Literature update week 07 (2018)

[1] *Browndyke JN, Heflin MT*. **Cognition and brain changes associated with high-dose atorvastatin: A BOLD proposition?** American heart journal 2018; 197:163-165.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29447777
ABSTRACT

[2] *Taylor BA, Dager AD, Panza GA et al.* **The effect of high-dose atorvastatin on neural activity and cognitive function**. American heart journal 2018; 197:166-174.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29447778
ABSTRACT
BACKGROUND: Functional magnetic resonance imaging (fMRI) has not been used to assess the effects of statins on the brain. We assessed the effect of statins on cognition using standard neuropsychological assessments and brain neural activation with fMRI on two tasks. METHODS: Healthy statin-naive men and women (48+/-15 years) were randomized to 80 mg/day atorvastatin (n=66; 27 men) or placebo (n=84; 48 men) for 6 months. Participants completed cognitive testing while on study drug and 2 months after treatment cessation using alternative test and task versions. RESULTS: There were few changes in standard neuropsychological tests with drug treatment (all P>.56). Total and delayed recall from the Hopkins Verbal Learning Test-Revised increased in both groups (P<.05). The Stroop Color-Word score increased (P<.01) and the 18-Point Clock Test decreased in the placebo group (P=.02) after drug cessation. There were, however, small but significant group-time interactions for each fMRI task: participants on placebo had greater activation in the right putamen/dorsal striatum during the maintenance phase of the Sternberg task while on placebo but the effect was reversed after drug washout (P<.001). Participants on atorvastatin had greater activation in the bilateral precuneus during the encoding phase of the Figural Memory task while on-drug but the effect was reversed after drug washout (P<.001). CONCLUSION: Six months of high dose atorvastatin therapy is not associated with measurable changes in neuropsychological test scores, but did evoke transient differences in brain activation patterns. Larger, longer-term clinical trials are necessary to confirm these findings and evaluate their clinical implications.

[3] *Baruch A, Mosesova S, Davis JD et al.* **Corrigendum to 'Effects of RG7652, a Monoclonal Antibody Against PCSK9, on Low-Density Lipoprotein Cholesterol (LDL-C), LDL-C Subfractions, and Inflammatory Biomarkers in Patients at High Risk of or with Established Coronary Heart Disease (From the Phase 2 EQUATOR Study)' The American Journal of Cardiology 119 (2017) 1576-1583**. The American journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29448977
ABSTRACT

[4] *Raal FJ, Alsheikh-Ali AA, Omar MI et al.* **Cardiovascular risk factor burden in Africa and the Middle East across country income categories: a post hoc analysis of the cross-sectional Africa Middle East Cardiovascular Epidemiological (ACE) study**. Archives of public health = Archives belges de sante publique 2018; 76:15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29449941
ABSTRACT

Background: A significant number of cardiovascular disease (CVD)-related deaths occur in developing countries. An increasing prevalence of CVD is associated with a change in the macro-economy of these countries. In this post hoc analysis, CVD risk factor (CVDRF) prevalence is evaluated across countries based on national income in the Africa and Middle East Region (AfME). Methods: Data from the Africa Middle East Cardiovascular Epidemiological (ACE) study were used; a cross-sectional study in 14 AfME countries (94 clinics) from July 2011-April 2012, which evaluated CVDRF prevalence in stable adult outpatients. World Bank definitions were used to classify countries as low-income (LI), lower-middle-income (LMI), upper-middle-income (UMI) or high-income (HI) countries. Four thousand three hundred seventy-eight subjects were recruited where 260 (6%), 1324 (30%), 1509 (35%) and 1285 (29%) were from LI, LMI, UMI, and HI countries, respectively. Results: Of all the CVDRFs evaluated, almost two-thirds of the study population across the national income groups had abdominal obesity and dyslipidemia. Countries in the HI category were associated with a higher prevalence of diabetes (32%), obesity (44%) and smoking (16%). UMI and HI countries were associated with higher clustering of CVDRFs where at least one-third of subjects having four or more CVDRFs. Lower income countries had lower blood pressure control rates and lower percentages of outpatients achieving LDL-cholesterol targets. Conclusion: The burden of CVDRFs in stable outpatients is high across the national income categories in the AfME region, with HI countries showing a higher prevalence of CVDRFs. The high burden in lower income countries is associated with sub-optimal control of dyslipidemia and hypertension. Lowering the CVDRF burden would need specific public health actions in line with positive changes in the macro-economy of these countries. Trial registration: The ACE trial is registered under NCT01243138.

[5] *Honda K, Matoba T, Antoku Y et al.* **Lipid-Lowering Therapy With Ezetimibe Decreases Spontaneous Atherothrombotic Occlusions in a Rabbit Model of Plaque Erosion: A Role of Serum Oxysterols**. Arteriosclerosis, thrombosis, and vascular biology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29449331

ABSTRACT

OBJECTIVE: Plaque erosion is increasing its importance as one of the mechanisms of acute coronary syndromes in this statin era. However, the clinical efficacy of currently used lipid-lowering agents in the prevention of thrombotic complications associated with plaque erosion has not been clarified. Therefore, we examined the therapeutic effects of ezetimibe or rosuvastatin monotherapy on spontaneous atherothrombotic occlusion. APPROACH AND RESULTS: Femoral arteries of Japanese white rabbits, fed a high-cholesterol diet, were injured by balloon catheter, and then angiotensin II was continuously administrated. In 94% of these arteries, spontaneous thrombotic occlusions were observed after 5 weeks (median) of balloon injury. Histochemical analyses indicated that the injured arteries had similar pathological features to human plaque erosions; (1) spontaneous thrombotic occlusion, (2) lack of endothelial cells, and (3) tissue factor expression in vascular smooth muscle cells. Ezetimibe (1.0 mg/kg per day), but not rosuvastatin (0.6 mg/kg per day), significantly decreased thrombotic occlusion of arteries accompanied with accelerated re-endothelialization and the decreases of serum oxysterols despite the comparable on-treatment serum cholesterol levels. The 7-ketocholesterol inhibited the migration of human umbilical vein endothelial cells. Both 7-ketocholesterol and 27-hydroxycholesterol increased tissue factor expression in cultured rat

vascular smooth muscle cells. Tissue factor expression was also induced by serum from vehicle- or rosuvastatin-treated rabbits, but the induction was attenuated with serum from ezetimibe-treated rabbits. CONCLUSIONS: We have established a novel rabbit model of spontaneous atherothromobotic occlusion without plaque rupture that is feasible to test the therapeutic effects of various pharmacotherapies. Ezetimibe may decrease atherothrombotic complications after superficial plaque erosion by reducing serum oxysterols.

[6] *Jang YO, Kim SH, Cho MY et al.* **Synergistic effects of simvastatin and bone marrow-derived mesenchymal stem cells on hepatic fibrosis**. Biochem Biophys Res Commun 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29428718
ABSTRACT
The beneficial effects of simvastatin on fibrosis in various organs have been reported. In addition, bone marrow (BM)-derived mesenchymal stem cells (MSCs) have been suggested as an effective therapy for hepatic fibrosis and cirrhosis. Recent evidence suggests that pharmacological treatment devoted to regulating stem cell function is a potential new therapeutic strategy that is drawing nearer to clinical practice. The aim of this study was to determine whether the combination treatment of simvastatin plus MSCs (Sim-MSCs) could have a synergistic effect on hepatic fibrosis in a thioacetamide (TAA)-induced cirrhotic rat model and hepatic stellate cells (HSCs). Cirrhotic livers from rats treated with Sim-MSCs exhibited histological improvement compared to those treated with simvastatin alone. Sim-MSCs combination treatment decreased hepatic collagen distribution, lowered the hydroxyproline content, and rescued liver function impairment in rats with TAA-induced cirrhosis. These protective effects were more potent with Sim-MSCs than with simvastatin alone. The upregulation of collagen-1, alpha-smooth muscle actin (alpha-SMA), transforming growth factor (TGF)-beta1, and phospho-Smad3 in cirrhotic livers was prevented by the administration of Sim-MSCs. Intriguingly, Sim-MSCs inhibited both TGF-beta/Smad3 signaling and alpha-SMA in HSCs. The Sim-MSCs combination treatment exerted strong protective effects against hepatic fibrosis by suppressing TGF-beta/Smad signaling. Simvastatin could act synergistically with MSCs as an efficient therapeutic approach for intractable cirrhosis.

[7] *Schairer C, Freedman DM, Gadalla SM, Pfeiffer RM*. **Lipid-lowering drugs, dyslipidemia, and breast cancer risk in a Medicare population**. Breast cancer research and treatment 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29450675
ABSTRACT
PURPOSE: We sought to disentangle the effects of statins and other lipid-lowering drugs and the underlying dyslipidemia for which they are prescribed on breast cancer risk. METHODS: We conducted a case-control study within the linked Surveillance, Epidemiology, and End results (SEER)-Medicare data. Cases were women with invasive breast cancer aged 66 + years (N = 30,004) identified by SEER registries (years 2007-2011). Controls were women (N = 198,969) identified from a 5% random sample of Medicare recipients alive and breast cancer free in year of selection. Participants had a minimum of 13 months of Part A, Part B non-health maintenance organization Medicare and Part D Medicare coverage at least 13 months preceding cancer diagnosis/selection. Exposures were assessed until 12 months before diagnosis/control selection. Odds ratios (OR) and 99.9% confidence intervals (CI) were

estimated using adjusted unconditional and multinomial logistic regression. RESULTS: ORs of invasive breast cancer associated with dyslipidemia, statins, and non-statin lipid-lowering drugs were 0.86 (99.9% CI 0.81-0.90), 1.07 (99.9% CI 1.03-1.13) and 1.03 (99.9% CI 0.95-1.11), respectively. Risk reductions with dyslipidemia were slightly greater when untreated than treated and did not vary much by time between dyslipidemia and breast cancer diagnosis. Whether treated or untreated, dyslipidemia was associated with greater reductions in risk for later stage than earlier stage breast cancer (p-heterogeneity < 0.0001). CONCLUSIONS: Lipid-lowering drugs did not account for the lower breast cancer risk associated with dyslipidemia. Our data do not support using statins or other lipid-lowering drugs to prevent breast cancer.

[8] *Huai J, Yang Z, Yi YH, Wang GJ*. **Different Effects of Pravastatin on Preeclampsia-like Symptoms in Different Mouse Models**. Chinese medical journal 2018; 131:461-470.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29451152

ABSTRACT

Background: Pravastatin (Pra) exerts protective effects on preeclampsia. Preeclampsia is a multifactorial and pathogenic pathway syndrome. The present study compared the effects of Pra on clinical manifestations of preeclampsia in different pathogenic pathways. Methods: Two different preeclampsia-like mouse models used in this study were generated with Nomega-nitro-L-arginine methyl ester (L-NAME) and used lipopolysaccharide (LPS) from day 7 of gestation, respectively. Pra treatment was administered on day 2 after the models were established in each group (L-NAME + Pra, LPS + Pra, and Control + Pra, n = 8) or normal saline (NS) for the control group (L-NAME + NS, LPS + NS, and Control + NS, n = 8). Maternal weight, serum lipids, the histopathological changes, and lipid deposition in the liver and placenta were observed. The pregnancy outcomes were compared. The blood pressure analysis was carried out on repeated measurements of variance. Student's t-test was used for comparing the two groups. The enumeration data were compared by Chi-square test. Results: The mean arterial pressure (MAP) and 24-h urinary protein in the L-NAME + NS and LPS + NS groups were significantly higher than the Control + NS group ($F = 211.05$ and 309.92 for MAP, $t = 6.63$ and 8.63 for 24-h urinary protein; all $P < 0.05$) and reduced in the L-NAME + Pra group as compared to the L-NAME + NS group ($F = 208.60$ for MAP, $t = 6.77$ for urinary protein; both $P < 0.05$). Urinary protein was decreased in the LPS + Pra group as compared to the LPS + NS group ($t = 5.33$; $P < 0.05$), whereas MAP had no statistical significance ($F = 3.37$; $P > 0.05$). Compared to the Control + NS group, the placental efficiency in the L-NAME + NS and LPS + NS groups decreased significantly ($t = 3.09$ and 2.89, respectively; both $P < 0.05$); however, no significant difference was observed in L-NAME + Pra and LPS + Pra groups ($t = 1.37$ and 0.58, respectively; both $P > 0.05$). Free fatty acid was elevated in the L-NAME + NS group as compared to the Control + NS group ($t = 3.99$; $P < 0.05$) at day 18 of pregnancy and decreased in the L-NAME + Pra group as compared to the L-NAME + NS group ($t = 3.28$; $P < 0.05$); however, no significant change was observed in the LPS model ($F = 0.32$; $P > 0.05$). Conclusion: This study suggested that Pra affected the clinical manifestations differently in preeclampsia-like mouse models generated in various pathogenic pathways.

[9] *Parish S, Hopewell JC, Hill MR et al.* **Impact of Apolipoprotein(a) Isoform Size on Lipoprotein(a) Lowering in the HPS2-THRIVE Study**. Circulation. Genomic and precision medicine 2018; 11:e001696.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29449329
ABSTRACT
BACKGROUND: Genetic studies have shown lipoprotein(a) (Lp[a]) to be an important causal risk factor for coronary disease. Apolipoprotein(a) isoform size is the chief determinant of Lp(a) levels, but its impact on the benefits of therapies that lower Lp(a) remains unclear. METHODS: HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) is a randomized trial of niacin-laropiprant versus placebo on a background of simvastatin therapy. Plasma Lp(a) levels at baseline and 1 year post-randomization were measured in 3978 participants from the United Kingdom and China. Apolipoprotein(a) isoform size, estimated by the number of kringle IV domains, was measured by agarose gel electrophoresis and the predominantly expressed isoform identified. RESULTS: Allocation to niacin-laropiprant reduced mean Lp(a) by 12 (SE, 1) nmol/L overall and 34 (6) nmol/L in the top quintile by baseline Lp(a) level (Lp[a] >/=128 nmol/L). The mean proportional reduction in Lp(a) with niacin-laropiprant was 31% but varied strongly with predominant apolipoprotein(a) isoform size (PTrend=4x10(-29)) and was only 18% in the quintile with the highest baseline Lp(a) level and low isoform size. Estimates from genetic studies suggest that these Lp(a) reductions during the short term of the trial might yield proportional reductions in coronary risk of approximately 2% overall and 6% in the top quintile by Lp(a) levels. CONCLUSIONS: Proportional reductions in Lp(a) were dependent on apolipoprotein(a) isoform size. Taking this into account, the likely benefits of niacin-laropiprant on coronary risk through Lp(a) lowering are small. Novel therapies that reduce high Lp(a) levels by at least 80 nmol/L (approximately 40%) may be needed to produce worthwhile benefits in people at the highest risk because of Lp(a). CLINICAL TRIAL REGISTRATION: URL: https://clinicaltrials.gov. Unique identifier: NCT00461630.

[10] *Koh KK*. **Letter by Koh Regarding Article, "Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label)"**. Circulation 2018; 137:639-640.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29431666
ABSTRACT

[11] *Kusters DM, Braamskamp M, Langslet G et al.* **Response by Kusters et al to Letter Regarding Article, "Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label)"**. Circulation 2018; 137:641-642.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29431667
ABSTRACT

Literature update week 07 (2018)

[12] *Chiorescu S, Andercou OA, Grad NO, Mironiuc IA*. **Intraperitoneal administration of rosuvastatin prevents postoperative peritoneal adhesions by decreasing the release of tumor necrosis factor**. Clujul medical (1957) 2018; 91:79-84.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29440955
ABSTRACT
Objectives: The purpose of this experimental study was to demonstrate the reduction of peritoneal adhesions formation in rats after intraperitoneal administration of rosuvastatin, due to its anti-inflammatory effect. Method: Peritoneal adhesions were induced in 120 Wistar-Bratislava rats divided into 4 groups (n=30), using a parietal and visceral (cecal) abrasion model. Group I was designated as control group; in group II, a saline solution was administered intraperitoneally; in groups III and IV, a single dose of rosuvastatin solution, 10 mg/kg and 5 mg/kg respectively, was injected intraperitoneally. The serum values of tumor necrosis factor (TNF-alpha) and interleukin-1 (IL-1alpha) were determined on day 1 and day 7 postoperatively (ELISA). Macroscopic assessment of the peritoneal adhesions was conducted on day 14. Results: Rosuvastatin therapy induced a significant decrease of tumor necrosis factor serum levels in groups III and IV, on day 1 and day 7 ($p<0.01$). Intraperitoneal administration of rosuvastatin correlated with a decrease of mean interleukin-1alpha levels on postoperative day 1 in groups III ($p=0.0013$) and IV ($p=0.00011$), but not on day 7, where the differences were no longer statistically significant ($p=0.8$) The reduction of postoperative peritoneal adhesions in the experimental rat model is supported by the anti-inflammatory effect of rosuvastatin, mediated mainly by the tumor necrosis factor. Conclusions: Rosuvastatin prevents the formation of postoperative peritoneal adhesions in rats. This effect may be linked to the inhibition of proinflammatory cytokines release in the early stages of adhesions formation. The present study suggests that rosuvastatin may be an efficient pharmacological agent in the prevention of postoperative peritoneal adhesions development, and requires further studies as it has a promising application value.

[13] *Sloop GD, Weidman JJ, St Cyr JA*. **Atherothrombosis is a Thrombotic, not Inflammatory Disease**. Cureus 2017; 9:e1909.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29435395
ABSTRACT
The authors hypothesize that thrombosis causes both the complications of atherosclerosis as well as the underlying lesion, the atherosclerotic plaque, which develops from the organization of mural thrombi. These form in areas of slow blood flow, which develop because of flow separation created by changing vascular geometry and elevated blood viscosity. Many phenomena typically ascribed to inflammation or "chronic oxidative stress", such as the development of fatty streaks, "endothelial dysfunction," "vulnerable plaques," and the association of mild elevations of C-reactive protein and cytokines with atherothrombosis are better explained by hemorheologic and hemodynamic abnormalities, particularly elevated blood viscosity. Elevated blood viscosity decreases the perfusion of skeletal muscle, leading to myocyte expression of the myokine IL-6, decreased glucose uptake, insulin resistance, hyperglycemia, and metabolic syndrome. The hyperfibrinogenemia and hypergammaglobulinemia present in true inflammatory diseases foster atherothrombosis by increasing blood viscosity.

[14] *Pirillo A, Bonacina F, Norata GD, Catapano AL*. **The Interplay of Lipids, Lipoproteins, and Immunity in Atherosclerosis**. Current atherosclerosis reports 2018; 20:12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29445885
ABSTRACT
PURPOSE OF REVIEW: Atherosclerosis is an inflammatory disorder of the arterial wall, in which several players contribute to the onset and progression of the disease. Besides the well-established role of lipids, specifically cholesterol, and immune cell activation, new insights on the molecular mechanisms underlying the atherogenic process have emerged. RECENT FINDINGS: Meta-inflammation, a condition of low-grade immune response caused by metabolic dysregulation, immunological memory of innate immune cells (referred to as "trained immunity"), cholesterol homeostasis in dendritic cells, and immunometabolism, i.e., the interplay between immunological and metabolic processes, have all emerged as new actors during atherogenesis. These observations reinforced the interest in directly targeting inflammation to reduce cardiovascular disease. The novel acquisitions in pathophysiology of atherosclerosis reinforce the tight link between lipids, inflammation, and immune response, and support the benefit of targeting LDL-C as well as inflammation to decrease the CVD burden. How this will translate into the clinic will depend on the balance between costs (monoclonal antibodies either to PCSK9 or to IL-1ss), side effects (increased incidence of death due to infections for anti-IL-1ss antibody), and the benefits for patients at high CVD risk.

[15] *Ray KK, Leiter LA, Muller-Wieland D et al.* **Alirocumab versus usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: The ODYSSEY DM-DYSLIPIDEMIA randomized trial**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29436756
ABSTRACT
AIMS: Individuals with type 2 diabetes (T2DM) and mixed dyslipidaemia represent a high-risk and difficult-to-treat population. ODYSSEY DM-DYSLIPIDEMIA (NCT02642159) compared alirocumab, a proprotein convertase subtilisin-kexin type 9 inhibitor, with usual care (UC) in individuals with T2DM and mixed dyslipidaemia not optimally managed by maximally-tolerated statins. MATERIALS AND METHODS: UC options (no additional lipid-lowering therapy; fenofibrate; ezetimibe; omega-3 fatty acid; nicotinic acid) were selected prior to stratified randomization to open-label alirocumab 75 mg every 2 weeks (Q2W; with increase to 150 mg Q2W at Week [W]12 if W8 non-high-density lipoprotein cholesterol [non-HDL-C] was >/=2.59 mmol/L [100 mg/dL]) or UC for 24 weeks. Primary efficacy endpoint was percentage change in non-HDL-C from baseline to W24. RESULTS: The randomized population comprised 413 individuals (409 intention-to-treat; 412 safety). At W24, mean non-HDL-C reductions were superior with alirocumab (-32.5% difference vs UC; 97.5% confidence interval: -38.1 to -27.0; P<.0001). Overall, 63.6% of alirocumab-treated individuals were maintained on 75 mg Q2W. Alirocumab also reduced low-density lipoprotein cholesterol (-43.0%), apolipoprotein B (-32.3%), total cholesterol (-24.6%), and LDL particle number (-37.8%) at W24 vs UC (all P<.0001). Consistent with the overall trial comparison, alirocumab reduced non-HDL-C to a greater degree within each UC stratum at W24. Incidence of treatment-emergent adverse events was 68.4% (alirocumab) and 66.4% (UC). No clinically meaningful effect on glycated hemoglobin, or

change in number of glucose-lowering agents, was seen. CONCLUSIONS: In individuals with T2DM and mixed dyslipidaemia on maximally tolerated statin, alirocumab showed superiority in non-HDL-C reduction vs UC and was generally well tolerated.

[16] *Jorde R, Grimnes G*. **Exploring the association between serum 25-hydroxyvitamin D and serum lipids-more than confounding?** European journal of clinical nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29434318
ABSTRACT
BACKGROUND/OBJECTIVES: In observational, but not interventional, studies there are strong associations between serum 25-hydroxyvitamin D (25(OH)D) and serum lipids. The purpose of the present study was to examine potential causes of this association. SUBJECTS/METHODS: A total of 17,411 subjects participating in the seventh survey of the Tromso Study were included in the cross-sectional study; 5384 subjects who participated in both the sixth and seventh survey were included in the longitudinal study; 2365 subjects who participated in both the fourth and seventh survey were included in the genetic study; and 479 subjects with impaired glucose tolerance were included in the vitamin D binding protein (DBP) analyses. RESULTS: For serum 25(OH)D, there were strong and positive associations with LDL-, HDL-, and total-cholesterol, and a negative association with triglycerides that remained after adjustment for gender, age, BMI, diet, supplements, and lifestyle factors. These associations were seen in winter as well as summer. Except for serum cholesterol, change of season for blood sampling did not affect lipid levels. However, when analyzing separately, subjects with low or no intake of vitamin D supplements, fish oil and fat fish, only the association between 25(OH)D and HDL-cholesterol remained significant. Serum DBP or single-nucleotide polymorphisms related to 25(OH)D had no relation to lipid levels. CONCLUSIONS: The associations between 25(OH)D and lipids (except for HDL-cholesterol) can be explained by known confounding factors. However, for HDL-cholesterol, the cause of the association with 25(OH)D still remains unknown.

[17] *Hu X, Song C, Fang M, Li C*. **Simvastatin inhibits the apoptosis of hippocampal cells in a mouse model of Alzheimer's disease**. Experimental and therapeutic medicine 2018; 15:1795-1802.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29434767
ABSTRACT
Alzheimer's disease is associated with cognitive impairments that affect memory and executive functions. Simvastatin is a cholesterol-lowering statin drug that is used to control levels of cholesterol in the blood, particularly in cases of hypercholesterolemia, and may be used in the treatment of aneurysmal subarachnoid hemorrhage. Previous results have indicated that the apoptosis of hippocampal cells may serve a critical role in the progression of Alzheimer's disease. In the present study, it was determined whether Simvastatin inhibited the apoptosis of hippocampal cells in vitro and in vivo. The therapeutic effects of Simvastatin were evaluated in 24-month-old triple-transgenic Alzheimer's disease (3xTg-AD) mice, and the efficacy of Simvastatin in attenuating memory and cognitive impairment was investigated. Levels of apoptosis-related gene expression in the hippocampus and hippocampal cells of experimental mice were also detected. In addition, neuron excitability was assessed in the functionally relevant brain regions in the hippocampus. The data indicated that Simvastatin significantly

suppressed the apoptosis of hippocampal cells in 3xTg-AD model mice compared with controls (P<0.01). Furthermore, treatment with Simvastatin improved the dementia status of 3xTg-AD mice, as determined by a learning task in which mice exhibited significantly reduced attention impairment, impulsivity and compulsivity (P<0.01). In addition, results demonstrated that Simvastatin significantly inhibited hippocampal damage and significantly improved neuronal loss in hippocampal structures classically associated with attentional performance when compared with untreated mice (P<0.01). Thus, Simvastatin prevented cognitive impairment by decreasing hippocampal cell apoptosis and improving learning-memory ability. Simvastatin treatment also increased the expression of anti-apoptotic genes and decreased the expression pro-apoptotic genes (P<0.01), which may have been associated with improved motor attention and cognitive competence in 3xTg-AD mice. Collectively, these preclinical data indicated that Simvastatin was efficient in attenuating memory lapse and hippocampal cell apoptosis in a 3xTg-AD mouse model. Thus, Simvastatin may be useful in improving the clinical outcome of patients with Alzheimer's disease.

[18] *Liu Y, Sun L, Chen W et al.* **Combined treatment with simvastatin and rapamycin attenuates cardiac allograft rejection through the regulation of T helper 17 and regulatory T cells**. Experimental and therapeutic medicine 2018; 15:1941-1949.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29434788
ABSTRACT
Allograft rejection is an important issue post cardiac transplantation. In order to investigate the effect of combined treatment with simvastatin and rapamycin on allograft rejection, a cardiac transplantation rat model was employed in the present study. The survival time of rats following cardiac transplantation was recorded, while histopathological alterations were assessed by hematoxylin and eosin staining. The levels of transcription factors were measured by reverse transcription-quantitative polymerase chain reaction. In addition, the levels of CD4(+) interleukin (IL)-17(+) cells and CD4(+) forkhead box P3 (FOXP3)(+) cells in the allografts and CD4(+) T cells and CD8(+) T cells in the spleens were detected by flow cytometry. The results of the current study demonstrated that, following treatment with simvastatin and rapamycin, the survival time of model rats was prolonged, and the histopathological damage was attenuated. Treatment with simvastatin and rapamycin also led to decreased retinoic acid receptor-related orphan receptor gammat (RORgammat) level, increased FOXP3 level, reduced levels of CD4(+)IL-17(+), CD4(+) T and CD8(+) T cells, and increased level of CD4(+)FOXP3(+) cells. In conclusion, the current study observed that simvastatin and rapamycin performed a synergistic effect to reduce cardiac transplantation rejection. Thus, combined therapy of simvastatin and rapamycin may be a promising adjuvant therapy to reduce rejection post cardiac transplantation.

[19] *Nishikido T, Ray KK*. **Inclisiran for the treatment of dyslipidemia**. Expert opinion on investigational drugs 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29451410
ABSTRACT
INTRODUCTION: Dyslipidemia is one of the most important risk factors for cardiovascular disease. Insufficient reduction in LDL-C from existing therapies in patients at high risk of

atherogenic cardiovascular disease is an unmet clinical need. Circulating PCSK9 causes hypercholesterolemia by reducing LDL receptors in hepatocytes. Areas covered: PCSK9 inhibition has emerged as a promising new therapeutic strategy to reduce LDL-C. Inclisiran, a novel, synthetic, siRNA molecule, inhibits PCSK9 synthesis in hepatocytes. Inclisiran targets intracellular PCSK9 synthesis specifically, resulting in a dose-dependent, long-term, significant reduction in LDL-C. Inclisiran has been well tolerated and safe, without severe adverse events so far. This review discusses current PCSK9 inhibitors and the results of phase I and II clinical trials of inclisiran. Expert opinion: Plasma PCSK9 enhances the degradation of LDL receptor, resulting in accumulation of LDL-C in the circulation. Current approaches with monoclonal antibodies sequester circulating PCSK9 but require frequent injections. Inclisiran inhibits translation of PCSK9 mRNA and thus switches off PCSK9 production and provides advantages over monoclonal antibodies with an infrequent dosing interval of twice a year to reduce LDL-C by over 50%. Ongoing studies will establish the long-term safety of inclisiran in patients with high cardiovascular risk and an elevated LDL-C.

[20] *Abdel-Daim MM, Abdeen A*. **Protective effects of rosuvastatin and vitamin E against fipronil-mediated oxidative damage and apoptosis in rat liver and kidney**. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2018; 114:69-77.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29432839
ABSTRACT
Fipronil (FPN) is a phenylpyrazole insecticide that is extensively used in agriculture and veterinary applications. However, FPN is also a potent environmental toxicant to animals and humans. Therefore, the current study aimed to investigate the protective role of rosuvastatin (ROSU) and vitamin E (Vit E) against FPN-induced hepatorenal toxicity in albino rats. Seven groups with eight rats each were used for this purpose; these groups included the control vehicle group that received corn oil, the Vit E group (1000mg/kg, orally), the ROSU group (10mg/kg, orally), the FPN group (20mg/kg, orally), the FPN-ROSU group, the FPN-Vit E group, and the FPN-Vit E-ROSU group. The results revealed that FPN significantly increased serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, cholesterol, urea, and creatinine. In addition, there were substantial increases in the liver and kidney contents of malondialdehyde and nitric oxide, along with significant decreases in glutathione, superoxide dismutase, catalase, and glutathione peroxidase. FPN also caused histological changes and increased the expression of caspase-3 in the liver and kidney tissues. However, administration of ROSU and Vit E alone or in combination ameliorated the FPN-induced oxidative damage and apoptosis, possibly through their antioxidant properties.

[21] *Chiurchiu V, Leuti A, Maccarrone M*. **Bioactive Lipids and Chronic Inflammation: Managing the Fire Within**. Frontiers in immunology 2018; 9:38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29434586
ABSTRACT
Inflammation is an immune response that works as a contained fire that is pre-emptively sparked as a defensive process during infections or upon any kind of tissue insult, and that is spontaneously extinguished after elimination or termination of the damage. However,

persistent and uncontrolled immune reactions act as a wildfire that promote chronic inflammation, unresolved tissue damage and, eventually, chronic diseases. A wide network of soluble mediators, among which endogenous bioactive lipids, governs all immune processes. They are secreted by basically all cells involved in inflammatory processes and constitute the crucial infrastructure that triggers, coordinates and confines inflammatory mechanisms. However, these molecules are also deeply involved in the detrimental transition from acute to chronic inflammation, be it for persistent or excessive action of pro-inflammatory lipids or for the impairment of the functions carried out by resolving ones. As a matter of fact, bioactive lipids have been linked, to date, to several chronic diseases, including rheumatoid arthritis, atherosclerosis, diabetes, cancer, inflammatory bowel disease, systemic lupus erythematosus, and multiple sclerosis. This review summarizes current knowledge on the involvement of the main classes of endogenous bioactive lipids-namely classical eicosanoids, pro-resolving lipid mediators, lysoglycerophospholipids/sphingolipids, and endocannabinoids-in the cellular and molecular mechanisms that lead to the pathogenesis of chronic disorders.

[22] *Vejux A, Namsi A, Nury T et al.* **Biomarkers of Amyotrophic Lateral Sclerosis: Current Status and Interest of Oxysterols and Phytosterols**. Frontiers in molecular neuroscience 2018; 11:12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29445325
ABSTRACT
Amyotrophic lateral sclerosis (ALS) is a non-demyelinating neurodegenerative disease in adults with motor disorders. Two forms exist: a sporadic form (90% of cases) and a family form due to mutations in more than 20 genes including the Superoxide dismutase 1, TAR DNA Binding Protein, Fused in Sarcoma, chromosome 9 open reading frame 72 and VAPB genes. The mechanisms associated with this pathology are beginning to be known: oxidative stress, glutamate excitotoxicity, protein aggregation, reticulum endoplasmic stress, neuroinflammation, alteration of RNA metabolism. In various neurodegenerative diseases, such as Alzheimer's disease or multiple sclerosis, the involvement of lipids is increasingly suggested based on lipid metabolism modifications. With regard to ALS, research has also focused on the possible involvement of lipids. Lipid involvement was suggested for clinical arguments where changes in cholesterol and LDL/HDL levels were reported with, however, differences in positivity between studies. Since lipids are involved in the membrane structure and certain signaling pathways, it may be considered to look for oxysterols, mainly 25-hydroxycholesterol and its metabolites involved in immune response, or phytosterols to find suitable biomarkers for this pathology.

[23] *Schmidt AF, Pearce LS, Wilkins JT et al.* **Cochrane corner: PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease**. Heart 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29444808
ABSTRACT

[24] *van Driel ML, Morledge MD, Ulep R et al.* **Cochrane corner: interventions to improve adherence to lipid-lowering medication**. Heart 2018; 104:367-369.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29440453

ABSTRACT

[25] *Setia N, Saxena R, Sawhney JPS, Verma IC*. **Familial Hypercholesterolemia: Cascade Screening in Children and Relatives of the Affected**. Indian journal of pediatrics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29450819

ABSTRACT

OBJECTIVE: Familial Hypercholesterolemia (FH) is an inherited disorder of lipid metabolism characterized by very high low density lipoprotein (LDL) cholesterol since birth, resulting in premature atherosclerosis and coronary artery disease (CAD). Cascade screening of children and family members of proven FH individuals can identify more subjects who have high LDL cholesterol or the family mutation and appropriate intervention can reduce their risk of atherosclerosis and prevent its complications. METHODS: Cascade screening by molecular testing, was carried out in 133 family members, comprising 24 children, of 31 probands with FH having a pathogenic mutation in LDLR/ApoB gene. Lipid profiles were obtained in 44 family members including 11 children. RESULTS: Of 133 family members tested, 88 (66.1%) were identified to carry the family mutation. Twelve of these were children below 18 y of age and 76 were adults. CAD was present in 15 (11.2%) family members and 63(47.4%) family members, including nine children, were already on Lipid Lowering Therapy. CONCLUSIONS: Cascade screening led to identification of 88 new cases, with a pathogenic mutation, who were at a very high risk of developing premature CAD. The authors identified 12 children with family specific mutation, out of which 9 were initiated on low dose statin therapy. Four homozygous children were treated with high dose statins because of substantially increased risk of CAD. Cascade screening, therefore, proved to be a successful initiative towards primary prevention of CAD in India.

[26] *Karachaliou M, de Sanjose S, Waterboer T et al.* **Is early life exposure to polyomaviruses and herpesviruses associated with obesity indices and metabolic traits in childhood?** International journal of obesity (2005) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29445241

ABSTRACT

BACKGROUND: Evidence for an infectious origin of obesity is emerging. We explored whether common viruses were associated with obesity and metabolic traits. METHODS: We used cross-sectional (n = 674) and prospective (n = 440) data from children participating at the 4 and 6 years of age follow-up in the Rhea birth cohort. Presence of IgG antibodies to ten polyomaviruses (BKPyV, JCPyV, KIPyV, WUPyV, HPyV6, HPyV7, TSPyV, MCPyV, HPyV9, and HPyV10) and four herpesviruses (EBV, CMV, HSV-1, and HSV-2) were measured at age 4. Body mass index, waist circumference, and skinfold thickness were measured at age 4 and 6. Data on serum lipids, leptin, and adiponectin were also available. Multivariable linear regression models were used to explore the associations. RESULTS: At 4 years of age, seroprevalence to polyomaviruses ranged from 21.0% for HPyV9 to 82.0% for HPyV10. Seroprevalence for EBV, CMV, HSV-1, and HSV-2 was 53.0%, 26.0%, 3.6%, and 1.5% respectively. BKPyV seropositivity was associated with lower BMI SD score at age 4 [-0.21 (95% CI: -0.39, -0.03)] and 6 [-0.27 (95% CI:-0.48, -0.05)], waist circumference at age 4 [-1.12 cm (95% CI: -2.10, -0.15)] and 6 [-1.73 cm (95% CI: -3.33, -0.12)], sum of four skinfolds [-2.97 mm (95% CI: -5.70, -0.24)], and leptin levels

at age 4 [ratio of geometric means, 0.83 (95% CI: 0.70, 0.98)]. CMV seropositivity was associated with higher BMI SD score at age 4 [0.28 (95% CI: 0.11, 0.45)] and 6 [0.24 (95% CI: 0.03, 0.45)] and sum of four skinfolds at age 6 [4.75 mm (95% CI: 0.67, 8.83)]. Having "2-3 herpesviruses infections" (versus "0 herpesvirus infections") was associated with higher BMI SD score [0.32, (95% CI: 0.12, 0.53)], waist circumference [1.22 cm (95% CI: 0.13, 2.31)], and sum of four skinfolds [3.26 mm (95% CI: 0.18, 6.35)] at age 4. Polyomaviruses burden was not associated with outcomes. CONCLUSIONS: A higher herpesviruses burden and CMV seropositivity were associated with obesity traits in childhood.

[27] *Zhou P, Cao Z, Wang P et al.* **The Effect of Intensive Statin Therapy on Symptomatic Intracranial Arterial Stenosis**. Iranian journal of public health 2018; 47:231-236.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29445633
ABSTRACT
Background: The aim of this study was to observe the effect of intensive statin therapy on symptomatic intracranial arterial stenosis. Methods: overall, 120 patients with symptomatic intracranial arterial stenosis were admitted to the Xiangyang No.1 People's Hospital, Hubei University of Medicine, Xiangyang, China from January 2010 to May 2013. They were randomly divided into three groups and were given different doses of atorvastatin orally for 1 year or more, and followed up for 12 months. The three groups were assessed for clinical end-point event rates and changes in cerebral blood flow value before and after treatment to assess the effectiveness of intensive statin therapy. Results: The incidence rates of end-point cerebrovascular events in the low-dose group (10 mg/d), the general-dose group (20 mg/d) and the intensive treatment group (40 mg/d) were 26.3%, 13.5% and 5.4% respectively during the 12-month follow-up after treatment. There was a significant difference between the low dose group and the intensive treatment group ($P<0.05$). The relative cerebral blood flow and relative cerebral blood volume of the three groups were significantly higher than those before treatment ($P<0.05$), and the relative time to peak for the intensive treatment group was shorter than that before treatment ($P<0.001$). Conclusion: Atorvastatin at 40 mg/d has a significant advantage compared with atorvastatin at 20 mg/d and 10 mg/d in reducing cerebrovascular events and improving cerebral blood flow.

[28] *Davel AP, Lu Q, Moss ME et al.* **Sex-Specific Mechanisms of Resistance Vessel Endothelial Dysfunction Induced by Cardiometabolic Risk Factors**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29453308
ABSTRACT
BACKGROUND: The incidence of obesity is rising, particularly among women. Microvascular dysfunction is more common with female sex, obesity, and hyperlipidemia and predicts adverse cardiovascular outcomes, but the molecular mechanisms are unclear. Because obesity is associated with mineralocorticoid receptor (MR) activation, we tested the hypothesis that MR in endothelial cells contribute to sex differences in resistance vessel dysfunction in response to cardiometabolic risk factors. METHODS AND RESULTS: Male and female endothelial cell-specific MR knockout mice and MR-intact littermates were randomized to high-fat-diet-induced obesity or obesity with hyperlipidemia induced by adeno-associated virus-based vector targeting

transfer of the mutant stable form (DY mutation) of the human PCSK9 (proprotein convertase subtilisin/kexin type 9) gene and compared with control diet. Female but not male mice were sensitive to obesity-induced endothelial dysfunction, whereas endothelial function was impaired in obese hyperlipidemic males and females. In males, obesity or hyperlipidemia decreased the nitric oxide component of vasodilation without altering superoxide production or endothelial nitric oxide synthase expression or phosphorylation. Decreased nitric oxide content in obese males was overcome by enhanced endothelium-derived hyperpolarization-mediated relaxation along with increased SK3 expression. Conversely, in females, endothelium-derived hyperpolarization was significantly impaired by obesity with lower IK1 expression and by hyperlipidemia with lower IK1 and SK3 expression, loss of H2O2-mediated vasodilation, and increased superoxide production. Endothelial cell-MR deletion prevented endothelial dysfunction induced by risk factors only in females. Rather than restoring endothelium-derived hyperpolarization in females, endothelial cell-MR deletion enhanced nitric oxide and prevented hyperlipidemia-induced oxidative stress. CONCLUSIONS: These data reveal distinct mechanisms driving resistance vessel dysfunction in males versus females and suggest that personalized treatments are needed to prevent the progression of vascular disease in the setting of obesity, depending on both the sex and the metabolic profile of each patient.

[29] *Bai J, Gong LL, Li QF, Wang ZH*. **Long-term efficacy and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibodies: A meta-analysis of 11 randomized controlled trials**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29428832
ABSTRACT
BACKGROUND: Monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) have been shown to significantly reduce low-density lipoprotein cholesterol (LDL-C) levels. OBJECTIVE: The purpose of this study was to assess the long-term efficacy and safety of PCSK9 antibodies. METHODS: PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were searched for relevant studies. RESULTS: A total of 11 studies including 38,235 participants who were treated for at least 48 weeks were included in this meta-analysis. The results suggested that PCSK9 antibody treatment significantly decreased LDL-C levels (mean difference, -50.23% [95% confidence interval {CI}, -56.65% to -43.82%]) compared with no PCSK9 antibody treatment and also decreased other atherogenic lipid fractions. PCSK9 antibody treatment also elicited a significant reduction in cardiovascular event rates compared with no antibody treatment (relative risk [RR], 0.86 [95% CI, 0.81-0.92]). This reduction consisted of separate significant reductions in the rates of myocardial infarction (RR, 0.73 [95% CI, 0.65-0.82]), coronary revascularization (RR, 0.79 [95% CI, 0.73-0.87]), and stroke (RR, 0.81 [95% CI, 0.68-0.96]). There were no clear differences in the incidences of treatment-emergent adverse events (TEAEs), serious TEAEs, or TEAEs of interest between the 2 groups; moreover, no differences between the 2 groups were found for other laboratory parameters. CONCLUSION: PCSK9 antibodies have significant effects on reducing LDL-C levels and improve cardiovascular outcomes. These antibodies have a satisfactory safety profile, which suggests that they are suitable for use as a long-term treatment.

[30] *Shah SR, Abbasi Z, Fatima M et al.* **Canakinumab and cardiovascular outcomes: results of the CANTOS trial**. Journal of community hospital internal medicine perspectives 2018; 8:21-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29441161

ABSTRACT

IL-1 cytokines are mainly responsible for controlling a series of pro-inflammatory reactions induced in response to pathogen mediated tissue injury. Among the IL-1 cytokine family, IL-1 beta results in upregulation of genes responsible for boosting immune system reactivity and inflammatory response. With growing pathophysiological relevance of IL-1beta in a myriad of disease pathogenesis, new biological drugs have been developed in recent years. One such drug, Canakinumab, targeting IL-1beta has been recently approved for clinical use. The recent results from the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial are encouraging in this aspect. The results suggest that anti-inflammatory therapy using canakinumab at a dose of 150 mg every 3 months led to significantly lower recurrent cardiovascular events than the placebo drug. These results were independent of lipid-lowering effects of these drugs. If the results are widely applicable, the CANTOS trial would reaffirm the hypothesis of atherothrombosis due to inflammation, hence supporting the need for a cytokine-based therapy for the secondary prevention of cardiovascular diseases. Moreover, the potential benefits of the phenomenal reduction in the inflammatory cascade induced by canakinumab should be carefully balanced against its long-term safety profile which is yet unknown. However, the inflammatory hypothesis of atherothrombosis supports a cytokine-based therapy for the secondary prevention of cardiovascular disease. Furthermore, the potential benefits from the reduction in inflammatory markers induced by canakinumab should be carefully balanced against its unknown long-term safety profile.

[31] *Zhang N, Hu X, Zhang Q et al.* **Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio is an independent risk factor for diabetes mellitus: results from a population-based cohort**. Journal of diabetes 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29437292

ABSTRACT

BACKGROUND: Dyslipidemia predicts development and progression of diabetes. Higher non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (nonHDL-C/HDL-C) was reported to be associated with metabolic syndrome and insulin resistance in previous studies, but its relationship with glycemic levels and diabetes remains unclear. This study aimed to investigate the association of nonHDL-C/HDL-C with diabetes and to evaluate stability of this relationship in different subgroups. METHODS: 4882 participants (40 years of age or older) without diabetes and not using lipid-lowering drugs, were enrolled in this three-year cohort. NonHDL-C/HDL-C ratio was log 10-transformed to reach normal distribution. Logistic regression was used to investigate the association of log10 nonHDL-C/HDL-C ratio with diabetes. RESULTS: After three years of follow-up, 711 participants developed diabetes. Each SD increase of log10 nonHDL-C/HDL-C ratio was associated with higher fasting blood glucose (FPG) levels (beta, 0.1; 95% CI, 0.1 to 0.1), 2h plasma glucose levels after 75g oral glucose tolerance test (postload glucose) levels (beta, 0.2; 95% CI, 0.1 to 0.2) and risk of diabetes (OR, 1.1; 95% CI, 1.0 to 1.2) in multivariate model. Participants in the top quartile had higher FPG levels (beta, 0.2; 95% CI, 0.2 to 0.3), postload glucose levels (beta, 0.5; 95% CI, 0.3 to 0.7), hemoglobin A1C

levels (beta, 0.1; 95% CI, 0.1 to 0.2) and 40% increased risk of diabetes (OR, 1.4; 95% CI, 1.1 to 1.8) than the participants in the bottom quartile after adjustment. CONCLUSIONS: In this study, nonHDL-C/HDL-C ratio was found to be an independent risk factor for diabetes.

[32] *Feinkohl I, Winterer G, Pischon T*. **Associations of dyslipidaemia and lipid-lowering treatment with risk of postoperative cognitive dysfunction: a systematic review and meta-analysis**. Journal of epidemiology and community health 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29437865
ABSTRACT
BACKGROUND: Lipid imbalance is linked to age-related cognitive impairment, but its role in postoperative cognitive dysfunction (POCD) is unknown. Here, we present a systematic review and meta-analysis on dyslipidaemia, lipid-lowering treatment and POCD risk. METHODS: PubMed, Ovid SP and Cochrane databases were searched for longitudinal studies that reported on associations of any measure of dyslipidaemia and/or lipid-lowering treatment with POCD as relative risks (RRs) or ORs. Fixed-effects inverse variance models were used to combine effects. RESULTS: Of 205 articles identified in the search, 17 studies on 2725 patients (grand mean age 67 years; mean age range 61-71 years) with follow-up periods of 1 day to 4 years (median 7 days; IQR 1-68 days) were included. Studies focused almost exclusively on hypercholesterolaemia as a measure of dyslipidaemia and on statins as lipid-lowering treatment. Across 12 studies on hypercholesterolaemia, we found no association with POCD risk (RR 0.93; 95% CI 0.80 to 1.08; P=0.34). Statin use before surgery was associated with a reduced POCD risk across eight studies (RR 0.81; 95% CI 0.67 to 0.98; P=0.03), but data on treatment duration were lacking. CONCLUSION: Statin users appear to be at reduced risk of POCD although hypercholesterolaemia per se may not be associated with POCD risk. Trial studies are needed to evaluate the usefulness of statins in POCD prevention.

[33] *Lutski M, Haratz S, Weinstein G et al.* **Impaired Cerebral Hemodynamics and Frailty in Patients with Cardiovascular Disease**. J Gerontol A Biol Sci Med Sci 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29432609
ABSTRACT
Background: Recent studies suggest that impaired cerebrovascular reactivity (CVR), a marker of cerebral microvascular damage, is associated with a higher risk of stroke, cognitive decline and mortality. We tested whether abnormal cerebrovascular status is associated with late-life frailty among men with pre-existing cardiovascular disease. Methods: A subset of 327 men (mean age at baseline 56.7+/-6.5 years) who previously participated in the Bezafibrate Infarction Prevention (BIP) trial (1990-1997) and then in the BIP Neurocognitive study underwent a neurovascular evaluation 14.6+/-1.9 years after baseline (T1) and were evaluated for frailty 19.9+/-1.0 years after baseline (T2). CVR was measured at T1 using the breath-holding index and carotid large-vessel disease using ultrasound. Frailty status was measured at T2 according to the physical phenotype developed by Fried. Patients were categorized into CVR tertiles with cut-off points at </=0.57, 0.58-0.94 and >/=0.95 and also as normal or impaired (<0.69) CVR. We assessed the change in the odds of being in the advanced rank of frailty status (normal, pre-frail and frail) using ordered logistic regression. Results: After adjustment, the estimated OR for increasing frailty in the lower tertile was 1.94 (1.09-3.46) and in the middle tertile 1.24 (0.70-

2.19), as compared to the higher CVR tertile. The estimated OR for increasing frailty for patients with impaired vs. normal CVR was 1.76 (1.11-2.80). Conclusions: These findings provide support that cerebral microvascular dysfunction among patients with pre-existing cardiovascular disease is related to pre-frailty and frailty and suggest an added value of assessing the cerebral vascular functional status for identifying patients at-risk of developing frailty.

[34] *Thereaux J, Lesuffleur T, Czernichow S et al.* **Association Between Bariatric Surgery and Rates of Continuation, Discontinuation, or Initiation of Antidiabetes Treatment 6 Years Later**. JAMA surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29450469

ABSTRACT

Importance: Few large-scale long-term prospective cohort studies have assessed changes in antidiabetes treatment after bariatric surgery. Objective: To describe the association between bariatric surgery and rates of continuation, discontinuation, or initiation of antidiabetes treatment 6 years after bariatric surgery compared with a matched control obese group. Design, Setting, and Participants: This nationwide observational population-based cohort study extracted health care reimbursement data from the French national health insurance database from January 1, 2008, to December 31, 2015. All patients undergoing primary bariatric surgery in France between January 1 and December 31, 2009, were matched on age, sex, body mass index category, and antidiabetes treatment with control patients hospitalized for obesity in 2009 with no bariatric surgery between 2005 and 2015. Exposures: Bariatric surgery, including adjustable gastric banding (AGB), gastric bypass (GBP), and sleeve gastrectomy (SG). Main Outcome and Measure: Reimbursement for antidiabetes drugs. Mixed-effects logistic regression models estimated factors of discontinuation or initiation of antidiabetes treatment over a period of 6 years. Results: In 2009, a total of 15650 patients (mean [SD] age, 38.9 [11.2] years; 84.6% female; 1633 receiving antidiabetes treatment) underwent primary bariatric surgery, with 48.5% undergoing AGB, 27.7% undergoing GBP, and 22.0% undergoing SG. Among patients receiving antidiabetes treatment at baseline, the antidiabetes treatment discontinuation rate was higher 6 years after bariatric surgery than in controls (-49.9% vs -9.0%, P < .001). In multivariable analysis, the main predictive factors for discontinuation were the following: GBP (odds ratio [OR], 16.7; 95% CI, 13.0-21.4), SG (OR, 7.30; 95% CI, 5.50-9.50), and AGB (OR, 4.30; 95% CI, 3.30-5.60) compared with no bariatric surgery, as well as insulin use (OR, 0.17; 95% CI, 0.13-0.22), dual therapy without insulin (OR, 0.38; 95% CI, 0.32-0.45) vs monotherapy, lipid-lowering treatment (OR, 0.76; 95% CI, 0.63-0.91), antidepressant treatment (OR, 0.67; 95% CI, 0.55-0.81), and age (OR, 0.96; 95% CI, 0.95-0.97) per year. For patients without antidiabetes treatment at baseline, the 6-year antidiabetes treatment initiation rate was much lower after bariatric surgery than in controls (1.4% vs 12.0%, P < .001). In multivariable analysis, protective factors were GBP (OR, 0.06; 95% CI, 0.04-0.09), SG (OR, 0.08; 95% CI, 0.06-0.11), and AGB (OR, 0.16; 95% CI, 0.14-0.20) vs controls, and risk factors were as follows: body mass index category (OR, 2.04; 95% CI, 1.68-2.47 for >/=50.0 vs 30.0-39.9 and OR, 1.68; 95% CI, 1.49-1.90 for 40.0-49.9 vs 30.0-39.9), antihypertensive treatment (OR, 1.49; 95% CI, 1.33-1.67), low income (OR, 1.43; 95 % CI, 1.26-1.62), and age (OR, 1.04; 95 % CI, 1.03-1.05) per year. Conclusions and Relevance: Bariatric surgery was associated with a significantly higher

6-year postoperative antidiabetes treatment discontinuation rate compared with baseline and with an obese control group without bariatric surgery.

[35] *Dhungel S, Malla R, Adhikari C et al.* **Prehospital Events in ST- Elevation Myocardial Infarction Undergoing Primary Angioplasty**. JNMA; journal of the Nepal Medical Association 2017; 56:421-425.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29453473
ABSTRACT
INTRODUCTION: Pre-hospital delay includes time from onset of symptoms of myocardial infarction till arrival to emergency room of the hospital. This defines time from symptom onset to first medical contact and first medical contact to emergency room. This study aims to study the prehospital events and determining factors in patients undergoing primary angioplasty. METHODS: This was a cross sectional study in Shahid Gangalal National Heart Centre for three months. Timings of chest pain, first medical contact time, transfer time to hospital and overall pre-hospital time for PCI and risk factors were analysed. RESULTS: There were 79 cases with 66 (83.5%) males and 13 (16.5%) females with mean age 56+/-11.2 years. Risk factors were 60 (75.9%), smoking, 47 (59.5%) hypertension, 25 (31.6%) diabetes, 22 (27.8%) dyslipidaemia and 16 (20.3%) heart failure. Chest pain was maximum in 5 to 9 AM. The median prehospital delay was 300 minutes (5.0 hours) of which symptom to first medical contact was 165 minutes and first medical contact to hospital was 80 minutes. The longer median prehospital delay for hypertension, diabetes, female and age >/=50 years and the shorter for male, age less than 50 years, dyslipidemia and heart failure, though not statistically significant. Private transport was the preferred from symptom to first medical contact and ambulance for first medical contact to emergency room. Patients received in ER had aspirin 72 (91.1%), atorvastatin 54 (68.4%) and double anti-platelets 45 (57%). CONCLUSIONS: Chest pain was common in morning and the prehospital delay can be minimized by improving time from symptom to first medical contact and first medical contact to Emergency room.

[36] *Dwivedi A, Al'Aref SJ, Lin FY, Min JK*. **Evaluation of Atherosclerotic Plaque in Non-invasive Coronary Imaging**. Korean circulation journal 2018; 48:124-133.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29441745
ABSTRACT
Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Over the last decade coronary computed tomography angiography (CCTA) has gained wide acceptance as a reliable, cost-effective and non-invasive modality for diagnosis and prognostication of CAD. Use of CCTA is now expanding to characterization of plaque morphology and identification of vulnerable plaque. Additionally, CCTA is developing as a non-invasive modality to monitor plaque progression, which holds future potential in individualizing treatment. In this review, we discuss the role of CCTA in diagnosis and management of CAD. Additionally, we discuss the recent advancements and the potential clinical applications of CCTA in management of CAD.

[37] *Wang Z, Wang D, Wang Y*. **Cigarette Smoking and Adipose Tissue: The Emerging Role in Progression of Atherosclerosis**. Mediators of inflammation 2017; 2017:3102737.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29445255

ABSTRACT

Smoking is an established risk factor for atherosclerosis through several underlying pathways. Moreover, in the development of atherosclerotic plaque formation, obesity, defined as excess fat mass accumulation, also plays a vital role in dyslipidemia and insulin resistance. Substantial evidence shows that cigarette smoking induces multiple pathological effects in adipose tissue, such as differentiation of adipocytes, lipolysis, and secretion properties in adipose tissue. Therefore, there is an emerging speculation in which adipose tissue abnormality induced by smoking or nicotine is likely to accelerate the progression of atherosclerosis. Herein, this review aims to investigate the possible interplay between smoking and adipose tissue dysfunction in the development of atherosclerosis.

[38] *Khan TJ, Ahmed YM, Zamzami MA et al.* **Atorvastatin Treatment Modulates the Gut Microbiota of the Hypercholesterolemic Patients**. Omics : a journal of integrative biology 2018; 22:154-163.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29432061

ABSTRACT

Hypercholesterolemia is one of the most important risk factors for development of cardiovascular diseases. The composition of gut microbiota (total microbes residing in the gut) impacts on cholesterol and lipid metabolism. On the contrary, alterations in gut microbiota in response to hypercholesterolemia or drug treatment with atorvastatin (a cholesterol-lowering agent) are rarely investigated. We performed 16S rDNA amplicon sequencing to evaluate the gut bacterial community of 15 untreated hypercholesterolemic patients (HP) and 27 atorvastatin-treated hypercholesterolemic patients (At-HP) and compared with 19 healthy subjects (HS). In total, 18 different phyla were identified in the study groups. An increase in relative abundance of Proteobacteria was observed in the HP group compared with At-HP and HS groups. The atherosclerosis-associated genus Collinsella was found at relatively higher abundance in the HP group. The anti-inflammation-associated bacteria (Faecalibacterium prausnitzii, Akkermansia muciniphila, and genus Oscillospira) were found in greater abundance, and proinflammatory species Desulfovibrio sp. was observed at decreased abundance in the drug-treated HP group compared with the untreated HP group. Relative abundances of the Bilophila wadsworthia and Bifidobacterium bifidum (bile acid-associated species) were decreased in the At-HP group. The At-HP and HS clustered separately from HP in the principal coordinate analysis. Decreased bacterial diversity was observed in the atorvastatin-treated group. In conclusion, these data suggest that atorvastatin treatment of patients with hypercholesterolemia may selectively restore the relative abundance of several dominant and functionally important taxa that were disrupted in the HP. Further studies are required to investigate the putative modifying effects of hypocholesterolemic drugs on functionality of gut microbiota, and the potential downstream effects on human health.

[39] *Baragetti A, Grejtakova D, Casula M et al.* **Proprotein Convertase Subtilisin-Kexin type-9 (PCSK9) and triglyceride-rich lipoprotein metabolism: Facts and gaps**. Pharmacological research : the official journal of the Italian Pharmacological Society 2018; 130:1-11.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29428206

ABSTRACT
After more than a decade of intense investigation, Pro-protein Convertase Subtilisin-Kexin type 9 (PCSK9) remains a hot topic of research both at experimental and clinical level. Interestingly PCSK9 is expressed in different tissues suggesting the existence of additional function(s) beyond the modulation of the Low-Density Lipoprotein (LDL) receptor in the liver. Emerging data suggest that PCSK9 might play a role in the modulation of triglyceride-rich lipoprotein (TGRL) metabolism, mainly Very Low-Density Lipoproteins (VLDL) and their remnants. In vitro, PCSK9 affects TGRLs production by intestinal cells as well as the catabolism of LDL receptor homologous and non-homologous targets such as VLDL receptor, CD36 and ApoE2R. However, the in vivo relevance of these findings is still debated. This review aims at critically discussing the role of PCSK9 on TGRLs metabolism with a major focus on the impact of its genetic and pharmacological modulation on circulating lipids and lipoproteins beyond LDL.

[40] *Mladenovska K, Grapci AD, Vavlukis M et al.* **Influence of SLCO1B1 polymorphisms on atorvastatin efficacy and safety in Macedonian subjects**. Pharmazie 2017; 72:288-295.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29441875

ABSTRACT
Atorvastatin, as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, is a widely prescribed medication for the treatment of dyslipidemia. However, despite its clinical efficacy in reducing major cardiovascular events, a wide inter-individual variability in its response exists. Several studies in this area point to the effect of polymorphisms in the solute carrier organic anion transporter 1B1 (SLCO1B1) gene encoding the multiple organic anion-transporting polypeptide 1B1 (OATP1B1) involved in hepatic uptake of atorvastatin. Hence, the aim of this study was to analyze the association between the SLCO1B1 c.388A>G, c.521T>C, c.571T>C, c.597C>T, c.1086C>T, c.1463G>C and c.*439T>G polymorphisms and lipid-lowering effect and safety of atorvastatin. A hundred and fifty six patients with hyperlipidemia IIa and IIb, all of Macedonian origin, were included in the study receiving atorvastatin 20 - 80 mg/day for 3 months. SLCO1B1 single nucleotide polymorphisms (SNPs) were genotyped using the TaqMan allelic discrimination assay. As parameters of atorvastatin response, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein A (ApoAI), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), creatine phosphokinase (CPK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured, using standard laboratory methods, at baseline and after 3 months of treatment. No statistically significant association between the different SLCO1B1 SNPs and atorvastatin response was observed. However, the carriers of c.521CC manifested a lower decrease in plasma levels of TG, TC, LDL-C and Lp(a), with percentage difference being 16%, 7%, 29% and 149%, respectively, compared to the carriers of c.521TT variant. Lower increase in HDL-C (271%) and ApoAI (293%) and higher increase in CPK (69%) in c.521CC carriers were also observed, confirming the lower OATP1B1 activity in carriers of the variant c.521 C allele. Similar results were obtained when a comparison between the percentage of biochemical parameter change was made between *15/*16/*17 heterozygotes and *15/*16/*17 non-carriers. The lack of a statistically significant association between the SLCO1B1 polymorphism and atorvastatin response can be explained dominantly by the low number of individuals homozygous for the rare c.521C variant allele. Despite this limitation, the study offers valuable information on the

influence of the genetic determinant SLCO1B1 on atorvastatin response in the Macedonian population.

[41] *Samardzic I, Benkovic I, Vrca VB*. **Incidence of statin-drug interactions in Croatian community pharmacy**. Pharmazie 2017; 72:187-191.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29442055
ABSTRACT
Statins are among the most frequently issued drugs that patients usually need to take for a lifetime. They are often an integral part of a polytherapeutic approach in preventing and treating cardiovascular diseases. As such, they might often interact with drugs prescribed for treating acute and chronic conditions. A pharmacist is the final professional control before a drug reaches the patient and his role in preventing drug-drug interactions is crucial. The objective of this research was to analyse the incidence and relevance of potential drug interactions with statins in community pharmacy. We retrospectively analysed the prescribed pharmacotherapy of 153 patients who were taking statins. Lexicomp(R) Lexi-Interact Online (Lexi-Comp, Inc., Hudson, USA) was used to identify interactions. The mean age of study patients was 65.5 (52.3% women). The most frequently used statin was atorvastatin and the least used was fluvastatin. The average number of coprescribed drugs was 4. The highest number of interactions which required enhanced patient surveillance were registered with atorvastatin, while interactions which might need specific therapy modification were mostly seen with simvastatin. Systematic and regular control of potential clinically significant drug-drug interactions in the prescribed pharmacotherapy is important for therapy outcomes and appropriate pharmaceutical surveillance in issuing pharmacotherapy.

[42] *Wang Y, Tian Y, Lv P et al.* **The effect of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Chinese people**. Pharmazie 2017; 72:365-368.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29442027
ABSTRACT
The pharmacokinetics of statins show substantial inter-subject variability. Increasing systemic exposure of statins may lead to adverse drug reactions such as myopathy. The variation in statin pharmacokinetics is partly explained by genetic factors. OATP1B1, coded by SLCO1B1 transports a large number of therapeutic drugs, such as atorvastatin. Here we investigated the effect of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and its metabolites. Two pharmacokinetic studies were conducted in Chinese Han volunteers and 132 volunteers were enrolled in our study as 72 in trial 1 and 60 in trial 2. A LC-MS/MS method was developed for the identification and quantification of atorvastatin acid and its metabolites. S LCO1B1 c.521T>C (rs4149056) was identified by the MALDI-TOF MS and Sequenom MassARRAY system. The distribution frequencies of SLCO1B1 c.521T>C were in agreement with Hardy-Weinberg equilibrium both in trial 1 and trial 2. In subjects with 521C allele the mean Cmax, AUC0-24h and AUC0-infinity of atorvastatin acid and 2-hydroxyatorvastatin acid were significantly higher than subjects with 521TT genotype, while the mean CL was lower. In conclusion, our results suggested that SLCO1B1 c.521T>C had an effect on the pharmacokinetics of atorvastatin and 2-

hydroxyatorvastatin in Chinese Han population. Subjects with 521C allele have an increased risk of toxic effects caused by atorvastatin.

[43] *Arama C, Diarra I, Kouriba B et al.* **Malaria severity: Possible influence of the E670G PCSK9 polymorphism: A preliminary case-control study in Malian children**. PloS one 2018; 13:e0192850.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29447211
ABSTRACT
AIM: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a hepatic secretory protein which promotes the degradation of low-density lipoprotein receptors leading to reduced hepatic uptake of plasma cholesterol. Non-synonymous single-nucleotide polymorphisms in its gene have been linked to hypo- or hyper- cholesterolemia, depending on whether they decrease or increase PCSK9 activity, respectively. Since the proliferation and the infectivity of Plasmodium spp. partially depend on cholesterol from the host, we hypothesize that these PCSK9 genetic polymorphisms could influence the course of malaria infection in individuals who carry them. Here we examined the frequency distribution of one dominant (C679X) and two recessive (A443T, I474V) hypocholesterolemic polymorphisms as well as that of one recessive hypercholesterolemic polymorphism (E670G) among healthy and malaria-infected Malian children. METHODS: Dried blood spots were collected in Bandiagara, Mali, from 752 age, residence and ethnicity-matched children: 253 healthy controls, 246 uncomplicated malaria patients and 253 severe malaria patients. Their genomic DNA was extracted and genotyped for the above PCSK9 polymorphisms using Taqman assays. Associations of genotype distributions and allele frequencies with malaria were evaluated. RESULTS: The minor allele frequency of the A443T, I474V, E670G, and C679X polymorphisms in the study population sample was 0.12, 0.20, 0.26, and 0.02, respectively. For each polymorphism, the genotype distribution among the three health conditions was statistically insignificant, but for the hypercholesterolemic E670G polymorphism, a trend towards association of the minor allele with malaria severity was observed (P = 0.035). The association proved to be stronger when allele frequencies between healthy controls and severe malaria cases were compared (Odd Ratio: 1.34; 95% Confidence Intervals: 1.04-1.83); P = 0.031). CONCLUSIONS: Carriers of the minor allele of the E670G PCSK9 polymorphism might be more susceptible to severe malaria. Further investigation of the cholesterol regulating function of PCSK9 in the pathophysiology of malaria is needed.

[44] *Kawakami R, Nozato Y, Nakagami H et al.* **Development of vaccine for dyslipidemia targeted to a proprotein convertase subtilisin/kexin type 9 (PCSK9) epitope in mice**. PloS one 2018; 13:e0191895.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29438441
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates expression of low-density lipoprotein (LDL) receptors via receptor internalization and subsequent lysosomal degradation. Thus, an anti-PCSK9 antibody is well known as an anti-hyperlipidemia drug. Here, we aimed to develop vaccine for a long-term treatment of dyslipidemia targeted to PCSK9. In This study, we designed a peptide vaccine for mouse PCSK-9, which consisted of short peptides conjugated to keyhole limpet hemocyanin (KLH) as a carrier protein. Vaccines were administered to male

apolipoprotein E (ApoE) deficient mice with adjuvants and significantly elicited an antibody response against PCSK9. The PCSK9 vaccines were administered to mice three times in 2-week intervals, and antibody titers and lipoprotein levels were evaluated up to 24 weeks after the first immunization to determine the therapeutic effect. Anti-PCSK9 antibody titers reached peak levels 6 weeks after the first immunization, and theses titers were maintained for up to 24 weeks. Decreased plasma levels of total cholesterol, very low-density lipoprotein (VLDL), and chylomicron (CM) were maintained for up to 24 weeks. Immunized mice exhibited a significant increase in cell-surface LDL receptor expression. Stimulation with KLH, but not PCSK9, induced the production of INF-gamma and interleukin-4 (IL-4), as determined with ELISPOT assays, thus indicating that PCSK9 vaccine did not elicit T-cell activation in our vaccine system. The present anti-PCSK9 vaccine induced long-lasting anti-PCSK9 antibody production and improved lipoprotein profiles. Thus, anti-PCSK9 vaccine could become a new option for the treatment of dyslipidemia as a long-acting therapy in future.

[45] *Wang Q, Guo L, Strawser CJ et al.* **Low apolipoprotein A-I levels in Friedreich's ataxia and in frataxin-deficient cells: Implications for therapy**. PloS one 2018; 13:e0192779.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29447225

ABSTRACT

Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder, which results primarily from reduced expression of the mitochondrial protein frataxin. FA has an estimated prevalence of one in 50,000 in the population, making it the most common hereditary ataxia. Paradoxically, mortality arises most frequently from cardiomyopathy and cardiac failure rather than from neurological effects. Decreased high-density lipoprotein (HDL) and apolipoprotein A-I (ApoA-I) levels in the general population are associated with an increased risk of mortality from cardiomyopathy and heart failure. However, the pathophysiology of heart disease in FA is non-vascular and there are conflicting data on HDL-cholesterol in FA. Two studies have shown a decrease in HDL-cholesterol compared with controls and two have shown there was no difference between FA and controls. One also showed that there was no difference in serum Apo-A-I levels in FA when compared with controls. Using a highly specific stable isotope dilution mass spectrometry-based assay, we demonstrated a 21.6% decrease in serum ApoA-I in FA patients (134.8 mg/dL, n = 95) compared with non-affected controls (172.1 mg/dL, n = 95). This is similar to the difference in serum ApoA-I levels between non-smokers and tobacco smokers. Knockdown of frataxin by > 70% in human hepatoma HepG2 cells caused a 20% reduction in secreted ApoA-I. Simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor caused a 200% increase in HMG-CoA in the control HepG2 cells with a similar increase in the frataxin knockdown HepG2 cells, back to levels found in the control cells. There was a concomitant 20% increase in secreted ApoA-I to levels found in the control cells that were treated with simvastatin. This study provides compelling evidence that ApoA-I levels are reduced in FA patients compared with controls and suggest that statin treatment would normalize the ApoA-I levels.

[46] *Bochud M*. **On the rationale of population screening for chronic kidney disease: a public health perspective**. Public health reviews 2015; 36:11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29450039

ABSTRACT
Unlike opportunistic screening, population screening is accompanied by stringent quality control measures and careful programme monitoring. Sufficient evidence for benefit together with acceptable harms and costs to society are needed before launching a programme. A screening programme is a complex process organized at the population level involving multiple actors of the health care system that should ideally be supervised by public health authorities and evaluated by an independent and trustful body. Chronic kidney disease is defined by reduced glomerular filtration rate and/or presence of kidney damage for at least three months. Chronic kidney disease is divided into 5 stages with stages 1 to 3 being usually asymptomatic. Chronic kidney disease affects one in ten adults worldwide and its prevalence sharply increases with age. Kidney function is measured using serum creatinine-based, and/or cystatin C-based, equations. Markers of renal function show high intra-individual and inter-laboratory variabilities, highlighting the need for standardized procedures. There is also large inter-individual variability in age-related kidney function decline. Despite these limitations, chronic kidney disease, as currently defined, has been consistently associated with high cardiovascular morbidity and mortality and high risk of end-stage renal disease. Major modifiable risk factors for chronic kidney disease are diabetes, hypertension, obesity and cardiovascular disease. Several treatment options, ranging from antihypertensive and lipid-lowering treatments to dietary measures, reduce all-cause mortality and/or end-stage renal disease in patients with stages 1-3 chronic kidney disease. So far, no randomized controlled trial comparing outcomes with and without population screening for stages 1-3 chronic kidney disease has been published. Population screening for stages 1-3 chronic kidney disease is currently not recommended because of insufficient evidence for benefit. Given the current and future burden attributable to chronic kidney disease, randomized controlled trials exploring benefits and harms of population screening are clearly needed to prioritize resource allocations.

[47] *Richter CP, Young H, Richter SV et al.* **Fluvastatin protects cochleae from damage by high-level noise**. Scientific reports 2018; 8:3033.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29445111

ABSTRACT
Exposure to noise and ototoxic drugs are responsible for much of the debilitating hearing loss experienced by about 350 million people worldwide. Beyond hearing aids and cochlear implants, there have been no other FDA approved drug interventions established in the clinic that would either protect or reverse the effects of hearing loss. Using Auditory Brainstem Responses (ABR) in a guinea pig model, we demonstrate that fluvastatin, an inhibitor of HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway, protects against loss of cochlear function initiated by high intensity noise. A novel synchrotron radiation based X-ray tomographic method that imaged soft tissues at micrometer resolution in unsectioned cochleae, allowed an efficient, qualitative evaluation of the three-dimensional internal structure of the intact organ. For quantitative measures, plastic embedded cochleae were sectioned followed by hair cell counting. Protection in noise-exposed cochleae is associated with retention of inner and outer hair cells. This study demonstrates the potential of HMG-CoA reductase inhibitors, already vetted in human medicine for other purposes, to protect against noise induced hearing loss.

[48] *Turner GM, Calvert M, Feltham MG et al.* **Clinical and Demographic Characteristics Associated With Suboptimal Primary Stroke and Transient Ischemic Attack Prevention: Retrospective Analysis**. Stroke 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29440471
ABSTRACT
BACKGROUND AND PURPOSE: Primary prevention of stroke and transient ischemic attack (TIA) is important to reduce the burden of these conditions; however, prescribing of prevention drugs is suboptimal. We aimed to identify individual clinical and demographic characteristics associated with potential missed opportunities for prevention therapy with lipid-lowering, anticoagulant, or antihypertensive drugs before stroke/TIA. METHODS: We analyzed anonymized electronic primary care records from a UK primary care database that covers 561 family practices. Patients with first-ever stroke/TIA, >/=18 years, with diagnosis between January 1, 2009, and December 31, 2013, were included. Missed opportunities for prevention were defined as people with clinical indications for lipid-lowering, anticoagulant, or antihypertensive drugs but not prescribed these drugs before their stroke/TIA. Mixed-effect logistic regression models evaluated the relationship between missed opportunities and individual clinical/demographic characteristics. RESULTS: The inclusion criteria were met by 29 043 people with stroke/TIA. Patients with coronary heart disease, chronic kidney disease, peripheral arterial disease, or diabetes mellitus were at less risk of a missed opportunity for prescription of lipid-lowering and antihypertensive drugs. However, patients with a 10-year cardiovascular disease risk >/=20% but without these diagnoses had increased risk of having a missed opportunity for prescription of lipid-lowering drugs or antihypertensive drugs. Women were less likely to be prescribed anticoagulants but more likely to be prescribed antihypertensive drugs. The elderly (>/=85 years of age) were less likely to be prescribed all 3 prevention drugs, compared with people aged 75 to 79 years. CONCLUSIONS: Knowing the patient characteristics predictive of missed opportunities for stroke prevention may help primary care identify and appropriately manage these patients. Improving the management of these groups may reduce their risk and potentially prevent large number of future strokes and TIAs in the population.

[49] *Schadt HS, Wolf A, Mahl JA et al.* **Bile acid sequestration by cholestyramine mitigates FGFR4 inhibition-induced ALT elevation**. Toxicological sciences : an official journal of the Society of Toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29432567
ABSTRACT
The FGF19-FGFR4-betaKlotho (KLB) pathway plays an important role in the regulation of bile acid (BA) homeostasis. Aberrant activation of this pathway has been described in the development and progression of a subset of liver cancers including hepatocellular carcinoma (HCC), establishing FGFR4 as an attractive therapeutic target for such solid tumors. FGF401 is a highly selective FGFR4 kinase inhibitor being developed for HCC, currently in Phase I/II clinical studies. In preclinical studies in mice and dogs, oral administration of FGF401 led to induction of Cyp7a1, elevation of its peripheral marker 7alpha-hydroxy-4-cholesten-3-one (C4), increased BA pool size, decreased serum cholesterol and diarrhea in dogs. FGF401 was also associated with

increases of serum aminotransferases, primarily alanine aminotransferase (ALT), in the absence of any observable adverse histopathological findings in the liver, or in any other organs. We hypothesized that the increase in ALT could be secondary to increased BAs and conducted an investigative study in dogs with FGF401 and co-administration of the BA sequestrant cholestyramine (CHO). CHO prevented and reversed FGF401-related increases in ALT in dogs in parallel to its ability to reduce BAs in the circulation. Correlation analysis showed that FGF401-mediated increases in ALT strongly correlated with increases in taurolithocholic acid (TLCA) and taurodeoxycholic acid (TDCA), the major secondary BAs in dog plasma, indicating a mechanistic link between ALT elevation and changes in BA pool hydrophobicity. Thus, CHO may offer the potential to mitigate elevations in serum aminotransferases in human subjects that are caused by targeted FGFR4 inhibition and elevated intracellular BA levels.

[50] *Power TP, Ke X, Zhao Z et al.* **Clinical characteristics, patterns of lipid-lowering medication use, and health care resource utilization and costs among patients with atherosclerotic cardiovascular disease**. Vascular health and risk management 2018; 14:23-36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29440909

ABSTRACT

Purpose: The aim of this study was to investigate real-world patient characteristics, medication use, and health care resource utilization (HCRU) and costs among patients with clinical atherosclerotic cardiovascular disease (ASCVD) as defined by 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, to examine burden of disease and unmet needs, such as potential undertreatment. Patients and methods: This retrospective cohort study utilized a nationally representative managed care database to identify newly diagnosed ASCVD patients between January 1, 2007, and November 30, 2012 (index = first ASCVD diagnosis date) in the USA. Patients had >/=12-month pre-index (baseline) and >/=12-month post-index (follow-up) health plan enrollment and no baseline lipid-lowering medication (LLM). Patient characteristics, LLM utilization patterns, HCRU, and costs were examined for all patients and by subgroups based on LLM use pattern and/or follow-up low-density lipoprotein cholesterol (LDL-C) levels. Results: A total of 128,017 ASCVD patients were identified with a mean (SD) age of 59 (13) years, 43.1% female, and 48.8% with >/=36-month follow-up. Within 12-month follow-up, 10.6% had high-intensity statins and 56.9% had no LLM fills. Baseline mean (SD) all-cause costs were $8,852 ($25,608). At 12-month follow-up, mean (SD) all-cause and ASCVD-related costs were $31,443 ($54,040) and $20,289 ($45,159), respectively. The 36-month analyses showed similar distributions. Multivariable analyses showed that age, gender, region, health insurance type, baseline comorbidities, baseline use of specific medications, baseline lipid profiles, and index ASCVD type were significantly associated with all-cause and ASCVD-related health care costs. Conclusion: Patients have nonoptimal treatment for ASCVD and substantial HCRU and costs associated with residual risk. Unmet needs and cost burdens of ASCVD patients merit additional investigation.