Literature update week 25 (2018)

[1] *Ida J, Kotani K, Miyoshi T et al.* **High Baseline Lipoprotein(a) Level as a Risk Factor for Coronary Artery Calcification Progression: Sub-analysis of a Prospective Multicenter Trial**. Acta medica Okayama 2018; 72:223-230.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29925999
ABSTRACT
Lipoprotein(a), or Lp(a), is a low-density lipoprotein-like particle largely independent of known risk factors for, and predictive of, cardiovascular disease (CVD). We investigated the association between baseline Lp(a) levels and the progression of coronary artery calcification (CAC) in patients with hypercholesterolemia undergoing statin therapy. This study was a sub-analysis of a multicenter prospective study that evaluated the annual progression of CAC under intensive and standard pitavastatin treatment with or without eicosapentaenoic acid in patients with an Agatston score of 1 to 999, and hypercholesterolemia treated with statins. We classified the patients into 3 groups according to CAC progression. A total of 147 patients (mean age, 67 years; men, 54%) were analyzed. The proportion of patients with Lp(a) > 30 mg/dL significantly increased as CAC progressed (non-progression; 5.4%, 0<CAC progression <==100; 7.7%, and CAC progression >100; 23.6%). Logistic regression analysis showed that Lp(a) > 30 mg/dL was an independent predictor of the annual change in Agatston score > 100 (OR: 5.51; 95% CI: 1.28-23.68; p=0.02), even after adjusting for age, sex, hypertension, diabetes mellitus, current smoking, body mass index, and lipid-lowering medications. Baseline Lp(a) >30 mg/dL was a predictor of CAC progression in this population of patients with hypercholesterolemia undergoing statin therapy.

[2] *Akouchekian S, Omranifard V, Moshfegh P et al.* **The Effect of Atorvastatin on Obsessive-compulsive Symptoms of Refractory Obsessive-compulsive Disorder (Add-on Therapy)**. Advanced biomedical research 2018; 7:90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29930930
ABSTRACT
Background: Considering the effect of statins on the regulation of dopamine neurotransmitters and glutamates and importance of the treatment of obsessive-compulsive disorder (OCD) due to its relatively high prevalence and disability of available drugs in treatment of many patients, we came to the point to examine effectiveness of statins in patients with OCD. Materials and Methods: This study is a double-blind randomized clinical trial, which is done in OCD clinic of Isfahan Shariati in 2014 for 1 year. The target population consists of 64 patients with OCD; one group is given a daily 40 mg atorvastatin tablets and the other group receives placebo. At baseline, 4- and 8-week severities of obsessive-compulsive symptoms are measured using Yale-Brown scale and compared in the two groups. Results: The study results show a statistically significant difference between the two groups of intervention and control ($P < 0.001$). Furthermore, the results show the intervention effect at the end of the 4(th) week and 8(th) week ($P < 0.001$) that this change is evident in the 4(th) week but remained almost constant in the 8(th) week. Conclusion: Overall, the evidences obtained from the study declare the effects of adding statins to treat obsessive-compulsive symptoms.

[3] *Zhou C, Lai S, Xie Y et al.* **Rhabdomyolysis in a patient complicated with hypopituitarism and multiple organ dysfunction syndrome and the literature review**. The American journal of emergency medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29910183
ABSTRACT
INTRODUCTION: Muscular symptoms, including stiffness, myalgia, cramps, and fatigue, are present in the majority of the patients with hypopituitarism, adrenal insufficiency and hypothyroidism, but rhabdomyolysis, the rapid breakdown of skeletal muscle, is a rare manifestation. In most patients who develop rhabdomyolysis, precipitating factors, such as strenuous exercise or use of lipid-lowering drugs, can be identified. CASE REPORT: We report the case of a 23-year-old male with primary hypopituitarism who developed acute renal impairment (AKI) with rhabdomyolysis after strenuous physical activity (push-ups). His blood test confirmed marked hypopituitarism. Severe elevation of serum CK consistent with rhabdomyolysis was noted and an elevated creatinine indicated AKI and multiple organ dysfunction syndrome (MODS). Patient's condition improved significantly after continuous renal replacement therapy (CRRT), glucocorticoid hormone replacement therapy and aggressive hydration. MODS with rhabdomyolysis in patients with hypothyroidism is quite rare and we expect that this case report adds to the existing literature on this subject. We also emphasize that thyroid and adrenal gland status should be evaluated in patients with unexplained AKI, MODS and presenting with the symptoms of muscle involvement. LITERATURE REVIEW: We respectively reviewed 23 patients with hypopituitarism, adrenal Insufficiency and hypothyroidism induced rhabdomyolysis who were involved in the past 40years relevant literatures. CONCLUSION: We report a successfully treated case of rhabdomyolysis, which is a rare but potentially serious complication of hypopituitarism. Screening for endocrine abnormality in patients with elevated muscle enzymes should be considered, since an early diagnosis and prompt treatment is essential to prevent rhabdomyolysis and its consequences.

[4] *Lemaster KA, Frisbee SJ, DuBois L et al.* **CHRONIC ATORVASTATIN AND EXERCISE CAN PARTIALLY REVERSE ESTABLISHED SKELETAL MUSCLE MICROVASCULOPATHY IN METABOLIC SYNDROME**. American journal of physiology. Heart and circulatory physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29932769
ABSTRACT
It has been long known that chronic metabolic disease is associated with a parallel increase in the risk for developing peripheral vascular disease. Although more clinically relevant, our understanding about reversing established vasculopathy is limited in comparison to our understanding of the mechanisms and development of impaired vascular structure/function under these conditions. Using the 13-week old obese Zucker rat (OZR) model of the metabolic syndrome, where microvascular dysfunction is sufficiently established to contribute to impaired skeletal muscle function, we imposed a 7-week intervention of chronic atorvastatin (ATOR) treatment, chronic treadmill exercise (EXER), or both. By 20 weeks of age, untreated OZR manifested a diverse vasculopathy that was a central contributor to poor muscle performance, perfusion and impaired O2 exchange. ATOR or EXER, with the combination being most effective, improved skeletal muscle vascular metabolite profiles (i.e., nitric oxide, PGI2 and TxA2 bioavailability), reactivity and perfusion distribution at both individual bifurcations and

within the entire microvascular network versus responses in untreated OZR. However, improvements to microvascular structure (i.e., wall mechanics and microvascular density) were less robust. The combination of the above improvements to vascular function with interventions resulted in an improved muscle performance and O2 transport and exchange versus untreated OZR, especially at moderate metabolic rates (3Hz twitch contraction). These results suggest that specific interventions can improve specific indices of function from established vasculopathy, but this process was either incomplete after 7 weeks duration or that measures of vascular structure are either resistant to reversal or require better targeted interventions.

[5] *Ayad MT, Taylor BD, Menon R*. **Regulation of p38 mitogen-activated kinase-mediated fetal membrane senescence by statins**. American journal of reproductive immunology (New York, N.Y. : 1989) 2018:e12999.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29911323
ABSTRACT
PROBLEM: Oxidative stress (OS)-induced, p38 mitogen-activated protein kinase (p38MAPK)-mediated chorioamniotic senescence and inflammation (senescence-associated secretory phenotype [SASP]) are associated with parturition. In response to OS-inducing risk factors, premature senescence contributes to preterm premature rupture of the membranes (pPROM) and spontaneous preterm birth (PTB). We determined the effect of simvastatin, rosuvastatin, and progesterone in downregulating p38MAPK-mediated senescence and SASP. METHOD OF STUDY: Normal term, not-in-labor fetal membranes (n = 8) were exposed to cigarette smoke extract (CSE: OS inducer) alone or combined with simvastatin (100 and 200 ng/mL), rosuvastatin (100 and 200 ng/mL), and progesterone (10(-6) mol/L). p38MAPK expression changes were studied by Western blot, senescence was determined by senescence-associated beta-Galactosidase (SA-beta-Gal) staining, and multiplex analysis determined changes associated with 4 SASP markers (IL-8, IL-10, TNF-alpha, and GM-CSF). A pairwise comparison between groups was conducted by ANOVA. RESULTS: Compared to untreated controls, CSE induced p38MAPK-mediated senescence and SASP. CSE cotreatment with simvastatin and rosuvastatin significantly reduced p38MAPK activation, senescence (decrease in SA-beta-Gal) and SASP markers, GM-CSF, and TNF, but not IL-8, while increasing anti-inflammatory IL-10 in a dose-dependent manner. Cotreatment of CSE and progesterone had no effect on reducing p38MAPK activation, senescence, or SASP. CONCLUSION: Both simvastatin and rosuvastatin downregulated OS-induced p38MAPK activation, senescence, and SASP, while rosuvastatin showed a pronounced effect. Progesterone did not reduce OS-induced fetal membrane senescence and SASP. Simvastatin or rosuvastatin may reduce the incidences of OS-associated PTB and pPROM by preventing premature senescence and SASP.

[6] *Kozlov SG, Khamchieva LS, Pogorelova OA et al.* **[Dynamics of asymptomatic atherosclerosis of carotid arteries depending on the achieved level of cholesterol in moderate-risk patients]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2018; 24:11-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29924771
ABSTRACT

The study was aimed at assessing the dynamics of asymptomatic atherosclerosis of carotid arteries (CA) depending upon the achieved level of low-density lipoprotein cholesterol (LDLC) in patients with moderate total risk by the SCORE scale. We followed up a total of eighty-two 40-to-65-year-old patients with the LDLC level above 2.6 mmol/l, being at moderate total risk by the SCORE scale and having symptom-free atherosclerosis of the extracranial portion of brachiocephalic arteries (up to 50% narrowing of their lumen) as diagnosed by duplex scanning. The patients were randomly divided into two groups. Group One patients (n=41) received therapy with atorvastatin in order to achieve the LDLC level less than 1.8 mmol/l. Group Two patients (n=41) were treated in order to achieve the LDLC level below 2.6 mmol/l. At 12 months of follow up we compared the dynamics of carotid atherosclerosis (change in the number, total height, structure, echogenicity, as well as the state of the surface of atherosclerotic plaques, alteration of the thickness of the CA intima-media complex). Group Two patients were found to have an increase in the number and average sum of the heights of atherosclerotic plaques. An increase of the maximum thickness of the intima-media complex of the wall of the right and left CA was more pronounced as compared with that in Group One patients. Aggressive hypolipidemic therapy aimed at achieving the LDLC level below 1.8 mmol/l turned out to be more effective in slowing down the progression of asymptomatic carotid atherosclerosis in patients with moderate cardiovascular risk than therapy targeted at achieving the LDLC level below 2.6 mmol/l.

[7] *Cansby E, Magnusson E, Nunez-Duran E et al.* **STK25 Regulates Cardiovascular Disease Progression in a Mouse Model of Hypercholesterolemia**. Arteriosclerosis, thrombosis, and vascular biology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29930001
ABSTRACT
OBJECTIVE: Recent cohort studies have shown that nonalcoholic fatty liver disease, and especially nonalcoholic steatohepatitis, associate with atherosclerosis and cardiovascular disease, independently of conventional cardiometabolic risk factors. However, the mechanisms underlying the pathophysiological link between nonalcoholic fatty liver disease/nonalcoholic steatohepatitis and cardiovascular disease still remain unclear. Our previous studies have identified STK25 (serine/threonine protein kinase 25) as a critical determinant in ectopic lipid storage, meta-inflammation, and progression of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. The aim of this study was to assess whether STK25 is also one of the mediators in the complex molecular network controlling the cardiovascular disease risk. APPROACH AND RESULTS: Atherosclerosis was induced in Stk25 knockout and transgenic mice, and their wild-type littermates, by gene transfer of gain-of-function mutant of PCSK9 (proprotein convertase subtilisin/kexin type 9), which induces the downregulation of hepatic LDLR (low-density lipoprotein receptor), combined with an atherogenic western-type diet. We found that Stk25(-)(/-) mice displayed reduced atherosclerosis lesion area as well as decreased lipid accumulation, macrophage infiltration, collagen formation, and oxidative stress in aortic lesions compared with wild-type littermates, independently from alterations in dyslipidemia. Reciprocally, Stk25 transgenic mice presented aggravated plaque formation and maturation compared with wild-type littermates despite similar levels of fasting plasma cholesterol. We also found that STK25 protein was expressed in all layers of the aorta, suggesting a possible direct role in

cardiovascular disease. CONCLUSIONS: This study provides the first evidence that STK25 plays a critical role in regulation of cardiovascular disease risk and suggests that pharmacological inhibition of STK25 function may provide new possibilities for prevention/treatment of atherosclerosis.

[8] *Ballantyne CM, Banach M, Mancini GBJ et al.* **Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29910030
ABSTRACT
BACKGROUND AND AIMS: Patients with hyperlipidemia who are unable to tolerate optimal statin therapy are at increased cardiovascular risk due to ongoing elevations in low-density lipoprotein cholesterol (LDL-C). The objective of CLEAR Tranquility (NCT03001076) was to evaluate the efficacy and safety of bempedoic acid when added to background lipid-modifying therapy in patients with a history of statin intolerance who require additional LDL-C lowering. METHODS: This phase 3, multicenter, randomized, double-blind, placebo-controlled study enrolled patients with a history of statin intolerance and an LDL-C >/=100mg/dL while on stable lipid-modifying therapy. After a 4-week ezetimibe 10mg/day run-in period, patients were randomized 2:1 to treatment with bempedoic acid 180mg or placebo once daily added to ezetimibe 10mg/day for 12 weeks. The primary endpoint was the percent change from baseline to week 12 in LDL-C. RESULTS: The study population comprised 269 patients (181 bempedoic acid, 88 placebo). Bempedoic acid added to background lipid-modifying therapy that included ezetimibe reduced LDL-C by 28.5% more than placebo ($p < 0.001$; -23.5% bempedoic acid, +5.0% placebo). Significant reductions in secondary endpoints, including non-high-density lipoprotein cholesterol (-23.6%), total cholesterol (-18.0%), apolipoprotein B (-19.3%), and high-sensitivity C-reactive protein (-31.0%), were observed with bempedoic acid vs. placebo ($p<0.001$). Bempedoic acid was well tolerated; rates of treatment-emergent adverse events, muscle-related adverse events, and discontinuations were similar in the bempedoic acid and placebo treatment groups. CONCLUSIONS: Bempedoic acid may provide an oral therapeutic option complementary to ezetimibe in statin intolerant patients who require additional LDL-C lowering.

[9] *Li H, Chen MH, Ibrahim JG et al.* **Bayesian inference for network meta-regression using multivariate random effects with applications to cholesterol lowering drugs**. Biostatistics (Oxford, England) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29912318
ABSTRACT
Low-density lipoprotein cholesterol (LDL-C) has been identified as a causative factor for atherosclerosis and related coronary heart disease, and as the main target for cholesterol- and lipid-lowering therapy. Statin drugs inhibit cholesterol synthesis in the liver and are typically the first line of therapy to lower elevated levels of LDL-C. On the other hand, a different drug, Ezetimibe, inhibits the absorption of cholesterol by the small intestine and provides a different mechanism of action. Many clinical trials have been carried out on safety and efficacy evaluation of cholesterol lowering drugs. To synthesize the results from different clinical trials,

we examine treatment level (aggregate) network meta-data from 29 double-blind, randomized, active, or placebo-controlled statins +/$-$ Ezetimibe clinical trials on adult treatment-naive patients with primary hypercholesterolemia. In this article, we propose a new approach to carry out Bayesian inference for arm-based network meta-regression. Specifically, we develop a new strategy of grouping the variances of random effects, in which we first formulate possible sets of the groups of the treatments based on their clinical mechanisms of action and then use Bayesian model comparison criteria to select the best set of groups. The proposed approach is especially useful when some treatment arms are involved in only a single trial. In addition, a Markov chain Monte Carlo sampling algorithm is developed to carry out the posterior computations. In particular, the correlation matrix is generated from its full conditional distribution via partial correlations. The proposed methodology is further applied to analyze the network meta-data from 29 trials with 11 treatment arms.

[10] *Dong R, Ma G, Zhang S et al.* **Simvastatin reverses multiple myeloma serum-induced prothrombotic phenotype in endothelial cells via ERK 1/2 signalling pathway**. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29916838
ABSTRACT
: The introduction of new agents in multiple myeloma therapy has increased the overall response rate and improved clinical outcomes, but the increased risk of thrombotic complications impairs the quality of life of patient and the optimal thromboprophylaxis remains unknown. Increasing evidence has shown that statins can prevent venous thrombosis. Hence, we investigated the effects of simvastatin on multiple myeloma serum-related haemostatic imbalance in endothelial cells in vitro. The effects of simvastatin on procoagulant and anticoagulant protein expression were assessed on mixed multiple myeloma serum-treated human umbilical vein endothelial cells (HUVECs). The activity of these proteins was measured by thrombin generation and protein C activation assay. Then, the effects of extracellular signal-regulated kinase (ERK) 1/2 on endothelial activation were assessed by western blot and inhibition assay. We found that simvastatin inhibited multiple myeloma serum-induced expression of procoagulant protein tissue factor and phosphatidylserine and generation of thrombin on HUVECs. In contrast, simvastatin increased multiple myeloma serum-inhibited expression of anticoagulant protein endothelial protein C receptor and activation of protein C on HUVECs. Moreover, simvastatin reversed the multiple myeloma serum-induced prothrombotic phenotype, at least in part, via the inhibition of ERK 1/2 activation in endothelial cells. This study supports the beneficial effects of simvastatin on multiple myeloma serum-induced endothelial haemostatic imbalance, which suggests that simvastatin may serve as a new and appropriate antithrombotic approach for multiple myeloma patients.

[11] *Withers TM, Croft L, Goosey-Tolfrey VL et al.* **Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol**. BMJ open 2018; 8:e021936.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29934392
ABSTRACT

INTRODUCTION: Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD) and could partly explain the increased prevalence of CVD in people with spinal cord injury (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute CVD risk marker response to breaking up prolonged sedentary time in people with SCI has not been investigated. METHODS AND ANALYSIS: A randomised two-condition laboratory crossover trial will compare: (1) breaking up prolonged sedentary time with 2 min moderate-intensity arm-crank activity every 20 min, with (2) uninterrupted prolonged sedentary time (control) in people with SCI. Outcomes will include acute effects on postprandial glucose, insulin, lipids and blood pressure. Blood samples will be collected and blood pressure measured at regular intervals during each 5(1/2)-hour condition. ETHICS AND DISSEMINATION: This study was approved by the Cambridge South National Health Service Research Ethics Committee. This research will help determine if breaking up prolonged sedentary time could be effective in lowering CVD risk in people with SCI. The findings of the research will be published in a peer-reviewed journal and disseminated to relevant user groups. TRIAL REGISTRATION NUMBER: ISRCTN51868437; Pre-results.

[12] *Noto D, Giammanco A, Barbagallo CM et al.* **Anti-PCSK9 treatment: Is ultra-low LDL always good?** Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29931148
ABSTRACT
Anti-pcsk9 (proprotein convertase subtilisin kexin 9) monoclonal antibodies (Mab) are novel, potent lipid-lowering drugs. They demonstrated to improve the lipid profile in high cardiovascular risk patients. Anti-pcsk9 Mab inhibit the targeted LDL-receptor degradation induced by pcsk9 protein and are able to reduce LDL cholesterol (LDL-C) levels on top of conventional lipid-lowering therapy.Though these drugs proved to be very safe in the short term, little is known about the possible long term effects, due to the short period of their marketing. The genetic low-cholesterol syndromes (LCS) represent the natural models of the lipid-lowering anti-PCSK9 therapy, and a valuable opportunity to predict the long term effects of these drugs. By looking at the clinical features of such models we could be able to foresee possible drug-induced side effects. In the present review the correspondences and discordances between the side effects of anti-pcsk9 therapy and the corresponding LCS models will be examined in the attempt to forecast possible long term consequences of these novel lipid lowering agents.

[13] *McMillin M, Grant S, Frampton G et al.* **FXR-Mediated Cortical Cholesterol Accumulation Contributes to the Pathogenesis of Type A Hepatic Encephalopathy**. Cellular and molecular gastroenterology and hepatology 2018; 6:47-63.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29928671
ABSTRACT
Background & Aims: Hepatic encephalopathy is a serious neurologic complication of acute and chronic liver diseases. We previously showed that aberrant bile acid signaling contributes to the development of hepatic encephalopathy via farnesoid X receptor (FXR)-mediated mechanisms in neurons. In the brain, a novel alternative bile acid synthesis pathway, catalyzed by

cytochrome p450 46A1 (Cyp46A1), is the primary mechanism by which the brain regulates cholesterol homeostasis. The aim of this study was to determine if FXR activation in the brain altered cholesterol homeostasis during hepatic encephalopathy. Methods: Cyp7A1(-/-) mice or C57Bl/6 mice pretreated with central infusion of FXR vivo morpholino, 2-hydroxypropyl-beta-cyclodextrin, or fed a cholestyramine-supplemented diet were injected with azoxymethane (AOM). Cognitive and neuromuscular impairment as well as liver damage and expression of Cyp46A1 were assessed using standard techniques. The subsequent cholesterol content in the frontal cortex was measured using commercially available kits and by Filipin III and Nile Red staining. Results: There was an increase in membrane-bound and intracellular cholesterol in the cortex of mice treated with AOM that was associated with decreased Cyp46A1 expression. Strategies to inhibit FXR signaling prevented the down-regulation of Cyp46A1 and the accumulation of cholesterol. Treatment of mice with 2-hydroxypropyl-beta-cyclodextrin attenuated the AOM-induced cholesterol accumulation in the brain and the cognitive and neuromuscular deficits without altering the underlying liver pathology. Conclusions: During hepatic encephalopathy, FXR signaling increases brain cholesterol and contributes to neurologic decline. Targeting cholesterol accumulation in the brain may be a possible therapeutic target for the management of hepatic encephalopathy.

[14] *Itoga NK, Tawfik DS, Lee CK et al.* **Association of Blood Pressure Measurements with Peripheral Arterial Disease Events: A Reanalysis of the ALLHAT Data**. Circulation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29930023

ABSTRACT

Background -Current guidelines recommend treating hypertension in patients with peripheral arterial disease (PAD) to reduce the risk of cardiac events and stroke, but the effect of reducing blood pressure on lower extremity PAD events is largely unknown. We investigated the association of blood pressure with lower extremity PAD events using data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Methods -ALLHAT investigated the effect of different antihypertensive medication classes (chlorthalidone, amlodipine, lisinopril, or doxazosin) on cardiovascular events. Using these data, the primary outcome in our analysis was time to first lower extremity PAD event, defined as PAD-related hospitalization, procedures, medical treatment, or PAD-related death. Given the availability of longitudinal standardized blood pressure measurements, we analyzed systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) as time-varying categorical variables (reference categories 120-129 mm Hg for SBP, 70-79 mm Hg for DBP, and 45-54 mm Hg for PP) in separate models. We used extended Cox regression with death as a competing risk to calculate the association of each BP component with PAD events, and report the results as sub-distribution hazard ratios (HR) and 95% confidence intervals (CI). Results -The present analysis included 33,357 patients with an average age of 67.4 years, 53.1% men, 59.7% white race, and 36.2% with diabetes mellitus. The median baseline blood pressure was 146/84 mm Hg. Participants were followed for a median of 4.3 (IQR 3.6-5.3) years, during which time 1,489 (4.5%) had a lower extremity PAD event, and 4,148 (12.4%) died. In models adjusted for demographic and clinical characteristics, SBP <120 mm Hg was associated with a 26% (CI 5-52%, P=0.015) higher hazard and SBP>/=160 mm Hg was associated with a 21% (CI 0-48%, P=0.050) higher hazard for a PAD event, compared with SBP 120-129 mm Hg. In contrast, lower, but not

higher, DBP was associated with higher hazard of PAD events: for DBP <60 mm Hg HR = 1.72 (CI 1.38 - 2.16). PP had a U-shaped association with PAD events. Conclusions -In this re-analysis of data from ALLHAT, we found a higher rate of lower extremity PAD events with higher and lower SBP and PP, and with lower DBP. Given the recent revised blood pressure guidelines advocating lower SBP targets for overall cardiovascular risk reduction, further refinement of optimal blood pressure targets specific to PAD is needed. Clinical Trial Registration -URL: www.clinicaltrials.gov Unique identifier: NCT00000542.

[15] *Rawla P, Sunkara T, Thandra KC, Gaduputi V*. **Hypertriglyceridemia-induced pancreatitis: updated review of current treatment and preventive strategies**. Clin J Gastroenterol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29923163
ABSTRACT
Hypertriglyceridemia (HTG) is an uncommon but well-established cause of acute pancreatitis (AP) comprising up to 7% of the cases. The clinical course of HTG-induced pancreatitis (HTGP) is highly similar to that of AP of other etiologies with HTG being the only distinguishing clinical feature. However, HTGP is often correlated with higher severity and elevated complication rate. At present, no approved treatment guideline for the management of HTGP is available, although different treatment modalities such as insulin, heparin, fibric acids, and omega 3 fatty acids have been successfully implemented to reduce serum triglycerides (TG). Plasmapheresis has also been used to counteract elevated TG levels in HTGP patients. However, it has been associated with complications. Following the management of acute phase, lifestyle modifications including dietary adjustments and drug therapy are essential in the long-term management of HTGP and the prevention of its relapse. Results from studies of small patient groups describing treatment and prevention of HTGP are not sufficient to draw solid conclusions resulting in no treatment algorithm being available for effective management of HTGP. Therefore, prospective randomized, active-controlled clinical studies are required to find a better treatment regimen for the management of HTGP. Until date, one randomized clinical trial has been performed to compare clinical outcomes of different treatment approaches for HTGP. However, further studies are required to outline a generalized and efficient treatment regimen for the management of HTGP.

[16] *Geovanini GR, Libby P*. **Atherosclerosis and inflammation: overview and updates**. Clinical science (London, England : 1979) 2018; 132:1243-1252.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29930142
ABSTRACT
The concept that inflammation participates pivotally in the pathogenesis of atherosclerosis and its complications has gained considerable attention, but has not yet entered clinical practice. Experimental work has elucidated molecular and cellular pathways of inflammation that promote atherosclerosis. The recognition of atherogenesis as an active process rather than a cholesterol storage disease or a repository of calcium has highlighted some key inflammatory mechanisms. For example, mononuclear phagocytes contribute to all stages of this disease, illustrating the link between inflammation and atherosclerosis. From a clinical perspective, harnessing inflammation may now help target therapeutics, change guidelines, and enter daily practice. Multiple lines of incontrovertible evidence have proven a causal role for low-density

lipoprotein (LDL) cholesterol in atherosclerosis, and we have highly effective tools for lowering LDL, consequently reducing events. Yet, even with intense LDL reduction, events still occur. Inflammation can explain some of this residual risk. An anti-inflammatory intervention has now proven capable of improving outcomes in individuals well treated with LDL-lowering agents. A suite of trials are now pursuing anti-inflammatory therapies in this context. Assessment and treatment of residual inflammatory risk are poised to provide new inroads into preventive cardiology. This brief review aims to explore the potential mechanisms underlying the association of inflammation and atherogenesis, and their clinical consequences.

[17] *Palmer MJ, Barnard S, Perel P, Free C*. **Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults**. The Cochrane database of systematic reviews 2018; 6:Cd012675.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29932455

ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is a major cause of disability and mortality globally. Premature fatal and non-fatal CVD is considered to be largely preventable through the control of risk factors via lifestyle modifications and preventive medication. Lipid-lowering and antihypertensive drug therapies for primary prevention are cost-effective in reducing CVD morbidity and mortality among high-risk people and are recommended by international guidelines. However, adherence to medication prescribed for the prevention of CVD can be poor. Approximately 9% of CVD cases in the EU are attributed to poor adherence to vascular medications. Low-cost, scalable interventions to improve adherence to medications for the primary prevention of CVD have potential to reduce morbidity, mortality and healthcare costs associated with CVD. OBJECTIVES: To establish the effectiveness of interventions delivered by mobile phone to improve adherence to medication prescribed for the primary prevention of CVD in adults. SEARCH METHODS: We searched CENTRAL, MEDLINE, Embase, and two other databases on 21 June 2017 and two clinical trial registries on 14 July 2017. We searched reference lists of relevant papers. We applied no language or date restrictions. SELECTION CRITERIA: We included randomised controlled trials investigating interventions delivered wholly or partly by mobile phones to improve adherence to cardiovascular medications prescribed for the primary prevention of CVD. We only included trials with a minimum of one-year follow-up in order that the outcome measures related to longer-term, sustained medication adherence behaviours and outcomes. Eligible comparators were usual care or control groups receiving no mobile phone-delivered component of the intervention. DATA COLLECTION AND ANALYSIS: We used standard methodological procedures recommended by Cochrane. We contacted study authors for disaggregated data when trials included a subset of eligible participants. MAIN RESULTS: We included four trials with 2429 randomised participants. Participants were recruited from community-based primary care or outpatient clinics in high-income (Canada, Spain) and upper- to middle-income countries (South Africa, China). The interventions received varied widely; one trial evaluated an intervention focused on blood pressure medication adherence delivered solely through short messaging service (SMS), and one intervention involved blood pressure monitoring combined with feedback delivered via smartphone. Two trials involved interventions which targeted a combination of lifestyle modifications, alongside CVD medication adherence, one of which was delivered through text messages, written

information pamphlets and self-completion cards for participants, and the other through a multi-component intervention comprising of text messages, a computerised CVD risk evaluation and face-to-face counselling. Due to heterogeneity in the nature and delivery of the interventions, we did not conduct a meta-analysis, and therefore reported results narratively.We judged the body of evidence for the effect of mobile phone-based interventions on objective outcomes (blood pressure and cholesterol) of low quality due to all included trials being at high risk of bias, and inconsistency in outcome effects. Of two trials targeting medication adherence alongside other lifestyle modifications, one reported a small beneficial intervention effect in reducing low-density lipoprotein cholesterol (mean difference (MD) -9.2 mg/dL, 95% confidence interval (CI) -17.70 to -0.70; 304 participants), and the other found no benefit (MD 0.77 mg/dL, 95% CI -4.64 to 6.18; 589 participants). One trial (1372 participants) of a text messaging-based intervention targeting adherence showed a small reduction in systolic blood pressure (SBP) for the intervention arm which delivered information-only text messages (MD -2.2 mmHg, 95% CI -4.4 to -0.04), but uncertain evidence of benefit for the second intervention arm that provided additional interactivity (MD -1.6 mmHg, 95% CI -3.7 to 0.5). One study examined the effect of blood pressure monitoring combined with smartphone messaging, and reported moderate intervention benefits on SBP and diastolic blood pressure (DBP) (SBP: MD -7.10 mmHg, 95% CI -11.61 to -2.59; DBP: -3.90 mmHg, 95% CI -6.45 to -1.35; 105 participants). There was mixed evidence from trials targeting medication adherence alongside lifestyle advice using multi-component interventions. One trial found large benefits for SBP and DBP (SBP: MD -12.45 mmHg, 95% CI -15.02 to -9.88; DBP: MD -12.23 mmHg, 95% CI -14.03 to -10.43; 589 participants), whereas the other trial demonstrated no beneficial effects on SBP or DBP (SBP: MD 0.83 mmHg, 95% CI -2.67 to 4.33; DBP: MD 1.64 mmHg, 95% CI -0.55 to 3.83; 304 participants).Two trials reported on adverse events and provided low-quality evidence that the interventions did not cause harm. One study provided low-quality evidence that there was no intervention effect on reported satisfaction with treatment.Two trials were conducted in high-income countries, and two in upper- to middle-income countries. The interventions evaluated employed between three and 16 behaviour change techniques according to coding using Michie's taxonomic method. Two trials evaluated interventions that involved potential users in their development. AUTHORS' CONCLUSIONS: There is low-quality evidence relating to the effects of mobile phone-delivered interventions to increase adherence to medication prescribed for the primary prevention of CVD; some trials reported small benefits while others found no effect. There is low-quality evidence that these interventions do not result in harm. On the basis of this review, there is currently uncertainty around the effectiveness of these interventions. We identified six ongoing trials being conducted in a range of contexts including low-income settings with potential to generate more precise estimates of the effect of primary prevention medication adherence interventions delivered by mobile phone.

[18] *Yoshida K, Guo C, Sane R*. **Quantitative prediction of OATP-mediated drug-drug interactions with model-based analysis of endogenous biomarker kinetics**. CPT: pharmacometrics & systems pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29924471
ABSTRACT

Quantitative prediction of the magnitude of transporter-mediated clinical drug-drug interactions (DDIs) solely from in vitro inhibition data remains challenging. The objective of the present work was to analyze kinetic profile of an endogenous biomarker for organic anion transporting polypeptides 1B (OATP1B), coproporphyrin I (CPI), and to predict clinical DDIs with a probe OATP1B substrate (pravastatin) based on "in vivo" inhibition constants (Ki). CPI kinetics in the presence and absence of strong and weak OATP1B inhibitors (rifampin and GDC-0810) were described well with a one-compartment model, and in vivo Ki were estimated. Clinical DDIs between pravastatin and these inhibitors were predicted using physiologically-based pharmacokinetic (PBPK) models coupled with the estimated in vivo Ki and predicted magnitude matched well with the observed DDIs. In conclusion, model-based analysis of the CPI profile has the potential to quantitatively predict liability of a new molecular entity (NME) as an OATP1B inhibitor early in drug development.

[19] *Karalis I, Jukema JW*. **HDL Mimetics Infusion and Regression of Atherosclerosis: Is It Still Considered a Valid Therapeutic Option?** Current cardiology reports 2018; 20:66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29926215
ABSTRACT
PURPOSE OF REVIEW: This review aims to summarize and discuss the recent findings in the field of using HDL mimetics for the treatment of patients with coronary artery disease. RECENT FINDINGS: Following the largely disappointing results with the cholesteryl ester transfer protein inhibitors, focus moved to HDL functionality rather than absolute HDL cholesterol values. A number of HDL/apoA-I mimicking molecules were developed, aiming to enhance reverse cholesterol transport that has been associated with an atheroprotective effect. Three HDL mimetics have made the step from bench-testing to clinical trials in humans and are discussed here: apoA-I Milano, CSL-112, and CER-001. Unfortunately, with the exception of CSL-112 where the results of the clinical trial are not yet known, none of the agents was able to demonstrate a clinical benefit. HDL mimetics have failed to date to prove a beneficial effect in clinical practice. Reverse cholesterol transport remains a challenging therapeutic pathway to be explored.

[20] *Vilahur G, Ben-Aicha S, Diaz E et al.* **Phytosterols and inflammation**. Curr Med Chem 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29932029
ABSTRACT
Besides the well-characterized effect of foods and supplements enriched with plant sterols/stanols on serum LDL-C concentrations, evidence is now emerging that phytosterols exert beneficial effects on non-lipid variables such as inflammatory and oxidative stress markers, coagulation parameters and endothelial function. This makes sterols and stanols an attractive alternative for dietary interventions in cardiovascular disease prevention, particularly in populations at low or medium risk. This review aims to summarize the current knowledge derived from experimental studies and human data on the anti-inflammatory effects of phytosterols/stanols and their relevance in promoting atheroprotection and preventing cardiovascular disease. The anti-inflammatory effects induced by plant sterols/stanols have been demonstrated in in vitro studies and in experimental animal models. However, not all the beneficial effects seen at an experimental level have translated into clinical benefit. Indeed,

clinical studies that evaluate the association between phytosterols consumption and inflammatory variables (CRP and cytokines) are inconsistent and have not yet provided a solid answer. Plant sterols have been proposed as useful adjuncts to statin therapy to further reduce the risk of cardiovascular disease. However, there is limited available data and more research needs to be done.

[21] *Burton JK, Papworth R, Haig C et al.* **Statin Use is Not Associated with Future Long-Term Care Admission: Extended Follow-Up of Two Randomised Controlled Trials**. Drugs Aging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29916140

ABSTRACT

BACKGROUND: Statins have been associated with later life, long-term care admission in observational studies. However, by preventing vascular events, statins may also prevent or delay admission. We wished to determine statin and long-term care admission associations in a randomised controlled trial context, and describe associations between long-term care admission and other clinical and demographic factors. METHODS: We used extended follow-up of two randomised trial populations, using national data to assign the long-term care admission outcome, and included individuals screened or recruited to two large randomised trials of pravastatin 40 mg daily-the West of Scotland Coronary Prevention Study (WOSCOPS) and the pravastatin in elderly individuals at risk of vascular disease (PROSPER) study. We described univariable and multivariable analyses of potential predictors of long-term care admission with corresponding survival curves of incident long-term care admission and analyses adjusted for competing risk. RESULTS: In total 11,015 (10%) of the trial participants were admitted to long-term care. There was no difference between participants in the statin or placebo arms of either trial in regard to admissions to long-term care. On multivariable analyses, independent associations with incident long-term care admission in the PROSPER trial were age (hazard ratio [HR] 1.06 per year, 95% confidence interval [CI] 1.03-1.09) and male sex (HR 0.72, 95% CI 0.53-0.99). In the WOSCOPS, age (HR 1.12 per year, 95% CI 1.10-1.13) and increasing social deprivation (HR 1.05, 95% CI 1.03-1.08) were associated with incident long-term care admission. CONCLUSION: We did not demonstrate an association between historical statin use and future long-term care admission. The strongest associations with incident long-term care admission were non-modifiable factors of age, sex and socioeconomic deprivation.

[22] *Bahar R, Wong KA, Liu CH, Bowlus CL*. **Update on New Drugs and Those in Development for the Treatment of Primary Biliary Cholangitis**. Gastroenterol Hepatol (N Y) 2018; 14:154-163.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29928160

ABSTRACT

Primary biliary cholangitis (PBC) is an autoimmune inflammatory liver disease of the interlobular bile ducts that can lead to cirrhosis and liver failure. Until recently, the only effective treatment was ursodeoxycholic acid (UDCA). However, up to 40% of PBC patients have an inadequate response to UDCA and may continue to have disease progression. Several models have been developed, including the UK-PBC and GLOBE scores, to assist in identifying patients who may benefit from second-line therapies, such as the farnesoid X receptor (FXR) agonist obeticholic acid (OCA). The addition of OCA can significantly improve serum alkaline

phosphatase and total bilirubin, which are strong surrogate markers of clinical outcomes in PBC. Other alternatives, including the peroxisome proliferator-activated receptor (PPAR)-alpha agonists fenofibrate and bezafibrate, may also improve liver biochemistries in PBC patients with an inadequate response to UDCA, but further study is needed to demonstrate their safety and long-term efficacy. Other novel agents, including those targeting the FXR pathway and PPAR-delta agonists, have shown promising results and may alter the therapeutic landscape of PBC in the near future. For now, OCA remains the only approved second-line agent for PBC patients with an inadequate response to UDCA while results of long-term studies of its safety and clinical benefit are awaited.

[23] *Ferrieres J, Lautsch D, Ambegaonkar BM et al.* **Use of guideline-recommended management in established coronary heart disease in the observational DYSIS II study**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29934227
ABSTRACT
BACKGROUND: Guidelines recommend lifestyle modification and medications to control risk factors in coronary heart disease (CHD). Using data from the observational DYSIS II study, we sought to evaluate the use of guideline-recommended treatments at discharge for acute coronary syndromes (ACS) or in the chronic phase for CHD, and participation in rehabilitation/secondary prevention programs. METHODS AND RESULTS: Between 2013 and 2014, 10,661 patients (3867 with ACS, 6794 with stable CHD) were enrolled in 332 primary and secondary care centers in 18 countries (Asia, Europe, Middle East). Patients with incident ACS were younger and more likely to be smokers than patients with recurrent ACS or stable CHD (both p<0.0001). Sedentary lifestyle was common (44.4% of ACS patients; 44.2% of stable CHD patients); 22.8% of ACS patients and 24.3% of stable CHD patients were obese. Prevalence of low high-density lipoprotein cholesterol (<40mg/dL in men/50mg/dL in women) was 46.9% in chronic CHD and 55.0% in ACS. Rates of secondary prevention medications were lower among CHD versus ACS (all p<0.0001): antiplatelet 94.3% vs 98.0%, beta-blocker 72.0% vs 80.0%, lipid-lowering therapy 94.7 vs 97.5%, and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers 69.4% vs 73.7%, respectively. Attendance at cardiac rehabilitation (16.8% of patients with a first ACS, 10.8% with recurrent ACS) or a secondary prevention program (3.7% of ACS and 11.7% of stable CHD patients) was infrequent. CONCLUSIONS: The high prevalence of risk factors in all CHD patients and reduced rates of secondary prevention medications in stable CHD offer areas for improvement. TRANSLATIONAL ASPECTS: The findings of DYSIS II may reinforce the importance of adopting a healthy lifestyle and prescribing (by clinicians) and adhering (by patients) to evidence-based medications in the management of CHD, not only during the short term but also over the longer term after a cardiac ischemic event. The results may help to increase the proportion of ACS patients who are referred to cardiac rehabilitation centres.

[24] *Fujisue K, Nagamatsu S, Shimomura H et al.* **Impact of statin-ezetimibe combination on coronary atheroma plaque in patients with and without chronic kidney disease - Sub-analysis of PRECISE-IVUS trial**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29925472

ABSTRACT
BACKGROUND: Chronic kidney disease (CKD) deteriorates the prognosis of patients undergoing percutaneous coronary intervention (PCI). Because coronary artery disease (CAD) is the major cause of death in CKD patients, cardiovascular risk reduction has been clinically important in CKD. We hypothesized intensive lipid-lowering with statin/ezetimibe attenuated coronary atherosclerotic development even in patients with CKD. METHODS: In the prospective, randomized, controlled, multicenter PRECISE-IVUS trial, 246 patients undergoing intravascular ultrasound (IVUS)-guided PCI were randomly assigned to receive atorvastatin/ezetimibe combination or atorvastatin alone (the dosage of atorvastatin was up-titrated to achieve the level of low-density lipoprotein cholesterol<70mg/dL). Serial volumetric IVUS findings obtained at baseline and 9-12month follow-up to quantify the coronary plaque response in 202 patients were compared stratified by the presence or absence of CKD. RESULTS: CKD was observed in 52 patients (26%) among 202 enrolled patients. Compared with the non-CKD group, the CKD group was significantly older (71.5+/-8.6years vs. 64.4+/-9.6years, P<0.001) with similar prevalence of comorbid coronary risk factors and lipid profiles. Similar to the non-CKD group (-1.4 [-2.8 to -0.1]% vs. -0.2 [-1.7 to 1.0]%, P=0.002), the atorvastatin/ezetimibe combination significantly reduced PAV compared with atorvastatin alone even in the CKD group (-2.6 [-5.6 to -0.4]% vs. -0.9 [-2.4 to 0.2]%, P=0.04). CONCLUSIONS: As with non-CKD, intensive lipid-lowering therapy with atorvastatin/ezetimibe demonstrated stronger coronary plaque regression effect even in patients with CKD compared with atorvastatin monotherapy. TRIAL REGISTRATION: NCT01043380 (ClinicalTrials.gov).

[25] *Larsson SC, Markus HS*. **Does Treating Vascular Risk Factors Prevent Dementia and Alzheimer's Disease? A Systematic Review and Meta-Analysis**. Journal of Alzheimer's disease : JAD 2018; 64:657-668.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29914039

ABSTRACT
BACKGROUND: Epidemiological evidence has associated Alzheimer's disease (AD) with vascular risk factors (VRFs), but whether treatment of VRFs reduces the incidence of dementia and AD is uncertain. OBJECTIVE: To conduct a systematic review and meta-analysis to summarize available data on the impact of treatment of VRFs on dementia and AD incidence. METHODS: Pertinent studies published until 1 January 2018 were identified from PubMed. Both randomized controlled trials (RCT) and prospective studies that investigated the impact of treatment of VRFs on dementia or AD incidence were included. RESULTS: Eight RCTs and 52 prospective studies were identified. Antihypertensive treatment was associated with a non-significant reduced risk of dementia in RCTs (n = 5; relative risk [RR], 0.84; 95% confidence interval [CI], 0.69-1.02) and prospective studies (n = 3; RR, 0.77; 95% CI, 0.58-1.01) and with reduced AD risk in prospective studies (n = 5; RR = 0.78; 95% CI, 0.66-0.91). In prospective studies, treatment of hyperlipidemia with statins, but not nonstatin lipid-lowering agents, was associated with reduced risk of dementia (n = 17; RR, 0.77; 95% CI, 0.63-0.95) and AD (n = 13; RR, 0.86; 95% CI, 0.80-0.92). The single RCT on statins and dementia incidence showed no association. Data from one RCT and six prospective studies did not support a beneficial impact of antidiabetic drugs or insulin therapy on dementia risk. CONCLUSION: Current evidence

indicates that antihypertensives and statins might reduce the incidence of dementia and AD. Further trials to determine the effect of VRF on AD are needed.

[26] *Handelsman Y, Lepor NE*. **PCSK9 Inhibitors in Lipid Management of Patients With Diabetes Mellitus and High Cardiovascular Risk: A Review**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29934421
ABSTRACT

[27] *De Ferrari GM, Perna GP, Nicosia A et al.* **Available oral lipid-lowering agents could bring most high-risk patients to target: an estimate based on the Dyslipidemia International Study II-Italy**. Journal of cardiovascular medicine (Hagerstown, Md.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29917002
ABSTRACT
AIMS: The analysis evaluated the contemporary percentage of patients with established coronary heart disease (CHD) reaching the European guidelines recommended LDL-cholesterol (LDL-C) levels of less than 70 mg/dl and the threshold required for proprotein convertase subtlisin/kexin type 9 reimbursement in Italy (100 mg/dl). It also assessed how these percentages would change in case of diffuse use of ezetimibe. METHODS: The Dyslipidemia International Study II enrolled CHD patients aged at least 18 either on lipid-lowering therapy (LLT) for at least 3 months or not on LLT at the time of the lipid profile. Distribution of LLTs and LDL-C target attainment were assessed. Multivariate logistic regression evaluated predictors of LDL-C target attainment. A 24% LDL-C lowering was modeled in patients not taking ezetimibe to assess its potential effects. RESULTS: Among 676 Italian CHD patients enrolled, LDL-C concentrations were lower among the 631 patients (93.3%) who were on LLT (82 versus 118 mg/dl; $P < 0.001$). The LDL-C target was attained by 35.4% of patients. Statin dose (median atorvastatin dose 40 mg/day) was the sole significant predictor of LDL-C target attainment. The simple addition of ezetimibe in the model reduced the percentage of patients more than 70 and 100 mg/dl from 64.6 to 37.9% and from 25.1 to 11.8%, respectively. CONCLUSION: Despite treatment in more than 90%, only one-third of Italian stable CHD patients attained the recommended LDL-C target. Statin dose was the sole predictor of the target achievement. The addition of ezetimibe would almost double patients at target and halve the potential candidates for reimbursement of more expensive agents such as proprotein convertase subtlisin/kexin type 9 inhibitors.

[28] *Hartgers ML, Besseling J, Stroes ES et al.* **Achieved LDL cholesterol levels in patients with heterozygous familial hypercholesterolemia: A model that explores the efficacy of conventional and novel lipid-lowering therapy**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29934068
ABSTRACT
BACKGROUND: A large proportion of patients with heterozygous familial hypercholesterolemia (heFH) do not reach low-density lipoprotein cholesterol (LDL-c) levels advocated by international guidelines (<70 mg/dL or <100 mg/dL). OBJECTIVE: We set out to model which proportion of patients reach targets using conventional and novel therapies. METHODS: We

performed a cross-sectional analysis in a large cohort of genetically identified heFH patients and calculated the proportion reaching treatment targets in four scenarios: (1) after 50% LDL-c reduction (representing maximal dose statin); (2) after 70% LDL-c reduction (maximal dose statin + ezetimibe); (3) additional 40% LDL-c reduction representing cholesteryl ester transfer protein inhibitor (CETPi); and (4) 60% LDL-c reduction (proprotein convertase subtilisin/kexin type 9 inhibitors [PCSK9i]), on top of scenario 2. We applied 100% adherence rates and literature-based adherence rates from 62% to 80%. RESULTS: We included 1,059 heFH patients with and 9,420 heFH patients without coronary heart disease (CHD). With maximal dose statin, 8.3% and 48.1% of patients with and without CHD would reach their recommended LDL-c targets, respectively. This increases to 54.3% and 93.2% when ezetimibe is added. Addition of CETPi increases these numbers to 95.7% and 99.7%, whereas adding PCSK9i would result in 99.8% and 100% goal attainment. Using literature-based adherence rates, these numbers decrease to 3.8% and 27.3% for maximal dose statin, 5.8% and 38.9% combined with ezetimibe, 31.4% and 81.2% when adding CETPi, and 40.3% and 87.1% for addition of PCSK9i. CONCLUSIONS: Less than 10% with and 50% of heFH patients without CHD would reach treatment targets with maximal dose statin, but this substantially increases on addition of ezetimibe, CETPi, or PCSK9i. However, considering recently published adherence data, this might be lower in real life, especially in heFH patients with CHD.

[29] *Paquette M, Hegele RA, Baass A*. **PCSK9 inhibitors in familial hypercholesterolemia: What is the evidence?** Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29909976
ABSTRACT

[30] *Lanzolla G, Sabini E, Profilo MA et al.* **Relationship between serum cholesterol and Graves' orbitopathy (GO): a confirmatory study**. Journal of endocrinological investigation 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29923059
ABSTRACT
BACKGROUND: It has been suggested that high cholesterol represents a risk factor for Graves' orbitopathy (GO). In a recent cross-sectional study, a correlation between cholesterol and the presence of GO was found in patients with a Graves' disease (GD) of recent onset. To confirm this observation, we conducted a retrospective investigation in consecutive patients with GD. The primary outcome was the relationship between the presence of GO and low-density lipoprotein (LDL)-cholesterol. METHODS: The design entailed the inclusion of consecutive patients with a GD of recent onset, with or without GO, who came to our observation to receive radioiodine over a period of 6 months, and a stratification aimed at having two homogeneous group of patients in terms of thyroid function. A total of 86 patients fulfilled the inclusion and evaded the exclusion criteria. All patients underwent an ophthalmological assessment and serum lipids were measured. RESULTS: Serum levels of LDL-cholesterol were significantly higher in patients with GO (135.3 +/- 41.3 mg/dL) compared with those without GO (106.6 +/- 23.9 mg/dL, P = 0.0007). In a similar manner, serum levels of total cholesterol were higher in patients with GO (211.6 +/- 44.0 mg/dL) than in those without GO (176.0 +/- 27.2 mg/dL, P = 0.0001). There was no relationship between GO severity and activity and cholesterol. There was no relationship between GO and high-density lipoprotein-cholesterol or triglycerides.

CONCLUSIONS: Our study confirms a relationship between the presence of GO and cholesterol in patients with GD of recent onset. Whether lowering of cholesterol ameliorates, GO remains to be established.

[31] *Jiang B, He D, Zhang L, Ye M*. **Risk prediction of cerebrovascular events with carotid plaque magneitc resonance analysis: a meta-analysis**. Journal of neuroradiology. Journal de neuroradiologie 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29920350
ABSTRACT
BACKGROUND AND PURPOSE: It is not conclusive that magnetic resonance (MR)-based carotid atherosclerotic plaque assessment identifies high-risk features associated with cerebrovascular events. We aimed to systematically summarize the association of MR imaging (MRI)-determined intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), and thinning/rupture of the fibrous cap (TRFC) with subsequent ischemic events. MATERIALS AND METHODS: We performed a comprehensive literature search evaluating the association of MRI-based carotid plaque composition with ischemic outcomes. We included cohort studies examining IPH, LRNC, or TRFC with mean follow-up of >/=6 months and an outcome measure of ipsilateral ischemic events. A meta-analysis was done according to the Cochrane guideline. RESULTS: We identified 13 studies including 1,150 patients and 1,208 analyzed carotid arteries, with mean follow-up of 21.1 months. The hazard ratios (HR) for IPH, LRNC, and TRFC as predictors of subsequent ischemic events were 4.41 (95% CI: 2.87, 6.79), 3.00 (95% CI: 1.51, 5.95), and 5.94 (95% CI: 2.66, 13.28), respectively. The predictive value of carotid plaque MRI for ischemic events was acceptable, with sensitivity of 0.80 (95% CI: 0.66, 0.90) and specificity of 0.63 (95% CI: 0.57, 0.68). However, it was limited to confirm or exclude future ischemic events in clinical context, with positive likelihood ratio (LR) of 2.2 (95% CI: 1.9, 2.5) and negative LR of 0.31 (95% CI: 0.18, 0.55). No statistically significant heterogeneity or publication bias was observed. CONCLUSION: The presence of IPH, LRNC, and TRFC determined by MRI is associated with increased risk of future ischemic events, but its predictive value is moderate and should not be used for confirmation or exclusion of future ischemic events in clinical context.

[32] *Daray FM, Mann JJ, Sublette ME*. **How lipids may affect risk for suicidal behavior**. Journal of psychiatric research 2018; 104:16-23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29920417
ABSTRACT
Suicide and nonfatal suicidal behaviors are major causes of mortality and morbidity worldwide. Variability in rates of suicide and suicidal behaviors within and between countries has been attributed to population and individual risk factors, including economic status and cultural differences, both of which can have suicide risk effects mediated through a variety of factors, of which perhaps the least understood is the role of diet. We therefore review the scientific literature concerning two major dietary lipid classes, cholesterol and polyunsaturated fatty acids (PUFAs), that have been associated with higher risk of suicide attempts and suicide. We consider potential mechanistic intermediates including serotonin transporters and receptors, toll-like receptors (TLRs), nuclear factor kappa-light-chain-enhancer of activated B cells (NFkappaB), and peroxisome proliferator activated receptors (PPARs). Based on this review, we

describe a theoretical model linking cholesterol and PUFA status to suicide risk, taking into account the effects of cholesterol-lowering interventions on PUFA balance, membrane lipid microdomains (rafts) as a nexus of interaction between cholesterol and omega-3 PUFAs, and downstream effects on serotonergic neurotransmission and specific inflammatory pathways.

[33] *Lee SE, Chang HJ, Sung JM et al.* **Effects of Statins on Coronary Atherosclerotic Plaques: The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) Study**. JACC. Cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29909109
ABSTRACT
OBJECTIVES: This study sought to describe the impact of statins on individual coronary atherosclerotic plaques. BACKGROUND: Although statins reduce the risk of major adverse cardiovascular events, their long-term effects on coronary atherosclerosis remain unclear. METHODS: We performed a prospective, multinational study consisting of a registry of consecutive patients without history of coronary artery disease who underwent serial coronary computed tomography angiography at an interscan interval of >/=2 years. Atherosclerotic plaques were quantitatively analyzed for percent diameter stenosis (%DS), percent atheroma volume (PAV), plaque composition, and presence of high-risk plaque (HRP), defined by the presence of >/=2 features of low-attenuation plaque, positive arterial remodeling, or spotty calcifications. RESULTS: Among 1,255 patients (60 +/- 9 years of age; 57% men), 1,079 coronary artery lesions were evaluated in statin-naive patients (n = 474), and 2,496 coronary artery lesions were evaluated in statin-taking patients (n = 781). Compared with lesions in statin-naive patients, those in statin-taking patients displayed a slower rate of overall PAV progression (1.76 +/- 2.40% per year vs. 2.04 +/- 2.37% per year, respectively; p = 0.002) but more rapid progression of calcified PAV (1.27 +/- 1.54% per year vs. 0.98 +/- 1.27% per year, respectively; p < 0.001). Progression of noncalcified PAV and annual incidence of new HRP features were lower in lesions in statin-taking patients (0.49 +/- 2.39% per year vs. 1.06 +/- 2.42% per year and 0.9% per year vs. 1.6% per year, respectively; all p < 0.001). The rates of progression to >50%DS were not different (1.0% vs. 1.4%, respectively; p > 0.05). Statins were associated with a 21% reduction in annualized total PAV progression above the median and 35% reduction in HRP development. CONCLUSIONS: Statins were associated with slower progression of overall coronary atherosclerosis volume, with increased plaque calcification and reduction of high-risk plaque features. Statins did not affect the progression of percentage of stenosis severity of coronary artery lesions but induced phenotypic plaque transformation. (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging [PARADIGM]; NCT02803411.).

[34] *Burgess S, Ference BA, Staley JR et al.* **Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis**. JAMA cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29926099
ABSTRACT
Importance: Human genetic studies have indicated that plasma lipoprotein(a) (Lp[a]) is causally associated with the risk of coronary heart disease (CHD), but randomized trials of several

therapies that reduce Lp(a) levels by 25% to 35% have not provided any evidence that lowering Lp(a) level reduces CHD risk. Objective: To estimate the magnitude of the change in plasma Lp(a) levels needed to have the same evidence of an association with CHD risk as a 38.67-mg/dL (ie, 1-mmol/L) change in low-density lipoprotein cholesterol (LDL-C) level, a change that has been shown to produce a clinically meaningful reduction in the risk of CHD. Design, Setting, and Participants: A mendelian randomization analysis was conducted using individual participant data from 5 studies and with external validation using summarized data from 48 studies. Population-based prospective cohort and case-control studies featured 20793 individuals with CHD and 27540 controls with individual participant data, whereas summarized data included 62240 patients with CHD and 127299 controls. Data were analyzed from November 2016 to March 2018. Exposures: Genetic LPA score and plasma Lp(a) mass concentration. Main Outcomes and Measures: Coronary heart disease. Results: Of the included study participants, 53% were men, all were of white European ancestry, and the mean age was 57.5 years. The association of genetically predicted Lp(a) with CHD risk was linearly proportional to the absolute change in Lp(a) concentration. A 10-mg/dL lower genetically predicted Lp(a) concentration was associated with a 5.8% lower CHD risk (odds ratio [OR], 0.942; 95% CI, 0.933-0.951; P = 3 x 10-37), whereas a 10-mg/dL lower genetically predicted LDL-C level estimated using an LDL-C genetic score was associated with a 14.5% lower CHD risk (OR, 0.855; 95% CI, 0.818-0.893; P = 2 x 10-12). Thus, a 101.5-mg/dL change (95% CI, 71.0-137.0) in Lp(a) concentration had the same association with CHD risk as a 38.67-mg/dL change in LDL-C level. The association of genetically predicted Lp(a) concentration with CHD risk appeared to be independent of changes in LDL-C level owing to genetic variants that mimic the relationship of statins, PCSK9 inhibitors, and ezetimibe with CHD risk. Conclusions and Relevance: The clinical benefit of lowering Lp(a) is likely to be proportional to the absolute reduction in Lp(a) concentration. Large absolute reductions in Lp(a) of approximately 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of CHD similar in magnitude to what can be achieved by lowering LDL-C level by 38.67 mg/dL (ie, 1 mmol/L).

[35] *Toure PS, Leye YM, Diop MM et al.* **[Thrombocytopenia purpura, myositis and cytolitic hepatitis: a rare association linked with atorvastatin]**. Le Mali medical 2013; 28:49-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29925222

ABSTRACT

Statins are generally well tolerated molecules. However, some cases have seen potentially lifethreatening consequences. We report a case of a 70-year-old woman with high blood pressure who was treating hypercholesterolemia by atorvastatin. Two weeks after beginning this new treatment, the patient developed muscular weakness in all four limbs with myalgias; and a purpura in the upper limbs and abdomen. A biological study revealed the presence of severe thrombocytopenia, myolysis and cytolytic hepatitis. Stopping the atorvastatin intake resulted in an improved situation within twenty days. This suggests that the medical anomalies found in the patient were drug-induced. The literature confirms the rarity of this association. The severity of some side effects of statins should remain in the minds of medicine prescribers.

[36] *Calabria B, Korda RJ, Lovett RW et al.* **Absolute cardiovascular disease risk and lipid-lowering therapy among Aboriginal and Torres Strait Islander Australians**. The Medical journal of Australia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29929455
ABSTRACT
OBJECTIVE: To quantify absolute cardiovascular disease (CVD) risk in Aboriginal and Torres Strait Islander people and their use of lipid-lowering therapies. DESIGN, PARTICIPANTS: Cross-sectional analysis of nationally representative data from 2820 participants aged 18-74 years who provided biomedical data for the National Aboriginal and Torres Strait Islander Health Measures Survey component of the 2012-13 Australian Aboriginal and Torres Strait Islander Health Survey. MAIN OUTCOME MEASURES: Prior CVD and use of lipid-lowering medications were ascertained at interview. 5-year absolute risk of a primary CVD event was calculated with the Australian National Vascular Disease Prevention Alliance algorithm, with categories low (< 10%), moderate (10-15%) and high risk (> 15%). RESULTS: Among participants aged 35-74 years, 9.6% (95% CI, 7.2-12.0%) had prior CVD; 15.7% (95% CI, 13.0-18.3%) were at high, 4.9% (95% CI, 3.3-6.6%) at moderate, and 69.8% (95% CI, 66.8-72.8%) at low absolute primary CVD risk. 82.6% of those at high primary risk were identified on the basis of clinical criteria. High primary absolute risk affected 1.1% (95% CI, 0.0-2.5%) of 18-24-year-olds, 4.7% (95% CI, 2.0-7.5%) of 25-34-year-olds, and 44.2% (95% CI, 33.1-55.3%) of 65-74-year-olds. Lipid-lowering therapy was being used by 52.9% (95% CI, 38.2-67.6%) of people aged 35-74 years with prior CVD and by 42.2% (95% CI, 30.5-53.8%) of those at high primary CVD risk. CONCLUSION: Absolute CVD risk is high among Aboriginal and Torres Strait Islander people, and most of those at high risk are undertreated. Substantial proportions of people under 35 years of age are at high risk, but are not targeted by current guidelines for absolute CVD risk assessment, compromising CVD prevention in this population.

[37] **Pitavastatin magnesium (Zypitamag) for hyperlipidemia**. The Medical letter on drugs and therapeutics 2018; 60:106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29913475
ABSTRACT

[38] *Ferronato S, Scuro A, Gomez-Lira M et al.* **Correlations between gene expression highlight a different activation of ACE/TLR4/PTGS2 signaling in symptomatic and asymptomatic plaques in atherosclerotic patients**. Molecular biology reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29923152
ABSTRACT
Inflammation has a key role and translates the effects of many known risk factors for the disease in atherosclerotic vulnerable plaques. Aiming to look into the elements that induce the development of either a vulnerable or stable atherosclerotic plaque, and considering that inflammation has a central role in the progression of lesions, we analyzed the expression of genes involved in the ACE/TLR4/PTGS2 signaling in carotid plaques of symptomatic and asymptomatic patients. Patients with internal carotid artery stenosis undergoing carotid endarterectomy at Verona University Hospital were included in this study. A total of 71 patients was considered for gene expression analysis (29 atherothrombotic stroke patients and 42

asymptomatic patients). Total RNA was extracted from the excised plaques and expression of PTGS2, ACE, TLR4, PTGER4, PTGER3, EPRAP and ACSL4 genes was analyzed by real-time PCR. The correlation between the pair of genes was studied by Spearman coefficient. From the analyzed genes, we did not observe any individual difference in gene expression but the network of co-expressed genes suggests a different activation of pathways in the two groups of plaques.

[39] *Nakashima Y, Miyagi-Shiohira C, Noguchi H, Omasa T*. **Atorvastatin Inhibits the HIF1alpha-PPAR Axis, Which Is Essential for Maintaining the Function of Human Induced Pluripotent Stem Cells**. Molecular therapy : the journal of the American Society of Gene Therapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29929789
ABSTRACT
We herein report a novel mechanism of action of statin preparations using a new drug discovery method. Milk fat globule-EGF factor 8 protein (MFG-E8) was identified from the secretory component of mouse embryonic fibroblast (MEF) as a cell adhesion-promoting factor effective for screening active cellular agents of human induced pluripotent stem cells (hiPSCs) in vitro using electrochemical impedance. Our analyses showed that atorvastatin did not cause death in myocardial cells differentiated from hiPSCs but reduced the pluripotent cell survival in vitro when using serum- and albumin-free media, and inhibited the ability to form teratomas in mice. This result could have been already the cytopathic effect of atorvastatin, and complete elimination of hiPSCs was confirmed in the xenotransplantation assay. The administration of atorvastatin to hiPSCs caused the expression of hypoxia inducible factor (HIF)1alpha mRNA to be unchanged at 6 hr and downregulated at 24 hr. In addition, the inhibition of the survival of hiPSCs was confirmed by HIF1alpha-peroxisome proliferator-activated receptor (PPAR) axis inhibition. These results suggest that the addition of atorvastatin to hiPSC cultures reduces the survival of pluripotent cells by suppressing the HIF1alpha-PPAR axis. In summary, the HIF1alpha-PPAR axis has an important role in maintaining the survival of pluripotent hiPSCs.

[40] *Wang HY, Peng HC, Chien YW et al.* **Effects of Fish Oil on Lipid Metabolism and Its Molecular Biological Regulators in Chronic Ethanol-Fed Rats**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29932129
ABSTRACT
The purpose of this study was to clarify the hepatoprotective mechanisms of fish oil in ethanol-fed rats based on lipid metabolism. Thirty eight-week-old male Wistar rats were divided into six groups: C (control), CF25 (control diet with 25% fish oil substitution), CF57 (control diet with 57% fish oil substitution), E (ethanol-containing diet) group, EF25 (ethanol-containing diet with 25% fish oil substitution), and EF57 (ethanol-containing diet with 57% fish oil substitution) groups. All of the groups were pair-fed an isoenergetic diet based on E group. Rats were sacrificed after eight weeks. When compared with C group, the plasma aspartate transaminase (AST) activity and hepatic steatosis and inflammatory cell infiltration were significantly higher, while plasma adiponectin level and hepatic AMP-activated protein kinase α (AMPKα) protein expression was significantly lower in the E group. However, the hepatic damage, including steatosis and inflammation were ameliorated in the EF25 and EF57 groups. Moreover, mRNA levels of fatty acid-oxidative enzymes, such as medium-chain acyl-coenzyme

A dehydrogenase (MCAD) and carnitine palmitoyltransferase I (CPT-1) were significantly elevated in the EF57 group than those in E group. Partial replacement with fish oil might improve the fatty acid oxidation by raising mRNA levels of downstream transcription factors, finally inhibit the ethanol-induced hepatic steatosis in rats.

[41] *Blom DJ, Cuchel M, Ager M, Phillips H*. **Target achievement and cardiovascular event rates with Lomitapide in homozygous Familial Hypercholesterolaemia**. Orphanet journal of rare diseases 2018; 13:96.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29925433
ABSTRACT
BACKGROUND: Homozygous familial hypercholesterolaemia (HoFH) is characterized by a markedly increased risk of premature cardiovascular (CV) events and cardiac death. Lomitapide reduces low-density lipoprotein cholesterol (LDL-C) levels; however, the probable impact on LDL-C goals and CV events is unknown. METHODS: We used data collected in the first 26 weeks of the lomitapide pivotal phase 3 study (NCT00730236) to evaluate achievement of European Atherosclerosis Society (EAS) LDL-C targets. We used publicly available data reporting major adverse CV events (MACE) rates from other cohorts of HoFH patients to compare event rates for an equivalent number of patient years of exposure (98) in the lomitapide extension trial (NCT00943306). RESULTS: Twenty-nine patients were included in the phase 3 study. During the first 26 weeks, 15 (51%) and eight (28%) reached LDL-C targets of 100 mg/dL and 70 mg/dL, respectively, at least once. Fourteen (74%) and 11 (58%) of the 19 patients who remained in the extension study after week 126 reached LDL-C targets of 100 mg/dL and 70 mg/dL at least once during the entire study period. Only two MACE were reported in the lomitapide trials (one cardiac death and one coronary artery bypass graft (CABG)) - equivalent to 1.7 events per 1000 patient months of treatment. MACE rates were 21.7, 9.5 and 1.8 per 1000 patient-months respectively in cohorts of HoFH patients pre- and post-mipomersen, and receiving evolocumab. On treatment LDL-C levels were 166, 331 and 286 mg/dL for lomitapide, mipomersen and evolocumab, respectively. CONCLUSIONS: Approximately three quarters and half of patients who took lomitapide for at least 2 years reached LDL-C goals of 100 mg/dL and 70 mg/dL, respectively. There were fewer major CV events per 1000 patient months of treatment in patients taking lomitapide, mipomersen or evolocumab than reported in the mipomersen cohort prior to starting mipomersen. These results support the hypothesis that novel lipid-lowering therapies may reduce CV events in HoFH patients by lowering LDL-C further. TRIAL REGISTRATION: NCT00730236 (registered 8 Aug 2008) and NCT00943306 (registered 22 July 2009).

[42] *Feitosa MF, Kraja AT, Chasman DI et al.* **Novel genetic associations for blood pressure identified via gene-alcohol interaction in up to 570K individuals across multiple ancestries**. PloS one 2018; 13:e0198166.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29912962
ABSTRACT
Heavy alcohol consumption is an established risk factor for hypertension; the mechanism by which alcohol consumption impact blood pressure (BP) regulation remains unknown. We hypothesized that a genome-wide association study accounting for gene-alcohol consumption

interaction for BP might identify additional BP loci and contribute to the understanding of alcohol-related BP regulation. We conducted a large two-stage investigation incorporating joint testing of main genetic effects and single nucleotide variant (SNV)-alcohol consumption interactions. In Stage 1, genome-wide discovery meta-analyses in approximately 131K individuals across several ancestry groups yielded 3,514 SNVs (245 loci) with suggestive evidence of association (P < 1.0 x 10-5). In Stage 2, these SNVs were tested for independent external replication in approximately 440K individuals across multiple ancestries. We identified and replicated (at Bonferroni correction threshold) five novel BP loci (380 SNVs in 21 genes) and 49 previously reported BP loci (2,159 SNVs in 109 genes) in European ancestry, and in multi-ancestry meta-analyses (P < 5.0 x 10-8). For African ancestry samples, we detected 18 potentially novel BP loci (P < 5.0 x 10-8) in Stage 1 that warrant further replication. Additionally, correlated meta-analysis identified eight novel BP loci (11 genes). Several genes in these loci (e.g., PINX1, GATA4, BLK, FTO and GABBR2) have been previously reported to be associated with alcohol consumption. These findings provide insights into the role of alcohol consumption in the genetic architecture of hypertension.

[43] *Perrotta P, Veseli BE, Van der Veken B et al.* **Pharmacological strategies to inhibit intra-plaque angiogenesis in atherosclerosis**. Vascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29933080
ABSTRACT
Atherosclerosis is a complex multifactorial disease that affects large and medium-sized arteries. Rupture of atherosclerotic plaques and subsequent acute cardiovascular complications remain a leading cause of death and morbidity in the Western world. There is a considerable difference in safety profile between a stable and a vulnerable, rupture-prone lesion. The need for plaque-stabilizing therapies is high, and for a long time the lack of a suitable animal model mimicking advanced human atherosclerotic plaques made it very difficult to make progress in this area. Evidence from human plaques indicates that intra-plaque (IP) angiogenesis promotes atherosclerosis and plaque destabilization. Although neovascularization has been widely investigated in cancer, studies on the pharmacological inhibition of this phenomenon in atherosclerosis are scarce, mainly due to the lack of an appropriate animal model. By using ApoE(-/-) Fbn1(C1039G+/-) mice, a novel model of vulnerable plaques, we were able to investigate the effect of pharmacological inhibition of various mechanisms of IP angiogenesis on plaque destabilization and atherogenesis. In the present review, we discuss the following potential pharmacological strategies to inhibit IP angiogenesis: (1) inhibition of vascular endothelial growth factor signalling, (2) inhibition of glycolytic flux, and (3) inhibition of fatty acid oxidation. On the long run, IP neovascularization might be applicable as a therapeutic target to induce plaque stabilization on top of lipid-lowering treatment.

[44] *Tang R, Shi J, Li X et al.* **Effects of Atorvastatin on Surgical Treatments of Chronic Subdural Hematoma**. World neurosurgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29920396
ABSTRACT
OBJECTIVE: To investigate the effects of atorvastatin on the surgical treatment of patients with chronic subdural hematoma (CSDH). METHODS: Our retrospective study included 245

consecutive adult patients undergoing burr hole craniotomy of CSDH. Data included baseline characteristics and recurrence, postoperative complications, and mortality. A univariate and multivariate regression model analyzed the association between administration of atorvastatin perioperatively and recurrence rates. RESULTS: Multivariate analysis showed perioperative atorvastatin administration (odds ratio [OR]0.336; P = 0.039), diabetes mellitus (OR 3.949, P = 0.010) and GCS of 15 preoperatively (OR 0.197; P = 0.020) to be significantly related to recurrence risk. Postoperative complications and mortality did not significantly differ between patients with or without atorvastatin therapy. CONCLUSION: Our findings demonstrate that the administration of atorvastatin perioperatively is associated with a lower risk of CSDH recurrence rate. The use of atorvastatin perioperatively was not associated with higher rates of morbidity or mortality.

[45] *Li LL, Ai JC, Li HY et al.* **[Impact of a noval PPARdelta agonist on blood lipids in hyperlipidemic golden hamsters]**. Yao xue xue bao = Acta pharmaceutica Sinica 2017; 52:86-90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29911782

ABSTRACT

The study was designed to explore the effects of HS060098 on activation of peroxisome proliferator-activated receptors (PPARalpha, gamma and delta) and in the down-regulation of hyperlipidemia in golden hamster. Luciferase gene reporters of PPARalpha, PPARgamma and PPARdelta were constructed in HepG2 cells and the green fluorescent protein (GFP) was used as an internal reference. Transfected cells were then cultured with various concentrations of HS060098 for 24 h. The peroxisome proliferator-response element luciferase activity was determined by the dual-luciferase reporter gene assay system. To investigate the lipid-lowering effect of HS060098, hyperlipidemic golden hamsters fed by high-diet were administered orally with HS060098 through prophylactic and therapeutic approaches respectively. The levels of blood lipids such as total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and fat index in hamsters were evaluated. The results showed that HS060098 was a potent activator of PPARdelta with a good selectivity and the median effective concentration (EC(50)) is 0.01 mumol.L(-1), while no obvious PPARalpha and PPARgamma activation was observed. In the golden hamster, oral administration of HS060098 (5, 10, 20 mg.kg(-1).d(-1)) for 2 weeks, led to a significant decrease the concentrations of plasma TC, TG, LDL-C and fat index ($P < 0.05$ or $P < 0.01$), whereas the contents of plasma HDL-C were increased significantly ($P < 0.05$ or $P < 0.01$). The data suggest that HS060098 is a novel PPARdelta agonist with a significant activity in the prevention and therapy of hyperlipemia in golden hamster.

[46] *Du RX, Ye P, Yan GT et al.* **[The effect of rosuvastatin therapy on CCR2 expression in mononuclear cells and its upstream pathway]**. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology 2016; 32:202-206.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29931877

ABSTRACT

OBJECTIVE: To investigate the effect of rosuvastatin therapy on C-C chemokine receptor(CCR2)expression in mononuclear cells in patients with carotid atherosclerosis and explore the possible upstream mechanism. METHODS: Twenty patients without previous statin

treatment were enrolled. Rosuvastatin were given 5 to 20 mg/day for 3 months. At baseline and 12 weeks, lipid profile and plasma monocyte chemotactic protein-1 (MCP-1) levels were examined. The mRNA and protein expressions of CCR2 in the mononuclear cells were measured with RT-PCR and flow cytometry, respectively. The mRNA and protein expression of peroxidase proliferator-activated receptor(PPAR beta) were detected with RT-PCR and Western blot, respectively. RESULTS: After 3-months rosuvastatin treatment, the patients' low-density lipoprotein cholesterol (LDL-C) levels decreased significantly (P<0.01). Compared with baseline, the mRNA and protein expressions of CCR2 in the mononuclear cells showed significantly decrease, as well as plasma MCP-1 levels (P<0.05). Both mRNA and protein expressions of PPAR beta in the mononuclear cells increased (P<0.05). CONCLUSIONS: Rosuvastatin may attenuate MCP-1/CCR2 through PPARbeta upstream pathway.

[47] *Hao WJ, Ke SZ, Liu L et al.* **[The experimental study of simvastatin on improving aspirin resistance in diabetic rats]**. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology 2016; 32:395-400.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29931841

ABSTRACT

OBJECTIVE: The purpose of the present study was to investigate the effects of the combination of aspirin, simvastatin in diabetic rat on platelet function. METHODS: Eight-week-old male Wistar rats were selected and randomly divided into diabetic group (n=48) and normal control group (n=48). Diabetic rats were injected with 1% STZ (65mg/kg, dissolved in 0.l mmol/L, pH 4.5 citrate buffer) to induce diabetic model and the rats in normal control group were injected with the same dose of citrate buffer. A rat with blood glucose greater than 16.8 mmol/L and along with diabetic symptoms of polydipsia, polyuria and weight loss was considered the successful model of diabetes. Diabetic rats and normal Wistar rats were randomly divided into 4 groups and given aspirin(10 mg/kg), simvastatin(2 mg/kg), combination of aspirin(10mg/kg) and simvastatin(2 mg/kg), PBS for 8 weeks, respectively. The platelet function and the expression of CD62P were evaluated. The levels of nitric oxide (NO), endothelin (ET), thromboxane B2(TXB2), prostacyclin (PGI2), adiponectin (APN), TXB2 were detected in the serum. The expressions of heme oxygenase-1(HO-1), HO-2, endothelial nitric oxide synthase(e-NOS), p-eNOS, B-cell lymphoma-2(Bcl-2), cyclooxygenase-2(COX-2) in thoracic aorta were evaluated by Western blot. RESULTS: Compared with control rats, diabetic rats had high platelet aggregation and activation (P<0.05), which treated aspirin also showed lower aspirin sensitivity (P<0.05). The combination of drugs upregulated the expression of HO-1, eNOS, p-eNOS, BCL-2, APN levels and decreased the expression of COX-2, and had a greater inhibitory effect on platelet aggregation and activation. The combination of drugs improved endothelial function, adjusted TXA2/PGI2 levels and increased NO levels, which resulted in a great potential antiplatelet effect. CONCLUSIONS: These results suggest that simvastatin may improvethe effect of aspirin on anti-platelet function in diabetic rats.

[48] *Wang XT, Chen SS, Qi MY*. **[Effects of ursolic acid on liver injury and its possible mechanism in diabetes mellitus mice]**. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology 2018; 34:134-136.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29926677

ABSTRACT
OBJECTIVES: To study the effects of ursolic acid on liver injury in diabetic mice induced by high-fat diet combined with streptozotocin(STZ), and to explore its possible mechanisms. METHODS: Diabetes mellitus was induced in twenty male ICR mice by a combination of high-fat diet for 6 weeks with low-dose streptozotocin (30 mg/kg, i. p.) for 5 consecutive days. After 9 days, fasting blood glucose levels were determined. Mice with fasting blood glucose levels exceeded 11. 1 mmol/L were diagnosed as diabetic mice and selected for further experiment. These mice were randomly divided into two groups(each group of 10):diabetic group, ursolic acid group (100 mg/kg, i. g.), and another 10 mice were set as control group. After continuous administration for 8 weeks, body weight (BW) were weighed, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), aspartate transaminase (AST) in serum and superoxide dismutase (SOD), malondialdehyde (MDA) in liver were measured. HE staining was used to observe pathological changes of liver tissue. RESULTS: Compared with the control group, the level of FBG, TC, TG, ALT, AST, MDA were dramatically increased (P<0. 05, P<0. 01) and SOD was markedly decreased (P<0.01) in the diabetic group; HE staining showed that parts of liver cells swelled and had a light fatty degeneration as well as lymphocyte infiltrated around the portal area in model group. Compared with the diabetic group, the level of FBG, TC, TG, ALT, AST, MDA were significantly declined (P<0.05, P<0.01) and SOD was considerably increased (P<0.01) in the ursolic acid group; HE staining showed that the liver cells relatively arranged in order, edema was not obvious and inflammatory cells infiltrated lightly in the ursolic acid group. CONCLUSIONS: Ursolic acid has a protective effect on liver injury in diabetic mice induced by high-fat diet combined with STZ by intraperitoneal ingector, and its mechanism may be associated with lowering blood glucose, regulating the lipid metabolism, reducing oxidative stress and enhancing the ability of anti-oxidation in liver.

[49] *Zhang Y, Wang TT, Guo SL et al.* **[Current status of blood pressure control in patients with coronary heart disease]**. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology 2018; 34:23-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29926654

ABSTRACT
OBJECTIVE: To evaluate the level of blood pressure control in patients with coronary heart disease (CHD) of China in order to provide guidance for the prevention and treatment of CHD. METHODS: The patients with CHD were retrospectively collected from 2011~2014 in PLA General Hospital and Hainan Branch Hospital. Then analyzed the difference of blood pressure compliance rate between different surgical methods percutaneous coronary intervention (PCI), coronary artery bypass grafting(CABG), secondary preventive drugs(aspirin, clopidogrel, nitrates, trimetazidine, nicorandil, hypotensor, hypoglycemic, lipid-lowering drugs) and lifestyle(smoking, drinking, exercise). RESULTS: 1 in circleEffects of surgical methods on blood pressure:Male's systolic blood pressure (SBP) and diastolic blood pressure(DBP) in the CABG group were lower in the PCI group and control group, and female's DBP in the CABG group were lower in the PCI group. 2 in circleUsage rate of secondary prevention drugs:usage rate of trimetazidine, calcium antagonist, beta-blockers, angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor antagonist (ARB) in hypertension group were higher than in normal blood pressure group. 3 in circle Lifestyle condition:compliance rate of blood pressure

in the smoking group was lower than that in the non smoking group. And there was no significant difference in blood pressure compliance rate among whether drinking and doing exercise or not. CONCLUSIONS: Blood pressure control in patients with CHD was still not satisfied. Compared with PCI, CABG may be more beneficial in the control of blood pressure in patients with CHD. Smoking cessation and improving the usage rate of secondary preventive drugs are still the main means of blood pressure control.

[50] *Zhou CZ, Pan SL, Lin H et al.* **[Effects of rosuvastatin in homocysteine induced mouse vascular smooth muscle cell dedifferentiation and endoplasmic reticulum stress and its mechanisms]**. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology 2018; 34:43-48.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29926658
ABSTRACT
OBJECTIVE: To investigate the effect of rosuvastatin on homocysteine (Hcy) induced mousevascular smooth muscle cells(VSMCs) dedifferentiation and endoplasmic reticulum stress(ERS). METHODS: VSMCs were co-cultured with Hcy and different concentration of rosuvastatin (0.1, 1.0 and 10 mumol/L). Cytoskeleton remodeling, VSMCs phenotype markers (smooth muscle actin-alpha, calponin and osteopontin) and ERS marker mRNAs (Herpud1, XBP1s and GRP78) were detected at predicted time. Tunicamycin was used to induce, respectively 4-phenylbutyrate(4-PBA) inhibition, ERS in VSMCs and cellular migration, proliferation and expression of phenotype proteins were analyzed. Mammalian target of rapamycin(mTOR)-P70S6 kinase (P70S6K) signaling agonist phosphatidic acid and inhibitor rapamycin were used in Rsv treated VSMCs. And then mTOR signaling and ERS associated mRNAs were detected. RESULTS: Compared with Hcy group, Hcy+ Rsv group (1.0 and 10 mumol/L) showed enhanced alpha-SMA and calponin expression (P<0.01), suppressed ERS mRNA levels (P<0.01) and promoted polarity of cytoskeleton. Compared with Hcy group, Hcy+Rsv group and Hcy+4-PBA group showed suppressed proliferation, migration and enhanced contractile protein expression (P<0.01); while tunicamycin could reverse the effect of Rsv on Hcy treated cells. Furthermore, alleviated mTOR-P70S6K phosphorylation and ERS (P<0.01)were observed in Hcy+Rsv group and Hcy+rapamycin group, compared with Hcy group; while phosphatidic acid inhibited the effect of Rsv on mTOR signaling activation and ERS mRNA levels (P<0.01). CONCLUSIONS: Rosuvastatin could inhibit Hcy induced VSMCs dedifferentiation via suppressing ERS, which might be regulated by mTOR-P70S6K signaling.

[51] *Ren H, Ding M, Ma H et al.* **[Protective effects of combined use of atorvastatin and low molecular weight heparin on the inflammatory reaction and pulmonary functions in rats with sepsis]**. Zhonghua wei zhong bing ji jiu yi xue 2016; 28:427-432.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29920039
ABSTRACT
Objective: To investigate the influence of combined use of atorvastatin (ATO) and low molecular weight heparin (LMWH) on the inflammatory reaction and pulmonary protection functions in rats with sepsis. Methods: A total of 122 healthy male Sprague-Dawley (SD) rats were divided into five groups using a random number table: sham-operated group (sham group, n =10),sepsis group (n =10),ATO group (n =34),LMWH group (n =34),and ATO combined

with LMWH group (ATO+LMWH group, n =34).The rat model of sepsis was reproduced by cecal ligation and puncture (CLP),while in sham group, rats were only subjected to laparotomy without cecum ligation and puncture. The rats of each pretreatment group received relevant therapies for 5 days, either gastric perfusion with ATO 20 mg/kg or subcutaneous injection with LMWH 100 U/kg or both before operation. The sepsis severities of the model animals were scored according to the modified sepsis severity assessment standards of experimental animals. Ten rats in each group were calculated the 7-day cumulative mortality rate. Blood samples from 6 rats in each group were collected to determine the levels of tumor necrosis factor-alpha (TNF-alpha),interleukin-1 beta (IL-1 beta) and high mobility group protein box-1 (HMGB1) contents in plasma using enzyme linked immunosorbent assay (ELISA)before operation (0 hour) and 4,8,12,and 24 hours post operation. The lung tissue was harvested 24 hours after operation, and the pulmonary pathology was assayed by hematoxylin and eosin (HE) staining using optical microscope. Results: 1 in circle The sepsis severity grades of sepsis group were significantly higher than those of sham group at 4 hours after operation (score:12.2 +/- 2.0 vs.7.2 +/- 0.5,P 0.05).Furthermore, they displayed a gradually increasing tendency, with the 7-day cumulative mortality rate being 90 (9/10).The sepsis severity grades in ATO group, LMWH group, and ATO+LMWH group showed a significant decrease compared with sepsis group at 8 hours after operation (12.2+/- 2.0,11.2+/-2.2,10.0+/- 1.7 vs.16.6+/-2.5,all P 0.05).The 7-day cumulative mortality rates in ATO group, LMWH group, and ATO+LMWH group were 60 (6/10),60 (6/10),and 40 (4/10),respectively, all of which was significantly lower than that of sepsis group (all P 0.05).2 in circle The levels of TNF-alpha,IL-1 beta and HMGB1 have not shown much variations in the sham group after operation; the levels of pro-inflammatory cytokines in other 4 groups were significantly increased after operation compared with those before operation; the levels of TNF-alpha,IL-1beta,and HMGB 1 reached peak at 4,8,and 24 hours, respectively. The levels of pro-inflammatory cytokines in sepsis group were significantly higher than those in the sham group. However, the levels of pro-inflammatory cytokines in ATO group, LMWH group, and ATO+LMWH group were significantly lower than those in sepsis group [4-hour TNF-alpha (ng/L):668.3 +/- 124.6,536.5 +/- 118.5,496.5 +/- 108.5 vs.783.8 +/- 134.7;8-hour IL-1 beta (ng/L):2 476.7 +/- 137.8,2 460.4+/- 171.2,2 090.0 +/- 151.2 vs.2 873.9 +/- 295.6;24-hour HMGB1 (mug/L):654.4+/- 154.4,659.0+/- 134.6,609.4+/-90.5 vs.859.3 +/- 167.5,P 0.05 or P 0.01].3 in circle It was showed by optical microscopy that the pulmonary tissue morphology was normal in sham group and that the damage of pulmonary pathology was relatively severe in sepsis group. Compared with sepsis group, the damage of pulmonary pathology in ATO group, LMWH group, and ATO + LMWH group was alleviated obviously, and the most obvious improvements were found in ATO + LMWH group. Conclusions: Either ATO or LMWH could decrease sepsis severity, suppress the release of plasma pro-inflammatory cytokines at the early and late stages, alleviate the damage of pulmonary pathology, and reduce the 7-day cumulative mortality rate. Therefore, the combined treatment of sepsis using both ATO and LMWH resulted in better outcomes than implemented individually.