and mediators such as blood pressure and lipids. RESULTS: After adjustment for age, sex, smoking, and education level, there was strong evidence of an association between all adiposity measures and log-transformed TPA, whereas only WHR was weakly associated with presence of plaque. WHR showed the largest adjusted effect size for both log-transformed TPA (beta 0.055, 95%CI 0.028-0.081) and the presence of plaque (OR 1.07, 95%CI 1.01-1.15). Adjustment for mediators led to appreciable attenuation of observed effects. CONCLUSIONS: Adiposity is more consistently associated with extent of plaque burden than with whether an individual does or does not have any plaque. There was evidence that established biomarkers mediate much of this association. Abdominal adiposity appears to show the strongest effect.

[8] *Thabit S, El Sayed NSE*. **Effect of pioglitazone and simvastatin in lipopolysaccharide-induced amyloidogenesis and cognitive impairment in mice: possible role of glutamatergic pathway and oxidative stress**. Behavioural pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29659380
ABSTRACT
Neuroinflammation and beta-amyloid (Abeta) deposition in the brain are well known characteristics of neurodegeneration. Diabetes and hypercholesterolemia are the main risk factors leading to memory loss and cognitive impairment. Recently, it was found that statins and thiazolidinediones have promising anti-inflammatory and neuroprotective effects that could delay neurodegeneration and neuronal loss in diabetic and hypercholesterolemic patients. The aim of the present study was to investigate the protective effect of simvastatin, pioglitazone, and their combination in lipopolysaccharide (LPS)-induced neuroinflammation and amyloidogenesis. Mice were divided into five groups: group 1 received 0.9% saline, group 2 received LPS (0.8 mg/kg in saline), group 3 received LPS (0.8 mgl kg)+simvastatin (5 mg/kg in saline), group 4 received LPS (0.8 mg/kg)+pioglitazone (20 mg/kg in saline), group 5 receiving LPS (0.8 mg/kg)+simvastatin (5 mg/kg)+pioglitazone (20 mg/kg). Y-maze and novel object recognition were used to assess the spatial and nonspatial behavioral changes. Nitric oxide levels and glutamate levels were measured to elucidate the anti-glutamatergic and anti-inflammatory effects of the tested drugs. Immunohistochemistry was performed to detect the presence of Abeta1-42 in the mice brain. LPS impaired memory, and increased Abeta deposition, nitric oxide, and glutamate brain levels. Both drugs produced a significant improvement in all parameters. We conclude that simvastatin and pioglitazone may have a protective effect against cognitive impairment induced by LPS, through targeting the glutamatergic and inflammatory pathways, especially in patients having hypercholesterolemia and diabetes.

[9] *Mondal K, Chakraborty P, Kabir SN*. **Hyperhomocysteinemia and hyperandrogenemia share PCSK9-LDLR pathway to disrupt lipid homeostasis in PCOS**. Biochem Biophys Res Commun 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29660344

ABSTRACT

Women with polycystic ovary syndrome (PCOS) are at increased risk of cardiovascular diseases (CVD); however, the independent role of PCOS in the incident CVD remains unknown. There are reports that hyperhomocysteinemia (HHcy), a potential cause of CVD, is frequently associated with PCOS. The present study investigates the independent attributes of hyperandrogenemia (HA), the integral associate of PCOS, and HHcy in causing atherogenic dyslipidemia. Twenty-five-day old rats were treated with homocysteine (Hcy) at 50mg/kg/day dose level for 12 weeks. The HepG2 cell lines transfected with siRNA directed to PCSK9 were challenged with Hcy, homocysteine thiolactone (HTL), testosterone, 5alpha-dihydroxytestosterone (5alpha-DHT), or estradiol for 24h. Rats administered with Hcy developed HHcy and displayed PCOS-like phenotypes with adversely altered lipid homeostasis and attenuated PI3K-AKT and Wnt signalling cascade. Overexpression of steroidogenic acute regulatory protein (StAR) and down-regulated expression of Aromatase together with elevated testosterone level marked the state of HA. In culture, the HepG2 cells responded independently to Hcy, HTL, testosterone, and 5alpha-DHT by an overt expression of PCSK9 and down-regulated expression of LDLR. The effect was magnified under the combined influence of Hcy and androgen(s). Estradiol, by contrast, exhibited the reverse effect. The findings suggest that HA may independently attribute to an increased cardiovascular risk in PCOS; however, the coexistence of HHcy catalyses the risk further.

[10] *Zhao ZW, Zhang M, Chen LY et al.* **Heat shock protein 70 accelerates atherosclerosis by downregulating the expression of ABCA1 and ABCG1 through the JNK/Elk-1 pathway**. Biochimica et biophysica acta 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29678642

ABSTRACT

BACKGROUND AND AIMS: Recent studies have suggested that heat shock protein 70 (HSP70) may play critical roles in cardiovascular disease. However, the effects of HSP70 on the development of atherosclerosis in apoE(-/-) mice remain largely unknown. This study was to investigate the role and potential mechanism of HSP70 in atherosclerosis. METHODS: HSP70 was overexpressed in apoE(-/-) mice and THP-1-derived macrophages with lentiviral vectors. Oil Red O, hematoxylin-eosin, and Masson staining were performed to evaluate atherosclerotic plaque in apoE(-/-) mice fed the Western type diet. Moreover, immunostaining was employed to detect the expression of relative proteins in aortic sinus. Reporter gene and chromatin immunoprecipitation were performed to analyze the effect of Elk-1 on the promoter activity of ABCA1 and ABCG1; [(3)H] labeled cholesterol was used to assess the capacity of cholesterol efflux and reverse cholesterol transport (RCT). RESULTS: Our results showed that HSP70 increased lipid accumulation in arteries and promoted the formation of atherosclerotic lesion. The capacity of cholesterol efflux was reduced in peritoneal macrophages isolated from HSP70-overexpressed apoE(-/-) mice. The levels of ABCA1 and ABCG1 expression were also reduced in the peritoneal macrophages and the aorta from apoE(-/-) mice in response to HSP70. The c-Jun N-terminal kinase (JNK) and ETS transcription factor (Elk-1) played a critical role in HSP70-induced downregulation ABCA1 and ABCG1. Further, HSP70 reduced RCT from macrophages to plasma, liver, and feces in apoE(-/-) mice. CONCLUSIONS: HSP70 promotes the progression of

atherosclerosis in apoE(-/-) mice by suppressing the expression of ABCA1 and ABCG1 through the JNK/Elk-1 pathway.

[11] *El-Ashmawy NE, Khedr NF, El-Bahrawy HA, Helal SA*. **Upregulation of PPAR-gamma mediates the renoprotective effect of omega-3 PUFA and ferulic acid in gentamicin-intoxicated rats**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 99:504-510.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29665653
ABSTRACT
Ferulic acid (FrA) is a natural product containing phenolic compounds. omega-3 PUFA is the major constituent of fish oil. The aim of this study was to investigate the renoprotective role of FrA and FO in gentamicin (GM)-induced nephrotoxicity in rats. Forty four male rats were divided equally into 4 groups: Control group, GM group, FrA+GM group and FO+GM group. Each of the treated groups was injected with GM (40mg/kg) i.p. for 9 consecutive days. FrA (100mg/kg) and FO (5mL/kg) were given to rats orally daily for 10 days prior to GM and then concomitantly with GM for additional 9 days. Kidney function was assessed by serum BUN and creatinine, urinary albumin excretion and N-acetyl-beta-D-glucosaminidase (NAG) activity and histopathological examination. The anti-inflammatory property was evaluated by measuring renal resolvin E1 and gene expression of PPAR-gamma. The antioxidant activity was indicated by renal catalase (CAT) activity. GM-induced nephrotoxicity was evidenced by the renal histopathological changes along with increased renal indices. Prior and concomitant treatment with FrA or FO ameliorated nephrotoxic effect of GM as indicated by the significant decrease of serum BUN and creatinine, urinary albumin excretion and urinary NAG activity. Both treatments significantly enhanced CAT activity and gene expression of PPAR-gamma. Resolvin E1 was significantly elevated in FO but not in FrA group. FrA and FO proved anti-inflammatory and renoprotective effects, which could be through their PPAR-gamma agonist activity. Because FrA and FO are natural products, they could provide a safe intervention strategy in cases of exposure to nephrotoxins.

[12] *van der Heijden C, Deinum J, Joosten LAB et al.* **The Mineralocorticoid Receptor as a Modulator Of Innate Immunity And Atherosclerosis**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29668907
ABSTRACT
The mineralocorticoid receptor (MR) is a member of the nuclear receptor steroid-binding family. The classical MR ligand aldosterone controls electrolyte and fluid homeostasis after binding in renal epithelial cells. However, more recent evidence suggests that activation of extrarenal MRs by aldosterone negatively impacts cardiovascular health independent of its effects on blood pressure: high levels of aldosterone associate with an increased cardiovascular event rate, where MR antagonists exert beneficial effects on cardiovascular mortality. The most important cause for cardiovascular events is atherosclerosis, that is currently considered a low-grade inflammatory disorder of the arterial wall. In this inflammatory process, the innate immune system plays a deciding role, with the monocyte-derived macrophage being the most abundant cell in the atherosclerotic plaque. Intriguingly, both monocytes and macrophages express the MR, and a growing body of evidence shows that these cells are skewed into a pro-

inflammatory and pro-atherosclerotic phenotype via MR stimulation. In this review, we detail the current perspective on the role of the monocyte and macrophage MR in atherosclerosis development and provide a comprehensive framework of the effects of MR activation of the innate immune system that might drive the pro-atherosclerotic outcome.

[13] *Chen Y, Chang Y, Zhang N et al.* **Atorvastatin Attenuates Myocardial Hypertrophy in Spontaneously Hypertensive Rats via the C/EBPbeta/PGC-1alpha/UCP3 Pathway**. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2018; 46:1009-1018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29669326

ABSTRACT
BACKGROUND/AIMS: Many clinical and experimental studies have shown that treatment with statins could prevent myocardial hypertrophy and remodeling induced by hypertension and myocardial infarction. But the molecular mechanism was not clear. We aimed to investigate the beneficial effects of atorvastatin on hypertension-induced myocardial hypertrophy and remodeling in spontaneously hypertensive rats (SHR) with the hope of revealing other potential mechanisms or target pathways to interpret the pleiotropic effects of atorvastatin on myocardial hypertrophy. METHODS: The male and age-matched animals were randomly divided into three groups: control group (8 WKY), SHR (8 rats) and intervention group (8 SHR). The SHR in intervention group were administered by oral gavage with atorvastatin (suspension in distilled water, 10 mg/Kg once a day) for 6 weeks, and the other two groups were administered by gavage with equal quantity distilled water. Blood pressure of rats was measured every weeks using a standard tail cuff sphygmomanometer. Left ventricular (LV) dimensions were measured from short-axis views of LV under M-mode tracings using Doppler echocardiograph. Cardiomyocyte apoptosis was assessed by the TUNEL assay. The protein expression of C/EBPbeta, PGC-1alpha and UCP3 were detected by immunohistochemistry or Western blot analysis. RESULTS: At the age of 16 weeks, the mean arterial pressure of rats in three groups were 103.6+/-6.1, 151.8+/-12.5 and 159.1+/-6.2 mmHg respectively, and there wasn't statistically significant difference between the SHR and intervention groups. Staining with Masson's trichrome demonstrated that the increased interstitial fibrosis of LV and ventricular remodeling in the SHR group were attenuated by atorvastatin treatment. Echocardiography examination exhibited that SHR with atorvastatin treatment showed an LV wall thickness that was obviously lower than that of water-treated SHR. In hypertrophic myocardium, accompanied by increasing C/EBPbeta expression and the percentage of TUNEL-positive cells, the expression of Bcl-2/Bax ratio, PGC-1alpha and UCP3 were reduced, all of which could be abrogated by treatment with atorvastatin for 6 weeks. CONCLUSION: This study further confirmed that atorvastatin could attenuate myocardial hypertrophy and remodeling in SHR by inhibiting apoptosis and reversing changes in mitochondrial metabolism. The C/EBPbeta/PGC-1alpha/UCP3 signaling pathway might also be important for elucidating the beneficial pleiotropic effects of atorvastatin on myocardial hypertrophy.

[14] *Zhang GQ, Tao YK, Bai YP et al.* **Inhibitory Effects of Simvastatin on Oxidized Low-Density Lipoprotein-Induced Endoplasmic Reticulum Stress and Apoptosis in Vascular Endothelial Cells**. Chinese medical journal 2018; 131:950-955.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29664056

ABSTRACT

Background: Oxidized low-density lipoprotein (ox-LDL)-induced oxidative stress and endothelial apoptosis are essential for atherosclerosis. Our previous study has shown that ox-LDL-induced apoptosis is mediated by the protein kinase RNA-like endoplasmic reticulum kinase (PERK)/eukaryotic translation initiation factor 2alpha-subunit (eIF2alpha)/CCAAT/enhancer-binding protein homologous protein (CHOP) endoplasmic reticulum (ER) stress pathway in endothelial cells. Statins are cholesterol-lowering drugs that exert pleiotropic effects including suppression of oxidative stress. This study aimed to explore the roles of simvastatin on ox-LDL-induced ER stress and apoptosis in endothelial cells. Methods: Human umbilical vein endothelial cells (HUVECs) were treated with simvastatin (0.1, 0.5, or 2.5 mumol/L) or DEVD-CHO (selective inhibitor of caspase-3, 100 mumol/L) for 1 h before the addition of ox-LDL (100 mug/ml) and then incubated for 24 h, and untreated cells were used as a control group. Apoptosis, expression of PERK, phosphorylation of eIF2alpha, CHOP mRNA level, and caspase-3 activity were measured. Comparisons among multiple groups were performed with one-way analysis of variance (ANOVA) followed by post hoc pairwise comparisons using Tukey's tests. A value of $P < 0.05$ was considered statistically significant. Results: Exposure of HUVECs to ox-LDL resulted in a significant increase in apoptosis (31.9% vs. 4.9%, $P < 0.05$). Simvastatin (0.1, 0.5, and 2.5 mumol/L) led to a suppression of ox-LDL-induced apoptosis (28.0%, 24.7%, and 13.8%, $F = 15.039$, all $P < 0.05$, compared with control group). Ox-LDL significantly increased the expression of PERK (499.5%, $P < 0.05$) and phosphorylation of eIF2alpha (451.6%, $P < 0.05$), if both of which in the control groups were considered as 100%. Simvastatin treatment (0.1, 0.5, and 2.5 mumol/L) blunted ox-LDL-induced expression of PERK (407.8%, 339.1%, and 187.5%, $F = 10.121$, all $P < 0.05$, compared with control group) and phosphorylation of eIF2alpha (407.8%, 339.1%, 187.5%, $F = 11.430$, all $P < 0.05$, compared with control group). In contrast, DEVD-CHO treatment had no significant effect on ox-LDL-induced expression of PERK (486.4%) and phosphorylation of eIF2alpha (418.8%). Exposure of HUVECs to ox-LDL also markedly induced caspase-3 activity together with increased CHOP mRNA level; these effects were inhibited by simvastatin treatment. Conclusions: This study suggested that simvastatin could inhibit ox-LDL-induced ER stress and apoptosis in vascular endothelial cells.

[15] *Rautureau Y, Deschambault V, Higgins ME et al.* **Adenylate Cyclase Type 9 (ADCY9) Inactivation Protects from Atherosclerosis Only in the Absence of Cholesteryl Ester Transfer Protein (CETP)**. Circulation 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29674325

ABSTRACT

Background -Pharmacogenomic studies have shown that ADCY9 genotype determines the effects of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib on cardiovascular events and atherosclerosis imaging. The underlying mechanisms responsible for the interactions between ADCY9 and CETP activity have not yet been determined. Methods -Adcy9-inactivated (Adcy9(Gt/Gt)) and wild-type (WT) mice, that were or not transgenic for the CETP gene (CETPtgAdcy9(Gt/Gt) and CETPtgAdcy9(WT)), were submitted to an atherogenic protocol (injection of an AAV8 expressing a PCSK9 gain-of-function variant and 0.75% cholesterol diet for 16 weeks). Atherosclerosis, vasorelaxation, telemetry and adipose tissue MRI were evaluated.

Results -Adcy9(Gt/Gt) mice had a 65% reduction in aortic atherosclerosis compared to WT (P<0.01). CD68-positive macrophage accumulation and proliferation in plaques were reduced in Adcy9(Gt/Gt) mice compared to WT animals (P<0.05 for both). Femoral artery endothelial-dependent vasorelaxation was improved in Adcy9(Gt/Gt) mice (versus WT, P<0.01). Selective pharmacological blockade showed that the nitric oxide, cyclooxygenase and endothelial-dependent hyperpolarization pathways were all responsible for the improvement of vasodilatation in Adcy9(Gt/Gt) (P<0.01 for all). Aortic endothelium from Adcy9(Gt/Gt) mice allowed significantly less adhesion of splenocytes compared to WT (P<0.05). Adcy9(Gt/Gt) mice gained more weight than WT with the atherogenic diet, and this was associated with an increase in whole body adipose tissue volume (P<0.05 for both). Feed efficiency was increased in Adcy9(Gt/Gt) compared to WT mice (P<0.05), which was accompanied by prolonged cardiac RR interval (P<0.05) and improved nocturnal heart rate variability (P=0.0572). Adcy9 inactivation-induced effects on atherosclerosis, endothelial function, weight gain, adipose tissue volume and feed efficiency were lost in CETPtgAdcy9(Gt/Gt) mice (P>0.05 versus CETPtgAdcy9(WT)). Conclusions -Adcy9 inactivation protects against atherosclerosis, but only in the absence of CETP activity. This atheroprotection may be explained by decreased macrophage accumulation and proliferation in the arterial wall and improved endothelial function and autonomic tone.

[16] *Park HS, Gu JY, Yoo HJ et al.* **Thrombin Generation Assay Detects Moderate-Intensity Statin-Induced Reduction of Hypercoagulability in Diabetes**. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2018:1076029618766254.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29669440
ABSTRACT
Statins not only have a lipid-lowering effect but also reduce inflammation and have an antithrombotic effect. Since hypercoagulability assessed by thrombin generation assay (TGA) and increased formation of neutrophil extracellular traps (NET) were demonstrated in diabetes, we investigated whether statin therapy in diabetes modifies coagulation status and NET formation. Twenty-five consecutive patients with diabetes were recruited. Global coagulation assays (prothrombin time [PT], activated partial thromboplastin time [aPTT], and TGA) and NET markers (DNA-histone complex, cell-free DNA, and neutrophil elastase) were measured before and after 3-month moderate-intensity statin therapy. In addition, all coagulation factors and 3 anticoagulation factors were measured. Statin therapy significantly reduced endogenous thrombin potential (ETP) value and blood lipids but did not change the PT and aPTT values or NET formation markers. Statin significantly decreased not only coagulation factors (II, V, VIII, IX, and X) but also the anticoagulation factor antithrombin. Statin-induced reduction of factor V and X significantly contributed to the reduction of ETP value. The extent of reduction in coagulation factors correlated with that of anticoagulation factors, but not that of cholesterol. It is possible to use TGA as a global coagulation assay that can detect coagulation status modified by statin therapy. Additional studies are needed to evaluate the clinical implications of statin-induced simultaneous reduction of coagulation and anticoagulation factors.

Literature update week 16 (2018)

[17] *Bodde MC, Welsh P, Bergheanu SC et al.* **A rapid (differential) effect of rosuvastatin and atorvastatin on high-sensitivity cardiac Troponin-I in subjects with stable cardiovascular disease**. Clinical pharmacology and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29672821
ABSTRACT
Serum troponin within the normal range is an emerging predictor of cardiovascular mortality. We aimed to determine how rapidly high-sensitivity troponin -I (hs-cTnI) levels are lowered by statin therapy in patients with stable cardiovascular disease. In the RADAR substudy, patients were randomized, to atorvastatin 20 mg/day (n = 39) or rosuvastatin 10 mg/day (n = 39) and up-titrated in 6 week intervals to 80 mg of atorvastatin or 40 mg of rosuvastatin. Hs-cTnI concentrations were measured at baseline and at 6 and 18 weeks of follow-up. Statin treatment resulted in a mean change of serum hs-cTnI of -8.2% (p=0.010) after 6 weeks and -12.3% (p=0.001) after 18 weeks. After 18 weeks, hs-cTnI levels were lowered by 21.8% with atorvastatin and by 4.1% with rosuvastatin (p=0.001 and p=0.133, respectively). During statin therapy serum hs-cTnI levels decreased rapidly within weeks of treatment, suggesting an effect beyond long-term atherosclerosis regression. Mechanisms that mediate this effect require further study.

[18] *Oh GC, Han JK, Han KH et al.* **Efficacy and Safety of Fixed-dose Combination Therapy With Telmisartan and Rosuvastatin in Korean Patients With Hypertension and Dyslipidemia: TELSTA-YU (TELmisartan-rosuvaSTAtin from YUhan), a Multicenter, Randomized, 4-Arm, Double-blind, Placebo-controlled, Phase III Study**. Clinical therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29673890
ABSTRACT
PURPOSE: Hypertension and dyslipidemia are 2 risk factors of cardiovascular disease that often present simultaneously. Traditionally, treatment of these multiple conditions required separate medications for each disease, which may result in poor compliance and thus lead to possible treatment failure. Fixed-dose combination (FDC) therapy with a single pill may be a solution in these situations. METHODS: This multicenter, 8-week, randomized, double-blind, Phase III study evaluated the efficacy and safety of FDC treatment with telmisartan (80 mg) and rosuvastatin calcium (20 mg) in Korean patients with mild to moderate hypertension and dyslipidemia. Patients were randomly assigned to 4 groups: (1) FDC drug (80 mg of telmisartan and 20 mg of rosuvastatin); (2) 80 mg of telmisartan; (3) 20 mg of rosuvastatin; or (4) placebo. After 8 weeks of treatment, the change in mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) between the FDC group and the rosuvastatin group, and the percent change in LDL-C between the FDC group and the telmisartan group, were compared. FINDINGS: A total of 210 patients were enrolled in the study (84 in the FDC group, 42 in the rosuvastatin group, 43 in the telmisartan group, and 41 in the placebo group). The reduction in blood pressure was significantly greater in the FDC group than in the rosuvastatin group after 8 weeks of treatment (least squares mean change from baseline, -16.1 [1.6] mm Hg vs -1.7 [2.2] mm Hg [P < 0.001] for MSSBP; -8.8 [1.0] mm Hg vs -1.6 [1.4] mm Hg [P < 0.001] for MSDBP). Least squares mean percent change in LDL-C from baseline was also significantly greater in the FDC group compared with the telmisartan group (-49.3% [2.2%] vs 1.5% [3.0%]; P < 0.001). FDC therapy also had a higher rate of achieving the treatment goal in both blood pressure (60% vs

45%; P = 0.024) and LDL-C (88.8% vs 16.3%; P < 0.001) compared with rosuvastatin or telmisartan alone, respectively. In regression analysis, higher baseline MSSBP, female sex, and lower body mass index were associated with increased reductions in MSSBP, whereas higher baseline LDL-C level and lower body mass index were associated with greater reductions in LDL-C. There were 48 adverse events in 36 patients (17.3% [36 of 208]), and 17 adverse drug reactions in 12 patients (5.8% [12 of 208]), indicating no significant differences in short-term safety among study groups. IMPLICATIONS: Treatment with an FDC drug containing telmisartan and rosuvastatin showed similar efficacy in lowering blood pressure and LDL-C levels compared with that of each single drug. ClinicalTrials.gov identifier: NCT01914432.

[19] *Lee J, Rhee SJ, Lee S, Yu KS*. **Evaluation of drug interactions between fimasartan and rosuvastatin after single and multiple doses in healthy Caucasians**. Drug design, development and therapy 2018; 12:787-794.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29670335
ABSTRACT
Objectives: As hypercholesterolemia is often accompanied by hypertension, statins are usually prescribed with angiotensin receptor blockers in clinical practice. This study was performed to evaluate the pharmacokinetics and safety of fimasartan and rosuvastatin when coadministered or administered alone as a single dose or as multiple doses to healthy Caucasians. Methods: Thirty-six subjects were enrolled into an open-labeled, randomized, 6-sequence, 3-period, 3-way crossover study, and randomly received fimasartan (120 mg), rosuvastatin (20 mg) or both. Blood samples for pharmacokinetics were collected up to 48 hours for fimasartan and 72 hours for rosuvastatin after the last dosing and plasma concentrations of study drugs were determined by liquid chromatography-tandem mass spectrometry. Maximum plasma concentration (Cmax), area under the concentration-time curve (AUC) from 0 to the last measurable time (AUClast), maximum plasma concentration at steady state (Cmax,ss) and AUC to the end of the dosing period at steady state (AUCtau,ss) were estimated using a non-compartmental method. Safety and tolerability were evaluated throughout the study. Results: Thirty subjects completed the study. After single dose administration, the geometric mean ratio (GMR) and 90% confidence intervals (CIs) of fimasartan with or without rosuvastatin were 0.95 (0.80-1.14) and 0.98 (0.91-1.07) for Cmax and AUClast, respectively. The corresponding values for rosuvastatin with or without fimasartan were 1.32 (1.16-1.50) and 0.97 (0.89-1.05), respectively. After administration of multiple doses, the GMRs (90% CIs) for Cmax,ss and AUCtau,ss of fimasartan with or without rosuvastatin were 0.94 (0.74-1.20) and 1.07 (0.90-1.16), respectively. The corresponding values for rosuvastatin with or without fimasartan were 1.16 (1.02-1.32) and 0.86 (0.79-0.94), respectively. A total of 74 adverse events (AEs) were reported and incidences of AEs did not increase significantly with co-administration. Conclusion: Co-administration of fimasartan and rosuvastatin did not result in clinically relevant changes in the systemic exposure of fimasartan or rosuvastatin after single and multiple administrations, and they were well tolerated.

[20] *Esquejo RM, Salatto CT, Delmore J et al.* **Activation of Liver AMPK with PF-06409577 Corrects NAFLD and Lowers Cholesterol in Rodent and Primate Preclinical Models**. EBioMedicine 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29673898

ABSTRACT

Dysregulation of hepatic lipid and cholesterol metabolism is a significant contributor to cardiometabolic health, resulting in excessive liver lipid accumulation and ultimately non-alcoholic steatohepatitis (NASH). Therapeutic activators of the AMP-Activated Protein Kinase (AMPK) have been proposed as a treatment for metabolic diseases; we show that the AMPK beta1-biased activator PF-06409577 is capable of lowering hepatic and systemic lipid and cholesterol levels in both rodent and monkey preclinical models. PF-06409577 is able to inhibit de novo lipid and cholesterol synthesis pathways, and causes a reduction in hepatic lipids and mRNA expression of markers of hepatic fibrosis. These effects require AMPK activity in the hepatocytes. Treatment of hyperlipidemic rats or cynomolgus monkeys with PF-06409577 for 6weeks resulted in a reduction in circulating cholesterol. Together these data suggest that activation of AMPK beta1 complexes with PF-06409577 is capable of impacting multiple facets of liver disease and represents a promising strategy for the treatment of NAFLD and NASH in humans.

[21] *Baviera M, Bertele V, Avanzini F et al.* **Peripheral arterial disease: Changes in clinical outcomes and therapeutic strategies in two cohorts, from 2002 to 2008 and from 2008 to 2014. A population-based study**. European journal of preventive cardiology 2018:2047487318770299.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29664343

ABSTRACT

Background The aim of our study was to evaluate whether treatments for peripheral artery disease changed in two different cohorts identified in 2002 and 2008, and whether this had an impact on mortality and major clinical outcomes after six years of follow-up. Methods Using administrative health databases of the largest region in Northern Italy, we identified patients admitted to hospital for peripheral artery disease in 2002 and 2008. Both cohorts were followed for six years. All cause death, acute coronary syndrome, stroke and major amputations, cardiovascular prevention drugs and revascularization procedures were collected. Incidence of events was plotted using adjusted cumulative incidence function estimates. The risk, for each outcome, was compared between 2002-2008 and 2008-2014 using a multivariable Fine and Gray's semiparametric proportional subdistribution hazards model. Results In 2002 and 2008, 2885 and 2848 patients were identified. Adjusting for age, sex, Charlson comorbidity index and severity of peripheral artery disease we observed a significant reduction (in 2008 vs. 2002) in the risk of acute coronary syndrome (28%), stroke (27%) and major amputation (17%). No change was observed in the risk of death. The percentages of patients with peripheral artery revascularizations, during the hospital stay, increased: 43.8% in 2002 vs. 49.0% in 2008, $p < 0.001$. From 2002 to 2008 there was a significant absolute increase in the prescription of lipid-lowering drugs (+18%), antiplatelets (+7.2%) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (+11.8%), $p < 0.001$. Conclusions In six years of follow-up we observed a reduction in risk of major cardiovascular events in 2008-2014 in comparison with the 2002-2008 cohort. Increasing use of revascularization interventions and cardiovascular prevention drugs could have contributed to the better prognosis.

Literature update week 16 (2018)

[22] *Jalloh MA, Ip EJ, Doroudgar S*. **What is the impact of the 2017 cochrane systematic review and meta-analysis that evaluated the use of PCSK9 inhibitors for lowering cardiovascular disease and mortality?** Expert opinion on pharmacotherapy 2018:1-3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29667439
ABSTRACT
INTRODUCTION: In 2017, Schmidt et al. conducted a Cochrane systematic review and meta-analysis to evaluate the effect of using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to reduce low-density-lipoprotein- cholesterol (LDL-C) and cardiovascular disease (CVD). The Cochrane review was a systematic review and meta-analysis of 20 randomized, double-blinded trials that compared the use of PCSK9 inhibitors with statins/ezetimibe, ezetimibe, or placebo for a treatment duration of at least 24 weeks. The use of PCSK9 inhibitors lowered the risk for CVD (OR 0.86 (0.80 to 0.92)) but not mortality (OR 1.02 (0.91 to 1.14)) when compared to placebo. Areas covered: The following article evaluates the recently published Cochrane review and clarifies the efficacy of PCSK9 inhibitors for improving cardiovascular morbidity and mortality. Expert opinion: The Cochrane review discussed suggests that PCSK9 inhibitors are effective in lowering LDL-C and the risk of CVD but not the risk of mortality. The higher price of PCSK9 inhibitors is a further deterrent for using them as a substitute for statins - cholesterol lowering medications with history showing they lower mortality. Statins should remain the gold-standard cholesterol-lowering drug class until PCSK9 inhibitors become more affordable and demonstrate consistent efficacy for reducing CVD and mortality.

[23] *Pereira P, Kapoor A, Sinha A et al.* **Do practice gaps exist in evidence-based medication prescription at hospital discharge in patients undergoing coronary artery bypass surgery & coronary angioplasty?** The Indian journal of medical research 2017; 146:722-729.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29664030
ABSTRACT
Background & objectives: Prescription patterns of guideline-directed medical therapy (GDMT) after coronary artery bypass surgery [coronary artery bypass graft (CABG)] and percutaneous coronary intervention (PCI) at hospital discharge are often not optimal. In view of scarce data from the developing world, a retrospective analysis of medication advice to patients following CABG and PCI was conducted. Methods: Records of 5948 patients (post-PCI: 5152, post-CABG: 796) who underwent revascularization from 2010 to 2014 at a single tertiary care centre in north India were analyzed. Results: While age and gender distributions were similar, diabetes and stable angina were more frequent in CABG group. Prescription rates for aspirin 100 per cent versus 98.2 per cent were similar, while beta-blockers (BBs, 95.2 vs 90%), statins (98.2 vs 91.6%), angiotensin-converting enzyme inhibitors (89.4 vs 41.4%), nitrates (51.2 vs 1.1%) and calcium channel blockers (6.6 vs 1.6%) were more frequently prescribed following PCI. Despite similar baseline left ventricular ejection fraction (48.1 vs 51.1%), diuretics were prescribed almost universally post-CABG (98.2 vs 10.9%, P<0.001). Nearly all (94.4%) post-CABG patients received a prescription for clopidogrel. Patients undergoing PCI were much more likely to receive higher statin dose; 40-80 mg atorvastatin (72 vs <1%, P<0.001) and a higher dose of BB. Interpretation & conclusions: Significant differences in prescription of GDMT between PCI and CABG patients existed at hospital discharge. A substantial proportion of post-CABG patients did

not receive BB and/or statins. These patients were also less likely to receive high-dose statin or optimal BB dose and more likely to routinely receive clopidogrel and diuretics. Such deviations from GDMT need to be rectified to improve quality of cardiac care after coronary revascularization.

[24] *Zhang K, Zhang F, Yang JM et al.* **Silencing of Non-POU-domain-containing octamer-binding protein stabilizes atherosclerotic plaque in apolipoprotein E-knockout mice via NF-kappaB signaling pathway**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29673854
ABSTRACT
BACKGROUND: It remains unknown whether Non-POU-domain-containing octamer-binding protein (NonO) plays a causative role in plaque destabilization. We hypothesized that NonO gene silencing may stabilize atherosclerotic plaque by increasing P4Halpha1 expression and inhibiting the inflammation. METHODS AND RESULTS: Vulnerable atherosclerotic plaques were induced in ApoE-/- mice by high fat diet, perivascular collar placement and mental stress. Compared with normal carotid arteries, those contained vulnerable plaques had high NonO expression. In another in vivo experiment, mice contained vulnerable plaques were randomly divided into 5 groups to receive physiological saline, si-N.C-lentivirus (LV), si-NonO-LV, pGC-GFP-LV and NonO-LV, respectively. NonO overexpression increased while NonO silencing decreased the incidence of carotid plaque disruption. NonO overexpression enhanced macrophage infiltration and lipid deposition but reduced the content of vascular smooth muscle cells and collagen in plaques, leading to an increased plaque vulnerability index, whereas NonO silencing exhibited the opposite effect. In addition, NonO overexpression increased the expression of proinflammatory cytokines and matrix metalloproteinases and decreased the expression of P4Halpha1 both in vivo and in vitro, whereas NonO silencing showed the contrary effect. NonO co-immunoprecipitated with NF-kappaB p65, and promoted its nuclear translocation and phosphorylation, and these effects were reversed by NonO silencing. CONCLUSION: NonO may promote plaque destabilization and increase the incidence of plaque disruption in ApoE-/- mice by inducing the expression of inflammatory cytokines and matrix metalloproteinases and suppressing that of P4Halpha1. The mechanism may involve the interaction of NonO with NF-kappaB leading to enhanced NF-kappaB nuclear translocation and phosphorylation.

[25] *Botta M, Audano M, Sahebkar A et al.* **PPAR Agonists and Metabolic Syndrome: An Established Role?** International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29662003
ABSTRACT
Therapeutic approaches to metabolic syndrome (MetS) are numerous and may target lipoproteins, blood pressure or anthropometric indices. Peroxisome proliferator-activated receptors (PPARs) are involved in the metabolic regulation of lipid and lipoprotein levels, i.e., triglycerides (TGs), blood glucose, and abdominal adiposity. PPARs may be classified into the alpha, beta/delta and gamma subtypes. The PPAR-alpha agonists, mainly fibrates (including newer molecules such as pemafibrate) and omega-3 fatty acids, are powerful TG-lowering agents. They mainly affect TG catabolism and, particularly with fibrates, raise the levels of high-

density lipoprotein cholesterol (HDL-C). PPAR-gamma agonists, mainly glitazones, show a smaller activity on TGs but are powerful glucose-lowering agents. Newer PPAR-alpha/delta agonists, e.g., elafibranor, have been designed to achieve single drugs with TG-lowering and HDL-C-raising effects, in addition to the insulin-sensitizing and antihyperglycemic effects of glitazones. They also hold promise for the treatment of non-alcoholic fatty liver disease (NAFLD) which is closely associated with the MetS. The PPAR system thus offers an important hope in the management of atherogenic dyslipidemias, although concerns regarding potential adverse events such as the rise of plasma creatinine, gallstone formation, drug-drug interactions (i.e., gemfibrozil) and myopathy should also be acknowledged.

[26] *Peters SAE, Colantonio LD, Zhao H et al.* **Sex Differences in High-Intensity Statin Use Following Myocardial Infarction in the United States**. Journal of the American College of Cardiology 2018; 71:1729-1737.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29673463
ABSTRACT
BACKGROUND: Historically, women have been less likely than men to receive guideline-recommended statin therapy for the secondary prevention of myocardial infarction (MI). OBJECTIVES: The authors examined contemporary sex differences in prescription fills for high-intensity statin therapy following an MI, overall and across population subgroups, and assessed whether sex differences were attenuated following recent efforts to reduce sex disparities in the use of cardiovascular disease preventive therapies. METHODS: The authors studied 16,898 (26% women) U.S. adults <65 years of age with commercial health insurance in the MarketScan database, and 71,358 (49% women) U.S. adults >/=66 years of age with government health insurance through Medicare who filled statin prescriptions within 30 days after hospital discharge for MI in 2014 to 2015. The authors calculated adjusted women-to-men risk ratios and 95% confidence intervals (CIs) for filling a high-intensity statin prescription (i.e., atorvastatin 40 to 80 mg, and rosuvastatin 20 to 40 mg) following hospital discharge for MI. RESULTS: In 2014 to 2015, 56% of men and 47% of women filled a high-intensity statin following hospital discharge for MI. Adjusted risk ratios for filling a high-intensity statin comparing women with men were 0.91 (95% CI: 0.90 to 0.92) in the total population, 0.91 (95% CI: 0.89 to 0.92) among those with no prior statin use, and 0.87 (95% CI: 0.85 to 0.90) and 0.98 (95% CI: 0.97 to 1.00) for those taking low/moderate-intensity and high-intensity statins prior to their MI, respectively. Women were less likely than men to fill high-intensity statins within all subgroups analyzed, and the disparity was largest in the youngest and oldest adults and for those without prevalent comorbid conditions. CONCLUSIONS: Despite recent efforts to reduce sex differences in guideline-recommended therapy, women continue to be less likely than men to fill a prescription for high-intensity statins following hospitalization for MI.

[27] *Tillman F, Kim J*. **Select medications that unexpectedly lower HbA1c levels**. Journal of clinical pharmacy and therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29671894
ABSTRACT
WHAT IS KNOWN AND OBJECTIVE: A variety of medication classes are available for diabetes; however, treatment options become limited due to adverse effect profiles and cost. Current

diabetes guidelines include agents not originally developed for diabetes treatment, bromocriptine and colesevelam. COMMENT: Other non-diabetes medications demonstrating haemoglobin A1c lowering, including agents for weight loss, depression, anaemia and coronary artery disease, are described in this review article. WHAT IS NEW AND CONCLUSION: More research looking into the impact of non-diabetes medications on blood glucose may offer additional diabetes treatment strategies.

[28] *Kamijo Y*. **Is hepatic peroxisome proliferator-activated receptor alpha essential for the metabolic effects of fibrates?** Journal of gastroenterology and hepatology 2018; 33:978-979.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29659082
ABSTRACT

[29] *Navar AM, Peterson ED*. **Challenges in Interpreting the Lipid-Lowering Trials: Biology vs Ecology**. Jama 2018; 319:1549-1551.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29677285
ABSTRACT

[30] *Navarese EP, Robinson JG, Kowalewski M et al.* **Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis**. Jama 2018; 319:1566-1579.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29677301
ABSTRACT
Importance: Effects on specific fatal and nonfatal end points appear to vary for low-density lipoprotein cholesterol (LDL-C)-lowering drug trials. Objective: To evaluate whether baseline LDL-C level is associated with total and cardiovascular mortality risk reductions. Data Sourcesand Study Selection: Electronic databases (Cochrane, MEDLINE, EMBASE, TCTMD, ClinicalTrials.gov, major congress proceedings) were searched through February 2, 2018, to identify randomized clinical trials of statins, ezetimibe, and PCSK9-inhibiting monoclonal antibodies. Data Extraction and Synthesis: Two investigators abstracted data and appraised risks of bias. Intervention groups were categorized as "more intensive" (more potent pharmacologic intervention) or "less intensive" (less potent, placebo, or control group). Main Outcomes and Measures: The coprimary end points were total mortality and cardiovascular mortality. Random-effects meta-regression and meta-analyses evaluated associations between baseline LDL-C level and reductions in mortality end points and secondary end points including major adverse cardiac events (MACE). Results: In 34 trials, 136299 patients received more intensive and 133989 received less intensive LDL-C lowering. All-cause mortality was lower for more vs less intensive therapy (7.08% vs 7.70%; rate ratio [RR], 0.92 [95% CI, 0.88 to 0.96]), but varied by baseline LDL-C level. Meta-regression showed more intensive LDL-C lowering was associated with greater reductions in all-cause mortality with higher baseline LDL-C levels (change in RRs per 40-mg/dL increase in baseline LDL-C, 0.91 [95% CI, 0.86 to 0.96]; P = .001; absolute risk difference [ARD], -1.05 incident cases per 1000 person-years [95% CI, -1.59 to -0.51]), but only when baseline LDL-C levels were 100 mg/dL or greater (P < .001 for interaction) in a meta-analysis. Cardiovascular mortality was lower for more vs less intensive therapy (3.48% vs 4.07%; RR, 0.84 [95% CI, 0.79 to 0.89]) but varied by baseline LDL-C level. Meta-regression

showed more intensive LDL-C lowering was associated with a greater reduction in cardiovascular mortality with higher baseline LDL-C levels (change in RRs per 40-mg/dL increase in baseline LDL-C, 0.86 [95% CI, 0.80 to 0.94]; P < .001; ARD, -1.0 incident cases per 1000 person-years [95% CI, -1.51 to -0.45]), but only when baseline LDL-C levels were 100 mg/dL or greater (P < .001 for interaction) in a meta-analysis. Trials with baseline LDL-C levels of 160 mg/dL or greater had the greatest reduction in all-cause mortality (RR, 0.72 [95% CI, 0.62 to 0.84]; P < .001; 4.3 fewer deaths per 1000 person-years) in a meta-analysis. More intensive LDL-C lowering was also associated with progressively greater risk reductions with higher baseline LDL-C level for myocardial infarction, revascularization, and MACE. Conclusions and Relevance: In these meta-analyses and meta-regressions, more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels. This association was not present when baseline LDL-C level was less than 100 mg/dL, suggesting that the greatest benefit from LDL-C-lowering therapy may occur for patients with higher baseline LDL-C levels.

[31] *Garrett N, Pombo J, Umpierrez M et al.* **Pravastatin therapy during preeclampsia prevents long-term adverse health effects in mice**. JCI insight 2018; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29669946
ABSTRACT
Preeclampsia (PE), associates with long-term increased risk for cardiovascular disease in women, suggesting that PE is not an isolated disease of pregnancy. It is not known if increased risk for long-term diseases is due to PE-specific factors or to prepregnancy renal and cardiovascular risk factors. We used a mouse model in which a WT female with normal prepregnancy health develops PE to investigate if preeclampsia causes long-term cardiovascular consequences after pregnancy for mothers and offspring. Mothers exhibited endothelial dysfunction and hypertension after PE and had glomerular injury that not only persisted but deteriorated, leading to fibrosis. Left ventricular (LV) remodeling characterized by increased collagen deposition and MMP-9 expression and enlarged cardiomyocytes were also detected after PE. Increased LV internal wall thickness and mass, increased end diastolic and end systolic volumes, and increased stroke volume were observed after PE in the mothers. Placenta-derived bioactive factors that modulate vascular function, markers of metabolic disease, vasoconstrictor isoprostane-8, and proinflammatory mediators were increased in sera during and after a preeclamptic pregnancy in the mother. Offspring of PE mice developed endothelial dysfunction, hypertension, and signs of metabolic disease. Microglia activation was increased in the neonatal brains after PE, suggesting neurogenic hypertension in offspring. Prevention of placental insufficiency with pravastatin prevented PE-associated cardiovascular complications in both mothers and offspring. In conclusion, factors that develop during PE have long-term, cardiovascular effects in the mother and offspring independent of prepregnancy risk factors.

[32] *Goedecke JH, Mendham AE, Clamp L et al.* **An Exercise Intervention to Unravel the Mechanisms Underlying Insulin Resistance in a Cohort of Black South African Women: Protocol for a Randomized Controlled Trial and Baseline Characteristics of Participants**. JMIR research protocols 2018; 7:e75.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29669711

ABSTRACT
BACKGROUND: The pathogenesis of type 2 diabetes (T2D) in black African women is complex and differs from that in their white counterparts. However, earlier studies have been cross-sectional and provide little insight into the causal pathways. Exercise training is consistently used as a model to examine the mechanisms underlying insulin resistance and risk for T2D. OBJECTIVE: The objective of the study was to examine the mechanisms underlying the changes in insulin sensitivity and secretion in response to a 12-week exercise intervention in obese black South African (SA) women. METHODS: A total of 45 obese (body mass index, BMI: 30-40 kg/m(2)) black SA women were randomized into a control (n=22) or experimental (exercise; n=23) group. The exercise group completed 12 weeks of supervised combined aerobic and resistance training (40-60 min, 4 days/week), while the control group maintained their typical physical activity patterns, and both groups were requested not to change their dietary patterns. Before and following the 12-week intervention period, insulin sensitivity and secretion (frequently sampled intravenous glucose tolerance test) and its primary and secondary determinants were measured. Dietary intake, sleep quality and quantity, physical activity, and sedentary behaviors were measured every 4 weeks. RESULTS: The final sample included 20 exercise and 15 control participants. Baseline sociodemographics, cardiorespiratory fitness, anthropometry, cardiometabolic risk factors, physical activity, and diet did not differ between the groups (P>.05). CONCLUSIONS: The study describes a research protocol for an exercise intervention to understand the mechanisms underlying insulin sensitivity and secretion in obese black SA women and aims to identify causal pathways underlying the high prevalence of insulin resistance and risk for T2D in black SA women, targeting specific areas for therapeutic intervention. TRIAL REGISTRATION: Pan African Clinical Trial Registry PACTR201711002789113; http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?_nfpb=true&_pageLabel=portals_app_atmregistry_portal_page_13 (Archived by WebCite at http://www.webcitation.org/6xLEFqKr0).

[33] *Liang L, Hur J, Kang JY et al.* **Effect of the anti-IL-17 antibody on allergic inflammation in an obesity-related asthma model**. The Korean journal of internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29665658

ABSTRACT
Background/Aims: The co-occurrence of obesity aggravates asthma symptoms. Diet-induced obesity increases helper T cell (TH) 17 cell differentiation in adipose tissue and the spleen. The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor pravastatin can potentially be used to treat asthma in obese patients by inhibiting interleukin 17 (IL-17) expression. This study investigated the combined effects of pravastatin and anti-IL-17 antibody treatment on allergic inflammation in a mouse model of obesity-related asthma. Methods: High-fat diet (HFD)-induced obesity was induced in C57BL/6 mice with or without ovalbumin (OVA) sensitization and challenge. Mice were administered the anti-IL-17 antibody, pravastatin, or both, and pathophysiological and immunological responses were analyzed. Results: HFD exacerbated allergic airway inflammation in the bronchoalveolar lavage fluid of HFD-OVA mice as compared to OVA mice. Blockading of the IL-17 in the HFD-OVA mice decreased airway hyper-responsiveness (AHR) and airway inflammation compared to the HFD-OVA mice. Moreover, the administration of the anti-IL-17 antibody decreased the leptin/adiponectin ratio in the HFD-

OVA but not the OVA mice. Co-administration of pravastatin and anti-IL-17 inhibited airway inflammation and AHR, decreased goblet cell numbers, and increased adipokine levels in obese asthmatic mice. Conclusions: These results suggest that the IL-17-leptin/adiponectin axis plays a key role in airway inflammation in obesity-related asthma. Our findings suggest a potential new treatment for IL-17 as a target that may benefit obesity-related asthma patients who respond poorly to typical asthma medications.

[34] *Ekerbicer N, Gurpinar T, Sisman AR et al.* **Statins reduce testicular and ocular VEGF: A potential compromise to microcirculation**. Microvascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29678729
ABSTRACT
Microcirculation has great importance in eye and testicular tissue and is necessary to have adequate and appropriate amount of angiogenesis. It is known that high levels of Vascular Endothelial Growth Factor (VEGF) trigger uncontrolled angiogenesis, whereas inadequate VEGF can lead to decreased tissue perfusion and oxygenation. The aim of this study was to investigate effects of VEGF in testicular and ocular tissues in both non-diabetic and diabetic rats treated by statin. Atorvastatin (10mg/kg daily given by orally gavage) was administered for two weeks. Diabetes was induced by streptozotocin, (STZ, 45mg/kg/ip) in diabetic group's rats. Two weeks later from STZ injection, atorvastatin treatment was initiated in diabetic group. VEGF levels were measured by using ELISA. The VEGF levels were decreased in vitrous, ocular and testicular tissues of all statin-administered rats. In diabetic group VEGF levels were found to be decreased in testicular tissue and increased in ocular tissues. CONCLUSION: Statin use decreased in VEGF levels of testicular and ocular tissues in diabetic and non-diabetic rats. Statin treatment (anti-VEGF effect) had a protective effect in the development of diabetic retinopathy, yet statins may have a negative impact on tissues that depend on microcirculation by reducing VEGF levels. Further research is needed for statins' microcellular effects.

[35] *Bernstein DL, Lobritto S, Iuga A et al.* **Lysosomal acid lipase deficiency allograft recurrence and liver failure- clinical outcomes of 18 liver transplantation patients**. Molecular genetics and metabolism 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29655841
ABSTRACT
Lysosomal acid lipase deficiency (LAL-D) results in progressive microvesicular hepatosteatosis, fibrosis, cirrhosis, dyslipidemia, and vascular disease. Interventions available prior to enzyme replacement therapy development, including lipid lowering medications, splenectomy, hematopoietic stem cell and liver transplantation were unsuccessful at preventing multi-systemic disease progression, and were associated with significant morbidity and mortality. We report two sisters, diagnosed in infancy, who succumbed to LAL-D with accelerated disease progression following splenectomy and liver transplantation. The index patient died one year after hematopoietic stem cell transplant and liver transplantation. Her younger sister survived five years post liver-transplantation, complicated by intermittent, acute rejection. Typical LAL-D hepatopathology, including progressive, microvesicular steatosis, foamy macrophage aggregates, vacuolated Kupffer cells, advanced fibrosis and micronodular cirrhosis recurred in the liver allograft. She died before a second liver transplant could occur for decompensated

liver failure. Neither patient received sebelipase alfa enzyme replacement therapy, human, recombinant, lysosomal acid lipase enzyme, FDA approved in 2015. Here are reviewed 18 LAL-D post-liver transplantation cases described in the literature. Multi-systemic LAL-D progression occurred in 11 patients (61%) and death in six (33%). These reports demonstrate that liver transplantation may be necessary for LAL-D-associated liver failure, but is not sufficient to prevent disease progression, or liver disease recurrence, since the pathophysiology is predominantly mediated by deficient enzyme activity in bone marrow-derived monocyte-macrophages. Enzyme replacement therapy addresses systemic disease and hepatopathology, potentially improving liver-transplantation outcomes. This is the first systematic review of liver transplantation for LAL-D, and the first account of liver allograft LAL-D-associated hepatopathology recurrence.

[36] *Lin SH, Cheng PC, Tu ST et al.* **Effect of metformin monotherapy on serum lipid profile in statin-naive individuals with newly diagnosed type 2 diabetes mellitus: a cohort study**. PeerJ 2018; 6:e4578.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29666753
ABSTRACT
Background: Cardiovascular disease is a major cause of mortality and morbidity in people with type 2 diabetes mellitus (T2DM). Studies have consistently identified dyslipidemia as an important risk factor for the development of macrovascular disease. The landmark United Kingdom Prospective Diabetes Study has shown that metformin therapy reduces cardiovascular events in overweight people with T2DM. This study investigates the effect of metformin monotherapy on serum lipid profile in statin-naive individuals with newly diagnosed T2DM, and whether the effect, if any, is dosage-related. Methods: This cohort study enrolled individuals exceeding 20 years of age, with recent onset T2DM, who received at least 12 months of metformin monotherapy and blood tests for serum lipid at 6-month intervals. Exclusion criteria involved people receiving any additional antidiabetic medication or lipid-lowering drug therapy. Lipid-modifying effect of metformin was recorded as levels of serum triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) measured at six month intervals. Results: The study enrolled 155 participants with a mean age of 58.6 years and average glycosylated hemoglobin A1c of 8%. After initiating metformin therapy, LDL-C was significantly reduced from 111 mg/dl to 102 mg/dL at 6 months ($P < 0.001$), TG was reduced from 132 mg/dl to 122 mg/dL at 12 months ($P = 0.046$), and HDL-C increased from 45.1 mg/dL to 46.9 mg/dL at 12 months ($P = 0.02$). However, increasing the dosage of metformin yielded no significant effect on its lipid-lowering efficacy. Discussion: Metformin monotherapy appreciably improves dyslipidemia in statin-naive people with T2DM. Its lipid-modifying effect may be attributable to insulin sensitization, reduction of irreversibly glycated LDL-C, and weight loss. In practice, people with dyslipidemia who are ineligible for lipid-lowering agents may benefit from metformin therapy. Moreover, previous studies report a synergistic effect between metformin and statin, which may further reduce cardiovascular events in at-risk individuals. Overall, metformin is a safe and efficacious approach to alleviate dyslipidemia in people with newly diagnosed T2DM.

[37] *Miranda HF, Sierralta F, Aranda N et al.* **Antinociception induced by rosuvastatin in murine neuropathic pain**. Pharmacological reports : PR 2017; 70:503-508.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29660653
ABSTRACT
BACKGROUND: Neuropathic pain, and subsequent hypernociception, can be induced in mice by paclitaxel (PTX) administration and partial sciatic nerve ligation (PSNL). Its pharmacotherapy has been a clinical challenge, due to a lack of effective treatment. In two models of mouse neuropathic pain (PTX and PSNL) the antinociception induced by rosuvastatin and the participation of proinflammatory biomarkers, interleukin (IL)- 1beta, TBARS and glutathione were evaluated. METHODS: A dose-response curve for rosuvastatin ip was obtained on cold plate, hot plate and Von Frey assays. Changes on spinal cord levels of IL-1beta, glutathione and lipid peroxidation were measured at 7 and 14days in PTX and PSNL murine models. RESULTS: PTX or PSNL were able to induce in mice peripheral neuropathy with hypernociception, either to 7 and 14days. Rosuvastatin induced a dose dependent antinociception in hot plate, cold plate and Von Frey assays. The increased levels of IL-1beta or TBARS induced by pretreatment with PTX or PSNL were reduced by rosuvastatin. The reduction of spinal cord glutathione, by PTX or PSNL, expressed as the ratio GSH/GSSG, were increased significantly in animals pretreated with rosuvastatin. The anti-inflammatory properties of statins could underlie their beneficial effects on neuropathic pain by reduction of proinflammatory biomarkers and activation of glia. CONCLUSION: The findings of this study suggest a potential usefulness of rosuvastatin in the treatment of neuropathic pain.

[38] *Clark CM, Monahan KD, Drew RC*. **Omega-3 polyunsaturated fatty acid supplementation reduces blood pressure but not renal vasoconstrictor response to orthostatic stress in healthy older adults**. Physiological reports 2018; 6:e13674.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29673104
ABSTRACT
Older adults exhibit augmented renal vasoconstriction during orthostatic stress compared to young adults. Consumption of omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil (FO), modulates autonomic nerve activity. However, the effect of omega-3 polyunsaturated fatty acid consumption on the renal vasoconstrictor response to orthostatic stress in young and older adults is unknown. Therefore, 10 young (25 +/- 1 years; mean +/- SEM) and 10 older (66 +/- 2 years) healthy adults ingested 4 g FO daily for 12 weeks, and underwent graded lower body negative pressure (LBNP; -15 and -30 mmHg) pre- and post-FO supplementation. Renal blood flow velocity (RBFV; Doppler ultrasound), arterial blood pressure (BP; photoplethysmographic finger cuff), and heart rate (electrocardiogram) were recorded. Renal vascular resistance (RVR), an index of renal vasoconstriction, was calculated as mean BP/RBFV. All baseline cardiovascular values were similar between groups and visits, except diastolic BP was higher in the older group ($P < 0.05$). FO supplementation increased erythrocyte EPA and DHA content in both groups ($P < 0.05$). FO did not affect RVR or RBFV responses to LBNP in either group, but attenuated the mean BP response to LBNP in the older group (older -30 mmHg: pre-FO -4 +/- 1 vs. post-FO 0 +/- 1 mmHg, $P < 0.05$; young -30 mmHg: pre-FO -5 +/- 1 vs. post-FO -5 +/- 2 mmHg). In conclusion, FO

supplementation attenuates the mean BP response but does not affect the renal vasoconstrictor response to orthostatic stress in older adults.

[39] *Welnicki M, Sliz D, Filipiak KJ et al.* **[Difference in efficacy of dyslipidaemia treatment in obese and not obese women. Analysis of date from 3ST-POL study]**. Przeglad lekarski 2016; 73:353-358.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29668197
ABSTRACT
Introduction: Cardiovascular diseases remain the first cause of premature death in polish society. In Poland mortality concerned with cardiovascular diseases is higher in women than in men. Dyslipidemia is one of the most important and one of the most common risk factor of cardiovascular diseases. The efficacy of treatment of dyslipidaemia in Poland remains poor however there is lack of date as far as influence of sex and coexistence obesity on efficacy of treatment of dyslipidaemia is concerned. Aim: Evaluation of difference in efficacy of treatment of dyslipidaemia in obese women and women with body mass index less than 30 kg/m2. Date from 3ST-POL Study. Methods: Post hoc analysis of date of 3ST-POL Study, conducted in 2007-2008. The Study refers to efficacy of treatment of dyslipidaemia in ambulatory polish patients which remain under supervision of general practitioners, cardiologist or dialectologist. Results: Women comprise 53% (n=26099) of population of 3ST-POL Study. In 21769 of those it was possible to calculate body mass index (BMI). 16% of women ware obese. 70% of those in comparison of with 67.6% of women with BMI<30 kg/m2 were at high cardiovascular risk. (p<0.01). There was no difference in mean doses of statins between all groups (mean daily dose was 20 mg and 24 mg for atorvastatin and simvastatin respectively). LDL goal was reached in 9.67% vs, 15.8% of obese high risk and not at high risk women respectively (p<0.01). Total cholesterol goal was reached in 9.01% vs. 12.39% obese high risk and not at high risk women respectively (p<0.01). In group with BMI<30 kg/m2 LDL and total cholesterol goals in high risk and not at high risk women were reached in 10.02% vs. 14.46% and in 8.86% vs. 13.05% respectively (p<0.01 for both). Mean concentration of all lipids, except for triglycerides, was higher in non-obese women. Conclusions: The efficacy of treatment of dyslipidaemia in women from 3ST-POL study was higher in patients with lower global cardiovascular risk. Obesity or lack of it has no influence of that difference. Nevertheless global efficacy was very poor as far as both - LDL and total cholesterol goals were concerned. Moreover there were now difference in mean statins doses between groups. This may be due to therapeutic inertia of physicians.

[40] *Matsubara A, Oda S, Akai S et al.* **Establishment of a drug-induced rhabdomyolysis mouse model by co-administration of ciprofloxacin and atorvastatin**. Toxicology letters 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29679711
ABSTRACT
Rhabdomyolysis is one of the serious side effects of ciprofloxacin (CPFX), a widely used antibacterial drug; and occasionally, acute kidney injury (AKI) occurs. Often, rhabdomyolysis has occurred in patients taking CPFX co-administered with statins. The purpose of this study is to establish a mouse model of drug-induced rhabdomyolysis by co-administration of CPFX and atorvastatin (ATV) and to clarify the mechanisms of its pathogenesis. C57BL/6J mice treated with L-buthionine-(S,R)-sulfoximine (BSO), a glutathione synthesis inhibitor, were orally

administered with CPFX and ATV for 4 days. Plasma levels of creatinine phosphokinase (CPK) and aspartate aminotransferase (AST) were significantly increased in the CPFX and ATV-co-administered group. Histopathological examination of skeletal muscle observed degeneration in gastrocnemius muscle and an increased number of the satellite cells. Expressions of skeletal muscle-specific microRNA and mRNA in plasma and skeletal muscle, respectively, were significantly increased. The area under the curve (AUC) of plasma CPFX was significantly increased in the CPFX and ATV-co-administered group. Furthermore, cytoplasmic vacuolization and a positively myoglobin-stained region in kidney tissue and high content of myoglobin in urine were observed. These results indicated that AKI was induced by myoglobin that leaked from skeletal muscle. The established mouse model in the present study would be useful for predicting potential rhabdomyolysis risks in preclinical drug development.

[41] *Dijk W, Le May C, Cariou B*. **Beyond LDL: What Role for PCSK9 in Triglyceride-Rich Lipoprotein Metabolism?** Trends in endocrinology and metabolism: TEM 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29665987
ABSTRACT
Elevated plasma triglyceride (TG) levels are an independent risk factor for cardiovascular disease (CVD). Proprotein convertase subtilisin-kexin 9 (PCSK9) - a protein therapeutically targeted to lower plasma cholesterol levels - might regulate plasma TG-rich lipoprotein (TRL) levels. We provide a timely and critical review of the current evidence for a role of PCSK9 in TRL metabolism by assessing the impact of PCSK9 gene variants, by reviewing recent clinical data with PCSK9 inhibitors, and by describing the potential mechanisms by which PCSK9 might regulate TRL metabolism. We conclude that the impact of PCSK9 on TRL metabolism is relatively modest, especially compared to its impact on cholesterol metabolism.

[42] *Wang JJ, Tian Y, Xu KL et al.* **[Statins Regulate the Proliferation and Apoptosis of T-ALL Cells through the Inhibition of Akt Pathway]**. Zhongguo shi yan xue ye xue za zhi 2018; 26:359-367.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29665899
ABSTRACT
OBJECTIVE: To investigate the effect of Statins on proliferation and apoptosis in human acute T lymphocytic leukemia (T-ALL) cells and its possible mechanism. METHODS: Jurkat and CCRF-CEM cells were cultured in different concentrations of Fluvastatin and Simvastatin for 24 h respectively. Then, the cell growth inhibition level was defected by CCK-8; the DNA replication was analyzed by EdU; the cell apoptosis was analyzed by Annexin V/7-AAD double labeling; the cell cycle changes were analyzed by flow cytometry; the expressions of Cyclin D1, p21, p27, BAX, BCL-2 and p-Akt were determined by Western blot. RESULTS: Fluvastatin and Simvastatin both significantly inhibited the growth of Jurkat and CCRF-CEM cells in a dose-dependent manner. The inhibitory rate of Jurkat and CCRF-CEM cells at 0.2 mmol/L Fluvastatin was 41.14% and 57.08% respectively, while the 0.2 mmol/L Simvastatin could supress 68.42% of Jurkat and 77.10% of CCRF-CEM cells. Half or more than half of cell inhibition were observed in Statins-treated groups with significantly statistical differences, compared with the control groups ($P<0.05$). After the Jurkat and CCRF-CEM cells were treated with Fluvastation and Simvastation of different concentrations for 24 hours, the proportion of early and later apoptotic cells both

increased; moreover, the total apoptotic rate increased significantly($P<0.05$) at 0.2 mmol/L and 0.3 mmol/L concentration of Fluvastatin and Simvastatin. The detection of cell cycle showed that both of Jurkat and CCRF-CEM cells were arrested in G1 phase. Western blot revealed that, in comparison with the control group, the expressions of BAX, p21 and p27 in cells treated with Statins were up-regulated, while Cyclin D1, BCL-2 and p-Akt expressions were down-regulated. CONCLUSION: Statins can suppress T-ALL cell proliferation and induce cell apoptosis through the inhibition of Akt pathway.