

Literature update week 14 (2018)

[1] *Shahid N, Adnan S, Farooq M et al. DEVELOPMENT OF COMPRESSED COATED POLYPILL WITH MUCOADHESIVE CORE COMPRISING OF ATORVASTATIN/CLOPIDOGREL/ASPIRIN USING COMPRESSION COATING TECHNIQUE. Acta poloniae pharmaceutica 2017; 74:477-487.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29624252>

ABSTRACT

The study was conducted to formulate and assess a novel polypill comprising of atorvastatin calcium (ATVC), clopidogrel bisulfate (CLB) and aspirin (ASP) which, after in vivo correlation, can be intended for use in hyperlipidemic chronic heart disease patients. Polypill was made by the compression coating technique (CCT) with multiple active ingredients along with different concentrations of mucoadhesive and sustained release polymers, i.e., Carbopol 934 (CAB), Methocel k15 (MTH) and sodium carboxymethyl cellulose (NaCMC). The effect of different concentration of polymers on physical properties, wash off time, mucoadhesion strength, swelling behavior, surface pH and drug release kinetics were investigated. In vitro drug release studies showed that combination of CAB-NaCMC (1 : 1) retarded drug release up to 96.7 +/- 1.15%, while combination of CAB-MTH and MTH-NaCMC retarded drug release up to 81.9 +/- 1.5% and 101.4 +/- 1.3%, respectively, at the same polymer concentration. Core enteric coated tablet of ATVC (K 11) was compressed over with CLB and ASP granules with the help of CCT and produced the desired results with zero order release rate thus indicating successful formulation of proposed polypill.

[2] *Cesena FHY, Laurinavicius AG, Valente VA et al. Statin Eligibility in Primary Prevention: From a Risk-Based Strategy to a Personalized Approach Based on the Predicted Benefit. The American journal of cardiology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29605080>

ABSTRACT

Guidelines have recommended statin initiation based on the absolute cardiovascular risk. We tested the hypothesis that a strategy based on the predicted cardiovascular benefit, compared with the risk-based approach, modifies statin eligibility and the estimated benefit in a population in primary cardiovascular prevention. The study included 16,008 subjects (48 +/- 6 years, 73% men) with low-density lipoprotein cholesterol levels of 70 to <190 mg/dl, not on lipid-lowering drugs, who underwent a routine health screening in a single center. For the risk-based strategy, criterion for statin eligibility was defined as a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of $\geq 7.5\%$. In the benefit-based strategy, subjects were considered for statin according to the predicted absolute cardiovascular risk reduction, so that the number of statin candidates would be the same as in the risk-based strategy. The benefit-based strategy would replace 11% of statin candidates allocated in the risk-based approach with younger, lower risk subjects with higher low-density lipoprotein cholesterol. Using the benefit-based strategy, 13% of subjects with 5.0% to < 7.5% ASCVD risk would shift from a statin-ineligible to a statin-eligible status, whereas 24% of those with 7.5% to <10.0% ASCVD risk would become statin ineligible. These effects would transfer the benefit from higher to lower risk subjects. In the entire population, no clinically meaningful change in the benefit would be expected. In conclusion, switching from a risk-based strategy to a benefit-based approach, while keeping the same rate of statin use in the population, is expected to promote

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substantial changes in statin eligibility in subjects at intermediate cardiovascular risk, modifying the subpopulation to be benefited by the treatment.

[3] Ong KL, Morris MJ, McClelland RL et al. **Relationship of Lipids and Lipid-Lowering Medications With Cognitive Function: The Multi-Ethnic Study of Atherosclerosis.** American journal of epidemiology 2018; 187:767-776.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617947>

ABSTRACT

Studies on the relationship of cholesterol concentrations and lipid-lowering medications with dementia risk have yielded inconsistent findings. Therefore, we investigated the association of lipid concentrations and lipid-lowering medications with cognitive function in the Multi-Ethnic Study of Atherosclerosis across 3 different cognitive domains assessed by means of the Cognitive Abilities Screening Instrument (CASI; version 2), the Digit Symbol Coding (DSC) Test, and the Digit Span (DS) Test in 2010-2012. After adjustment for sociodemographic and confounding factors, including concentrations of other lipids and use of lipid-lowering medication, higher total cholesterol, low-density lipoprotein cholesterol, and non-high-density-lipoprotein cholesterol concentrations were modestly associated with higher DS Test scores. None of the lipid parameters were associated with CASI or DSC Test scores. Similarly, changes in lipid concentrations were not associated with any cognitive function test score. Using treatment effects model analysis and after adjusting for confounding factors, including lipid concentrations, the use of any lipid-lowering medication, especially statins, was associated with higher scores on the CASI and backward DS tests but not on the DSC and forward DS tests. Our study does not support a robust association between lipid concentrations and cognitive function or between the use of lipid-lowering medication, especially statins, and worse cognitive function.

[4] Dhar I, Lysne V, Seifert R et al. **Plasma methionine and risk of acute myocardial infarction: Effect modification by established risk factors.** Atherosclerosis 2018; 272:175-181.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29621698>

ABSTRACT

BACKGROUND AND AIMS: Methionine (Met) is an essential amino acid involved in methylation reactions and lipid metabolism. A Met-deficient diet may cause hepatic lipid accumulation, which is considered an independent risk factor for atherosclerosis. However, the prospective relationship between circulating Met and incident acute myocardial infarction (AMI) is unknown. METHODS: We studied the associations of plasma Met and incident AMI in 4156 patients (77% men; median age 62 years) with stable angina pectoris, among whom the majority received lipid lowering therapy with statins. Risk associations were estimated using Cox-regression analyses. RESULTS: Plasma Met was negatively related to age, serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and apolipoprotein (apo) B at baseline (all $p < / = 0.05$). During a median follow-up of 7.5 years, 534 (12.8%) patients experienced an AMI. There was no overall association between plasma Met and incident AMI; however, plasma Met was inversely associated with risk among patients with high as compared to low levels of serum LDL-C or apo B 100 (multivariate adjusted HRs per SD [95% CI] 0.84 [0.73-0.96] and 0.83[0.73-0.95], respectively; p -interaction $< / = 0.02$). Trends towards an inverse risk

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relationship were also observed among those younger than 62 years and patients without diabetes or hypertension. **CONCLUSIONS:** Low plasma Met was associated with increased risk of AMI in patients with high circulating levels of atherogenic lipids, but also in subgroups with presumably lower cardiovascular risk. The determinants of Met status and their relation with residual cardiovascular risk in patients with coronary heart disease should be further investigated.

[5] Masuda Y, Kurikawa N, Nishizawa T. **Overexpressing human GPR109A leads to pronounced reduction in plasma triglyceride levels in BAC transgenic rats.** *Atherosclerosis* 2018; 272:182-192.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29625294>

ABSTRACT

BACKGROUND AND AIMS: Nicotinic acid administration causes plasma non-esterified fatty acid (NEFA) reduction and plasma lipid changes, including reduced triglyceride levels. GPR109A, which is expressed mainly in adipose tissue and has anti-lipolytic activity, was reported to be a molecular target for nicotinic acid. However, recent clinical reports have shown that most GPR109A agonists failed to induce clinically meaningful plasma lipid changes. In addition, a recent study has shown that the TG lowering effect of nicotinic acid was not diminished in Gpr109a deficient mice, which is different from the original finding. Therefore, whether GPR109A activation can lead to plasma lipid changes is unclear. **METHODS:** We created a bacterial artificial chromosome (BAC) transgenic rat expressing human GPR109A (Tg rat) and examined the in vivo role of GPR109A. **RESULTS:** Under fasted conditions, plasma NEFA and triglyceride levels in Tg rats were lower than those in non-Tg rats. In this condition, a positive correlation between plasma NEFA and triglyceride or beta-hydroxybutyrate levels was observed. Furthermore, insulin levels in Tg rats were lower than those in non-Tg rats only when a reduction in NEFAs was observed, which is a phenomenon also reported for nicotinic acid. Interestingly, body weight gain in Tg rats was significantly lower than in non-Tg rats. **CONCLUSIONS:** These results suggest that GPR109A signaling leads to a reduction in triglyceride and insulin levels, and that the triglyceride-lowering effect of nicotinic acid is at least partially mediated by GPR109A signaling.

[6] Rossmeisl M, Pavlisova J, Janovska P et al. **Differential modulation of white adipose tissue endocannabinoid levels by n-3 fatty acids in obese mice and type 2 diabetic patients.** *Biochimica et biophysica acta* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29626526>

ABSTRACT

n-3 polyunsaturated fatty acids (n-3 PUFA) might regulate metabolism by lowering endocannabinoid levels. We examined time-dependent changes in adipose tissue levels of endocannabinoids as well as in parameters of glucose homeostasis induced by n-3 PUFA in dietary-obese mice, and compared these results with the effect of n-3 PUFA intervention in type 2 diabetic (T2DM) subjects. Male C57BL/6J mice were fed for 8, 16 or 24 weeks a high-fat diet alone (cHF) or supplemented with n-3 PUFA (cHF+F). Overweight/obese, T2DM patients on metformin therapy were given for 24 weeks corn oil (Placebo; 5g/day) or n-3 PUFA concentrate as above (Omega-3; 5g/day). Endocannabinoids were measured by liquid chromatography-

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tandem mass-spectrometry. Compared to cHF-fed controls, the cHF+F mice consistently reduced 2-arachidonoylglycerol (up to ~2-fold at week 24) and anandamide (~2-fold) in adipose tissue, while the levels of endocannabinoid-related anti-inflammatory molecules N-eicosapentaenoyl ethanolamine (EPEA) and N-docosahexaenoyl ethanolamine (DHEA) increased more than ~10-fold and ~8-fold, respectively. At week 24, the cHF+F mice improved glucose tolerance and fasting blood glucose, the latter being positively correlated with adipose 2-arachidonoylglycerol levels only in obese cHF-fed controls, like fasting insulin and HOMA-IR. In the patients, n-3 PUFA failed to reduce 2-arachidonoylglycerol and anandamide levels in adipose tissue and serum, but they increased both adipose tissue and serum levels of EPEA and DHEA. In conclusion, the inability of n-3 PUFA to reduce adipose tissue and serum levels of classical endocannabinoids might contribute to a lack of beneficial effects of these lipids on glucose homeostasis in T2DM patients.

[7] *Pontes HBD, Pontes J, Azevedo Neto E et al. Evaluation of the Effects of Atorvastatin and Ischemic Postconditioning Preventing on the Ischemia and Reperfusion Injury: Experimental Study in Rats. Brazilian journal of cardiovascular surgery* 2018; 33:72-81.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617505>

ABSTRACT

INTRODUCTION: Reperfusion injury leads to systemic morphological and functional pathological alterations. Some techniques are already established to attenuate the damage induced by reperfusion. Ischemic preconditioning is one of the standard procedures. In the last 20 years, several experimental trials demonstrated that the ischemic postconditioning presents similar effectiveness. Recently experimental trials demonstrated that statins could be used as pharmacological preconditioning. METHODS: 41 Wistar rats (*Rattus norvegicus albinus*) were distributed in 5 groups: Ischemia and Reperfusion (A), Ischemic Postconditioning (B), Statin (C), Ischemic Postconditioning + Statins (D) and SHAM (E). After euthanasia, lungs, liver, kidneys and ileum were resected and submitted to histopathological analysis. RESULTS: The average of lung parenchymal injury was A=3.6, B=1.6, C=1.2, D=1.2, E=1 (P=0.0029). The average of liver parenchymal injury was A=3, B=1.5, C=1.2, D=1.2, E = 0 (P<0.0001). The average of renal parenchymal injury was A=4, B=2.44, C=1.22, D=1.11, E=1 (P<0.0001). The average of intestinal parenchymal injury was A=2, B=0.66, C=0, D=0, E=0 (P=0.0006). The results were submitted to statistics applying Kruskal-Wallis test, establishing level of significance P<0.05. CONCLUSION: Groups submitted to ischemic postconditioning, to pre-treatment with statins and both methods associated demonstrated less remote reperfusion injuries, compared to the group submitted to ischemia and reperfusion without protection.

[8] *Banach M, Mikhailidis DP. Statin Intolerance: Some Practical Hints. Cardiol Clin* 2018; 36:225-231.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609752>

ABSTRACT

Statin intolerance is the inability to tolerate a dose of statin required to sufficiently reduce cardiovascular risk. With the five-step approach, more than 90% of these patients might be treated with statins. The principal approaches are to try not to discontinue statin therapy and to treat these patients as effectively as possible. New therapies with the proprotein convertase

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subtilisin-kexin type 9 inhibitors and bempedoic acid might be an effective response to these needs. In case of lack of achieved goal of the therapy nutraceuticals with confirmed low-density lipoprotein cholesterol reduction properties may be considered as a part of the lipid-lowering combination therapy.

[9] *Barter PJ, Rye KA. Cholesteryl Ester Transfer Protein Inhibitors as Agents to Reduce Coronary Heart Disease Risk. Cardiol Clin 2018; 36:299-310.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609759>

ABSTRACT

Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesteryl esters from the nonatherogenic high density lipoprotein (HDL) fraction to potentially proatherogenic non-HDL fractions. Inhibition of CETP reduces the concentration of non-HDL cholesterol, enhances HDL functionality, and increases the concentration of HDL cholesterol and apoA-I. Despite an absence of benefit in earlier trials of CETP inhibition, the REVEAL trial has shown that treatment with the CETP inhibitor anacetrapib reduces the risk of having a coronary event in high-risk, statin-treated patients.

[10] *Bin Abdulhak AA, Robinson JG. Optimizing Statins and Ezetimibe in Guideline-Focused Management. Cardiol Clin 2018; 36:221-223.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609751>

ABSTRACT

Statins are essential medications in the management of patients with clinical atherosclerotic cardiovascular disease, and have been supported by numerous clinical trials. Emerging evidence suggests that adding ezetimibe to statin therapy is associated with a net benefit and improved hard clinical outcomes, particularly in patients with significantly elevated atherosclerotic cardiovascular disease risk and elevated low-density lipoprotein cholesterol levels.

[11] *Ference BA. Causal Effect of Lipids and Lipoproteins on Atherosclerosis: Lessons from Genomic Studies. Cardiol Clin 2018; 36:203-211.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609749>

ABSTRACT

Mendelian randomization studies demonstrate that apolipoprotein B-containing lipoproteins have both causal and cumulative effects on the risk of atherosclerotic cardiovascular disease. The clinical benefit of lipid-lowering therapies depends on both the absolute reduction in circulating apolipoprotein B-containing lipoproteins and the total duration of exposure to these particles. Because atherosclerosis seems to be caused by the retention of apolipoprotein B-containing lipoproteins rather than by the cholesterol content carried by those lipoproteins, high-density lipoprotein-mediated efflux of cholesterol from the arterial wall may not reduce the risk of atherosclerotic cardiovascular disease.

[12] *Hadjiphilippou S, Ray KK. Lipids and Lipoproteins in Risk Prediction. Cardiol Clin 2018; 36:213-220.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609750>

ABSTRACT

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Ischemic heart disease remains the leading cause of death worldwide. Low-density lipoprotein cholesterol (LDL-C) has proved to have a causal relationship with atherosclerotic cardiovascular disease. Lowering LDL-C improves outcomes, although some patients continue to have residual risk of cardiovascular disease. Cardiovascular risk prediction calculators are routinely used in to identify patients most at risk. Research into other lipoprotein factors has suggested that they may have advantages over LDL-C and improve the ability to identify those most at risk. Although some technology is not widely available, there is potential for better risk prediction in specific groups.

[13] Pirillo A, Catapano AL. **Proprotein Convertase Subtilisin Kexin 9 Inhibitors.** *Cardiol Clin* 2018; 36:241-256.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609754>

ABSTRACT

High levels of low-density lipoprotein cholesterol (LDL-C) are directly associated with an increased risk of cardiovascular disease. Reducing LDL-C levels reduces the incidence of cardiovascular events. Several lipid-lowering approaches are available to achieve the LDL-C levels recommended by current guidelines, statins being the first-line therapy. However, many patients cannot achieve the recommended LDL-C levels with current therapies. The discovery of the role of proprotein convertase subtilisin kexin 9 (PCSK9) in the regulation of plasma LDL-C levels suggested it as a potential pharmacologic target and led to the development of PCSK9 inhibitors for the management of LDL-C levels.

[14] Saeed A, Ballantyne CM. **Bempedoic Acid (ETC-1002): A Current Review.** *Cardiol Clin* 2018; 36:257-264.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609755>

ABSTRACT

Although statins are first-line therapy for low-density lipoprotein cholesterol (LDL-C) reduction, many individuals on maximally tolerated statin therapy have elevated LDL-C. Bempedoic acid (ETC-1002) is a novel once-daily LDL-C-lowering agent in phase 3 clinical trials. In phase 1 and 2 studies, ETC-1002 was efficacious in lowering LDL-C when used as monotherapy and when added to statin and/or ezetimibe and was well tolerated in patients with statin intolerance. ETC-1002 also improved cardiometabolic risk factors. Ongoing phase 3 studies of ETC-1002 are evaluating its long-term efficacy and safety, and effects on cardiovascular events. This article discusses current evidence and future directions for ETC-1002.

[15] Shishikura D, Honda S, Andrews J, Nicholls SJ. **Intravascular Ultrasound Studies of Plaque Progression and Regression: Impact of Lipid-Modifying Therapies.** *Cardiol Clin* 2018; 36:329-334.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609762>

ABSTRACT

Application of serial intravascular ultrasound imaging within the coronary arteries enables characterization of the factors associated with progression of atherosclerotic plaque. Integration into clinical trials has enabled determination of the impact of medical therapies on coronary disease. These trials have provided important insights into the effects of lipid-

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modifying agents currently used in clinical practice and of experimental agents at early stages of clinical development. The results of these trials are reviewed.

[16] *Muniyappa R, Noureldin RA, Abd-Elmoniem KZ et al. Personalized Statin Therapy and Coronary Atherosclerotic Plaque Burden in Asymptomatic Low/Intermediate-Risk Individuals. Cardiorenal Med 2018; 8:140-150.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617001>

ABSTRACT

BACKGROUND: Current guidelines for the primary prevention of atherosclerotic cardiovascular disease are based on the estimation of a predicted 10-year cardiovascular disease risk and the average relative risk reduction estimates from statin trials. In the clinical setting, however, decision-making is better informed by the expected benefit for the individual patient, which is typically lacking. Consequently, a personalized statin benefit approach based on absolute risk reduction over 10 years (ARR10 benefit threshold $\geq 2.3\%$) has been proposed as a novel approach. However, how this benefit threshold relates with coronary plaque burden in asymptomatic individuals with low/intermediate cardiovascular disease risk is unknown. **AIMS:** In this study, we compared the predicted ARR10 obtained in each individual with plaque burden detected by coronary computed tomography angiography. **METHODS AND RESULTS:** Plaque burden (segment volume score, segment stenosis score, and segment involvement score) was assessed in prospectively recruited asymptomatic subjects ($n = 70$; 52% male; median age 56 years [interquartile range 51-64 years]) with low/intermediate Framingham risk score ($< 20\%$). The expected ARR10 with statin in the entire cohort was 2.7% (1.5-4.6%) with a corresponding number needed to treat over 10 years of 36 (22-63). In subjects with an ARR10 benefit threshold $\geq 2.3\%$ (vs. $< 2.3\%$), plaque burden was significantly higher ($p = 0.02$). **CONCLUSION:** These findings suggest that individuals with higher coronary plaque burden are more likely to get greater benefit from statin therapy even among asymptomatic individuals with low cardiovascular risk.

[17] *Yang SH, Xu RX, Cui CJ et al. Liraglutide downregulates hepatic LDL receptor and PCSK9 expression in HepG2 cells and db/db mice through a HNF-1a dependent mechanism. Cardiovascular diabetology 2018; 17:48.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29618348>

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9), a major regulator of cholesterol homeostasis, is associated with glucose metabolism. Liraglutide, a glucagon-like peptide-1 receptor agonist, can increase insulin secretion in a glucose-dependent manner and lower blood glucose. We aimed to investigate the relationship between liraglutide and PCSK9. **METHODS:** At the cellular level, the expressions of PCSK9 and hepatocyte nuclear factor 1 alpha (HNF1alpha) protein in HepG2 cells stimulated by liraglutide was examined using Western blot. Seven-week old db/db mice and wild type (WT) mice were administered either liraglutide (200 $\mu\text{g}/\text{kg}$) or equivoluminal saline subcutaneously, twice daily for 7 weeks. Fasting glucose level, food intake and body weight were measured every week. After the 7-week treatment, the blood was collected for lipid and PCSK9 levels detection and the liver was removed from the mice for oil red O staining, immunohistochemical analysis, immunofluorescence test and

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Western bolt. RESULTS: Firstly, liraglutide suppressed both PCSK9 and HNF1alpha expression in HepG2 cells in a time and concentration dependent manner. Secondly, liraglutide induced weight loss in WT and db/db mice, decreased serum PCSK9, glucose and lipid levels and improved hepatic accumulation in db/db but not WT mice. Thirdly, liraglutide reduced both hepatic PCSK9 and low-density lipoprotein receptor (LDLR) expression with a decrease in HNF1alpha in db/db mice but not in WT mice. CONCLUSIONS: Liraglutide suppressed PCSK9 expression through HNF1alpha-dependent mechanism in HepG2 cells and db/db mice, and decreased LDLR possibly via PCSK9-independent pathways in db/db mice.

[18] *Ding Z, Liu S, Wang X et al. PCSK9 regulates expression of scavenger receptors and ox-LDL uptake in macrophages. Cardiovascular research* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617722>

ABSTRACT

Aims: PCSK9 has been shown to influence macrophage biology and modulate atherogenesis. We conducted this study to examine the regulation of scavenger receptors (SRs) (LOX-1, SRA and CD36) and oxidized lipoprotein cholesterol (ox-LDL) uptake in macrophages by PCSK9. Methods and Results: Treatment of mouse peritoneal macrophages with TNF-alpha resulted in concentration-dependent modest, but significant, increase in PCSK9 expression. Importantly, treatment of TNF-alpha primed macrophages with recombinant murine PCSK9 increased the expression of LOX-1, SRA and CD36 2-5 fold, and enhanced ox-LDL uptake by approximately 5-fold. The increase in LOX-1 was much greater than in SRA or CD36. PCSK9 inhibition (by siRNA transfection or use of macrophages from PCSK9^{-/-} mice) reduced the expression of SRs (LOX-1 >> SRA or CD36). Ox-LDL uptake in response to PCSK9 was also inhibited in macrophages from LOX-1^{-/-} mice (P < 0.05 vs. macrophages from SRA^{-/-} and CD36^{-/-} mice). Upregulation of PCSK9 by cDNA transfection induced intense ox-LDL uptake which was inhibited by co-transfection of cells with siRNA LOX-1 (P < 0.05 vs. siRNA SRA or siRNA CD36). Further, TNF-alpha-mediated PCSK9 upregulation and subsequent expression of SRs and ox-LDL uptake were reduced in macrophages from gp91phox^{-/-}, p47phox^{-/-} and p22phox^{-/-} mice (vs. macrophages from wild-type mice). Conclusions: This study shows that in an inflammatory milieu, elevated levels of PCSK9 potentially stimulate the expression of SRs (principally LOX-1) and ox-LDL uptake in macrophages, and thus contribute to the process of atherogenesis.

[19] *Wang N, Lu Y, Wang K et al. Simvastatin Attenuates Neurogenetic Damage and Improves Neurocognitive Deficits Induced by Isoflurane in Neonatal Rats. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology* 2018; 46:618-632.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617679>

ABSTRACT

BACKGROUND/AIMS: Isoflurane inhibited neurogenesis and induced subsequent neurocognitive deficits in developing brain. Simvastatin exerts neuroprotection in a wide range of brain injury models. In the present study, we investigated whether simvastatin could attenuate neurogenetic inhibition and cognitive deficits induced by isoflurane exposure in neonatal rats. METHODS: Sprague-Dawley rats at postnatal day (PND) 7 and neural stem cells (NSCs) were treated with either gas mixture, isoflurane, or simvastatin 60 min prior to

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isoflurane exposure, respectively. The rats were decapitated at PND 8 and PND 10 for detection of neurogenesis in the subventricular zone (SVZ) and subgranular zone (SGZ) of the hippocampus by immunostaining. NSC proliferation, viability and apoptosis were assessed by immunohistochemistry, CCK-8 and TUNEL, respectively. The protein expressions of caspase-3, p-Akt and p-GSK-3beta both in vivo and in vitro were assessed by western blotting. Cognitive functions were assessed by Morris Water Maze test and context fear conditioning test at the adult. RESULTS: Isoflurane exposure inhibited neurogenesis in the SVZ and SGZ, decreased NSC proliferation and viability, promoted NSC apoptosis and led to late cognitive deficits. Furthermore, isoflurane increased caspase-3 expression and decreased protein expressions of p-Akt and p-GSK-3beta both in vivo and in vitro. Pretreatment with simvastatin attenuated isoflurane-elicited changes in NSCs and cognitive function. Co-treatment with LY294002 reversed the effect of simvastatin on NSCs in vitro. CONCLUSION: We for the first time showed that simvastatin, by upregulating Akt/GSK-3beta signaling pathway, alleviated isoflurane-induced neurogenetic damage and neurocognitive deficits in developing rat brain.

[20] *Joly AL, Seitz C, Liu S et al. Alternative Splicing of FOXP3 Controls Regulatory T Cell Effector Functions and Is Associated with Human Atherosclerotic Plaque Stability. Circulation research* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29618596>

ABSTRACT

Rationale: Regulatory T (Treg) cells suppress immune responses and have been shown to attenuate atherosclerosis. The Treg cell lineage specification factor FOXP3 is essential for Treg cells' ability to uphold immunological tolerance. In humans, FOXP3 exists in several different isoforms, however, their specific role is poorly understood. Objective: To define the regulation and functions of the two major FOXP3 isoforms, FOXP3fl and FOXP3Delta2, as well as to establish whether their expression is associated with ischemic atherosclerotic disease. Methods and Results: Human primary T-cells were transduced with lentiviruses encoding distinct FOXP3 isoforms. The phenotype and function of these cells were analyzed by flow cytometry, in vitro suppression assays and RNA-sequencing. We also assessed the effect of activation on Treg cells isolated from healthy volunteers. Treg cell activation resulted in increased FOXP3 expression that predominantly was made up of FOXP3Delta2. FOXP3Delta2 induced specific transcription of GARP, which functions by tethering the immunosuppressive cytokine TGF-beta to the cell membrane of activated Treg cells. RT-PCR was used to determine the impact of alternative splicing of FOXP3 in relation with atherosclerotic plaque stability in a cohort of over 150 patients that underwent carotid endarterectomy. Plaque instability was associated with a lower FOXP3Delta2 transcript usage, when comparing plaques from patients without symptoms and patients with occurrence of recent (<1 month) vascular symptoms including minor stroke, transient ischemic attack or amaurosis fugax. No difference was detected in total levels of FOXP3 mRNA between these two groups. Conclusions: These results suggest that activated Treg cells suppress the atherosclerotic disease process and that FOXP3Delta2 controls a transcriptional program that acts protectively in human atherosclerotic plaques.

[21] *Sabatine MS, De Ferrari GM, Giugliano RP et al. Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: An Analysis from FOURIER. Circulation* 2018.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29626068>

ABSTRACT

Background -The FOURIER trial recently showed that the PCSK9 inhibitor evolocumab significantly reduced major vascular events in patients with stable atherosclerotic cardiovascular disease, including patients with prior MI. Within the broad group of patients with prior MI, we hypothesized that readily ascertainable features would identify subsets that derive greater clinical risk reduction with evolocumab. **Methods** -The 22,351 patients with a prior MI were characterized based on time from most recent MI, number of prior MIs, and presence of residual multivessel coronary artery disease ($\geq 40\%$ stenosis in ≥ 2 large vessels). The relative and absolute risk reductions in major vascular events including the primary endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and the key secondary endpoint (CV death, MI or stroke) with evolocumab in these subgroups were compared. **Results** -A total of 8402 patients (38%) were within 2 years of their most recent MI, 5285 patients (24%) had ≥ 2 prior MIs, and 5618 patients (25%) had residual multivessel CAD. In a multivariable adjusted model that simultaneously included all three high-risk features as well as other baseline covariates, more recent MI, multiple prior MIs, and residual multivessel coronary disease remained independent predictors of cardiovascular outcomes, with adjusted HRs for the primary endpoint of 1.37 (1.22-1.53), 1.78 (1.59-1.99) and 1.39 (1.24-1.56), all $P < 0.001$. The relative risk reductions with evolocumab for the primary endpoint tended to be greater in the high-risk subgroups and were 20% (HR 0.80, 0.71-0.91), 18% (HR 0.82, 0.72-0.93), and 21% (HR 0.79, 0.69-0.91) for those with more recent MI, multiple prior MIs, and residual multivessel CAD, whereas they were 5% (HR 0.95, 0.85-1.05), 8% (HR 0.92, 0.84-1.02), and 7% (HR 0.93, 0.85-1.02) in those without, respectively. Given the higher baseline risk, the respective absolute risk reductions at 3 years exceeded 3% in the high-risk groups (3.4%, 3.7%, and 3.6%) vs. approximately 1% in the low-risk groups (0.8%, 1.3%, and 1.2%). **Conclusions** -Patients closer to their most recent MI, with multiple prior MIs or with residual multivessel CAD are at high risk for major vascular events and experience substantial risk reductions with LDL-C lowering with evolocumab. **Clinical Trial Registration** -URL: <https://www.clinicaltrials.gov> Unique identifier: NCT01764633.

[22] *Vallejo-Vaz AJ, Fayyad R, Boekholdt SM et al. Triglyceride-Rich Lipoprotein Cholesterol and Risk of Cardiovascular Events Among Patients Receiving Statin Therapy in the Treating to New Targets (TNT) Trial. Circulation 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29618599>

ABSTRACT

Background -Mendelian randomization data suggest genetic determinants of lifetime higher triglyceride-rich lipoprotein-cholesterol (TRL-C) are causally related to cardiovascular disease and therefore a potential therapeutic target. The relevance of TRL-C among patients receiving statins is unknown. We assessed the relationship between TRL-C and cardiovascular risk, and whether this risk was modifiable among patients receiving statins in the TNT trial. **Methods** - Patients with coronary heart disease [CHD] and LDL-C 130-250mg/dL entered an 8-week run-in phase with atorvastatin 10mg/day (ATV10). After this period, participants with LDL-C < 130 mg/dL entered the randomised phase with ATV10 (n=5006) vs. atorvastatin 80mg/day (ATV80, n=4995). **Primary endpoint:** CHD death, non-fatal myocardial infarction, resuscitated

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cardiac arrest, or stroke (major adverse cardiovascular events [MACE]). TRL-C was calculated as total cholesterol minus HDL-C minus LDL-C. The effect of atorvastatin on TRL-C was assessed during the run-in phase (ATV10) and randomised phase (ATV80 vs. ATV10). The risk of MACE was assessed across quintiles (Q) of baseline TRL-C (and, for comparison, by baseline triglycerides and non-HDL-C) during the randomised period. Finally, the association between TRL-C changes with atorvastatin and cardiovascular risk was assessed by multivariate Cox-regression. Results -ATV10 reduced TRL-C a 10.7% from an initial TRL-C of 33.9+/-16.6 mg/dL. ATV80 led to an additional 15.4% reduction. Cardiovascular risk factors positively correlated with TRL-C. Among patients receiving ATV10, higher TRL-C associated higher 5-year MACE rates (Q1=9.7%, Q5=13.8%; HR Q5-vs-Q1: 1.48 [95%CI 1.15-1.92]; p-trend<0.0001). ATV80 (vs. ATV10) did not significantly alter the risk of MACE in Q1-Q2, but significantly reduced risk in Q3-Q5 (RRR: 29%-41%; all p<0.0250), with evidence of effect modification (p-homogeneity=0.0053); results were consistent for triglycerides (p-homogeneity=0.0101) and directionally similar for non-HDL-C (p-homogeneity=0.1387). Finally, in adjusted analyses, a 1SD percentage reduction in TRL-C with atorvastatin resulted in a significant lower risk of MACE (HR 0.93, 95%CI 0.86-1.00, p=0.0482) independent of the reduction in LDL-C and of similar magnitude to that per 1SD lowering in LDL-C (HR 0.89, 95%CI 0.83-0.95, p=0.0008). Conclusions -The present post-hoc analysis from TNT shows that increased TRL-C levels associate an increased cardiovascular risk and provides evidence for the cardiovascular benefit of lipid-lowering with statins among CHD patients with high TRL-C. Clinical Trial Registration -URL: <https://clinicaltrials.gov> Unique Identifier: NCT00327691.

[23] Lee TC, Kaouache M, Grover SA. **Evaluation of the cost-effectiveness of evolocumab in the FOURIER study: a Canadian analysis.** *CMAJ open* 2018; 6:E162-e167.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29622685>

ABSTRACT

BACKGROUND: Evolocumab, a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor, has been shown to reduce low-density lipoprotein levels by up to 60%. Despite the absence of a reduction in overall or cardiovascular mortality in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, some believe that, with longer treatment, such a benefit might eventually be realized. Our aim was to estimate the potential mortality benefit over a patient's lifetime and the cost per year of life saved (YOLS) for an average Canadian with established coronary artery disease. We also sought to estimate the price threshold at which evolocumab might be considered cost-effective for secondary prevention in Canada. **METHODS:** We calibrated the Cardio-metabolic Model, a well-validated tool for predicting cardiovascular events and life expectancy, to the reduction in nonfatal events seen in the FOURIER trial. Assuming that long-term treatment will eventually result in mortality benefits, we estimated YOLSs and cost per YOLS with evolocumab treatment plus a statin compared to a statin alone. We then estimated the annual drug costs that would provide a 50% chance of being cost-effective at willingness-to-pay values of \$50 000 and \$100 000. **RESULTS:** In secondary prevention in patients similar to those in the FOURIER study, evolocumab treatment would save an average of 0.34 (95% confidence interval [CI] 0.27-0.41) life-years at a cost of \$101899 (95% CI \$97325-\$106473), yielding a cost per YOLS of \$299482. We estimate that to have a 50% probability of achieving a cost per YOLS below \$50000 and

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\$100000 would require annual drug costs below \$1200 and \$2300, respectively.

INTERPRETATION: At current pricing, the use of evolocumab for secondary prevention is unlikely to be cost-effective in Canada.

[24] *Itoh H, Komuro I, Takeuchi M et al. Intensive Treat-to-Target Statin Therapy in High-Risk Japanese Patients With Hypercholesterolemia and Diabetic Retinopathy: Report of a Randomized Study. Diabetes Care* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29626074>

ABSTRACT

OBJECTIVE: Diabetes is associated with high risk of cardiovascular (CV) events, particularly in patients with dyslipidemia and diabetic complications. We investigated the incidence of CV events with intensive or standard lipid-lowering therapy in patients with hypercholesterolemia, diabetic retinopathy, and no history of coronary artery disease (treat-to-target approach). RESEARCH DESIGN AND METHODS: In this multicenter, prospective, randomized, open-label, blinded end point study, eligible patients were randomly assigned (1:1) to intensive statin therapy targeting LDL cholesterol (LDL-C) <70 mg/dL (n = 2,518) or standard statin therapy targeting LDL-C 100-120 mg/dL (n = 2,524). RESULTS: Mean follow-up was 37 +/- 13 months. LDL-C at 36 months was 76.5 +/- 21.6 mg/dL in the intensive group and 104.1 +/- 22.1 mg/dL in the standard group (P < 0.001). The primary end point events occurred in 129 intensive group patients and 153 standard group patients (hazard ratio [HR] 0.84 [95% CI 0.67-1.07]; P = 0.15). The relationship between the LDL-C difference in the two groups and the event reduction rate was consistent with primary prevention studies in patients with diabetes. Exploratory findings showed significantly fewer cerebral events in the intensive group (HR 0.52 [95% CI 0.31-0.88]; P = 0.01). Safety did not differ significantly between the two groups. CONCLUSIONS: We found no significant decrease in CV events or CV-associated deaths with intensive therapy, possibly because our between-group difference of LDL-C was lower than expected (27.7 mg/dL at 36 months of treatment). The potential benefit of achieving LDL-C <70 mg/dL in a treat-to-target strategy in high-risk patients deserves further investigation.

[25] *San Mauro Martin I, Blumenfeld Olivares JA, Perez Arruche E et al. Genomic Influence in the Prevention of Cardiovascular Diseases with a Sterol-Based Treatment. Diseases (Basel, Switzerland)* 2018; 6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29614023>

ABSTRACT

Raised serum cholesterol concentration is a well-established risk factor in cardiovascular disease. In addition, genetic load may have an indirect influence on cardiovascular risk. Plant-based sterol-supplemented foods are recommended to help reduce the serum low-density lipoprotein cholesterol level. The objective was to analyse the influence of different polymorphisms in hypercholesterolemia patients following a dietary treatment with plant sterols. A randomised double-blind cross-over controlled clinical trial was carried out in 45 people (25 women). Commercial milk, containing 2.24 g of sterols, was ingested daily during a 3-week period, and then the same amount of skim milk, without sterols, was consumed daily during the 3-week placebo phase. Both phases were separated by a washout period of 2 weeks. At the beginning and end of each phase, blood draws were performed. Genes LIPC C-514T and

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APOA5 C56G are Ser19Trp carriers and greatly benefit from sterol intake in the diet. LIPC C-514T TT homozygous carriers had lower low-density lipoprotein cholesterol (LDL-c) levels than CC homozygote and CT heterozygote carriers after the ingestion of plant sterols ($p = 0.001$). These two genes also showed statistically significant changes in total cholesterol levels ($p = 0.025$; $p = 0.005$), and no significant changes in high-density lipoprotein (HDL) cholesterol levels ($p = 0.032$; $p = 0.003$), respectively. No statistically significant differences were observed for other genes. Further studies are needed to establish which genotype combinations would be the most protective against hypercholesterolemia.

[26] *Sreckovic B, Soldatovic I, Colak E et al. Homocysteine is the confounding factor of metabolic syndrome-confirmed by siMS score. Drug metabolism and personalized therapy* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29624500>

ABSTRACT

BACKGROUND: Abdominal adiposity has a central role in developing insulin resistance (IR) by releasing pro-inflammatory cytokines. Patients with metabolic syndrome (MS) have higher values of homocysteine. Hyperhomocysteinemia correlates with IR, increasing the oxidative stress. Oxidative stress causes endothelial dysfunction, hypertension and atherosclerosis. The objective of the study was to examine the correlation of homocysteine with siMS score and siMS risk score and with other MS co-founding factors. **METHODS:** The study included 69 obese individuals (age over 30, body mass index [BMI] >25 kg/m²), classified into two groups: I-with MS (33 patients); II-without MS (36 patients). Measurements included: anthropometric parameters, lipids, glucose regulation parameters and inflammation parameters. IR was determined by homeostatic model assessment for insulin resistance (HOMA-IR). ATP III classification was applied for diagnosing MS. SiMS score was used as continuous measure of metabolic syndrome. **RESULTS:** A significant difference between groups was found for C-reactive protein (CRP) ($p < 0.01$) apolipoprotein (Apo) B, HOMA-IR and acidum uricum ($p < 0.05$). siMS risk score showed a positive correlation with homocysteine ($p = 0.023$), while siMS score correlated positively with fibrinogen ($p = 0.013$), CRP and acidum uricum ($p = 0.000$) and homocysteine ($p = 0.08$). Homocysteine correlated positively with ApoB ($p = 0.036$), HbA1c ($p = 0.047$), HOMA-IR ($p = 0.008$) and negatively with ApoE ($p = 0.042$). **CONCLUSIONS:** Correlation of siMS score with homocysteine, fibrinogen, CRP and acidum uricum indicates that they are co-founding factors of MS. siMS risk score correlation with homocysteine indicates that hyperhomocysteinemia increases with age. Hyperhomocysteinemia is linked with genetic factors and family nutritional scheme, increasing the risk for atherosclerosis.

[27] *Poulsen CB, Pedrigo RM, Pareek N et al. Plaque Burden Influences Accurate Classification of Fibrous Cap Atheroma by In-Vivo Optical Coherence Tomography in a Porcine Model of Advanced Coronary Atherosclerosis. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29616625>

ABSTRACT

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AIMS: In-vivo validation of coronary optical coherence tomography (OCT) against histology and the effects of plaque burden (PB) on plaque classification remain unreported. We investigated this in a porcine model with human-like coronary atherosclerosis. METHODS AND RESULTS: Five female Yucatan D374Y-PCSK9 transgenic hypercholesterolemic mini-pigs were implanted with a coronary shear-modifying stent to induce advanced atherosclerosis. OCT frames (n=201) were obtained 34 weeks after implantation. Coronary arteries were perfusion-fixed, serially sectioned and co-registered with OCT using a validated algorithm. Lesions were adjudicated using the Virmani classification and PB assessed from histology. OCT had a high sensitivity, but modest specificity (92.9% and 74.6%), for identifying fibrous cap atheroma (FCA). The reduced specificity for OCT was due to misclassification of plaques with histologically defined pathological intimal thickening (PIT) as FCA (46.1% of the frames with histological PIT were misclassified). PIT lesions misclassified as FCA by OCT had a statistically higher PB than in other OCT frames (median 32.0% versus 13.4%; $p < 0.0001$). Misclassification of PIT lesions by OCT occurred when PB exceeded approximately 20%. CONCLUSIONS: Compared with histology, in-vivo OCT classification of FCA had high sensitivity but reduced specificity due to misclassification of PITs with high PB.

[28] Liu Y, Song X, Zhou H et al. **Gut Microbiome Associates With Lipid-Lowering Effect of Rosuvastatin in Vivo.** *Frontiers in microbiology* 2018; 9:530.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29623075>

ABSTRACT

Background: Statin has been widely used to treat hyperlipidemia because of its high potency in decreasing cholesterol levels. The present study aimed to examine the lipid-lowering effect of rosuvastatin and the composition, diversity and species abundance of gut microbiome in association with rosuvastatin efficacy. TRIAL REGISTRATION: ChiCTR-ORC-17013212 at the First Affiliated Hospital of Dalian Medical University, November 2, 2017. Results: Totally 64 patients with hyperlipidemia were treated with 10 mg/day of rosuvastatin for 4-8 weeks. Blood lipid indicators triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL-C) were measured before and after the treatment. Stool samples were collected right after the treatment. Following total DNA extraction and PCR amplification of 16S rRNA gene, Illumina sequencing was performed for gut microbiome identification, classification and characterization. All the patients showed a significant blood lipid reduction after the treatment. The patients were grouped according to parallel manner design. Group I had 33 patients whose blood lipid levels dropped to the normal levels from week 4, with 58.5% reduction in LDL-C and 26.6% reduction in TC. Group II had 31 patients whose blood lipid levels were still above the normal levels after 8 weeks therapy, but with 41.9% reduction in LDL-C and 31.2% reduction in TC. Based on Operational Taxonomic Unit data, Alpha-diversity by Shannon Index was different between the two groups, and beta-diversity by Principle Component Analysis exhibited separated patterns of the two groups. The differences were also observed in the relative-abundance at phylum, family, and genus levels of the two groups. Linear discriminate analysis illustrated that the abundance of 29 taxa was higher in group I, while the abundance of other 13 taxa was higher in group II. Phyla Firmicutes and Fusobacteria had negative correlation to LDL-C level, but Cyanobacteria and Lentisphaerae had a positive correlation to LDL-C level. Moreover, gender and age were also found somehow correlated to

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microbial community composition. Conclusion: Rosuvastatin therapy had different blood lipid-lowering effect on hyperlipidemia. The gut microbiota exhibited variation in community composition, diversity and taxa in association to rosuvastatin hypolipidemic effect. These results indicate that modulation of gut microflora, especially the negative/positive correlated species might strengthen statin efficacy in statin-inadequate patients.

[29] *Chen YA, Lin YJ, Lin CL et al. Simvastatin Therapy for Drug Repositioning to Reduce the Risk of Prostate Cancer Mortality in Patients With Hyperlipidemia. Frontiers in pharmacology 2018; 9:225.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29623039>

ABSTRACT

Prostate cancer (PCa) is one of the most commonly diagnosed cancers in the western world, and the mortality rate from PCa in Asia has been increasing recently. Statins are potent inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase and are commonly used for treating hyperlipidemia, with beneficial effects for cardiovascular disease and they also exhibit anti-cancer activity. However, the protective effects of statins against PCa are controversial. In this study, we investigated the effect of two types of statins (simvastatin and lovastatin) and the mortality rate of PCa patients by using the Taiwan National Health Insurance Research Database (NHIRD). A total of 15,264 PCa patients with hyperlipidemia records and medical claims from the Registry of Catastrophic Illness were enrolled. The patients were divided into two cohorts based on their statin use before the diagnosis of PCa: statin users (n = 1,827) and non-statin users (n = 1,826). The results showed that patients who used statins exhibited a significantly reduced risk of mortality from PCa [adjusted hazard ratio (HR) = 0.84, 95% CI = 0.73-0.97]. Analysis of the cumulative defined daily dose (DDD) indicated that patients who were prescribed simvastatin \geq 180 DDD had a dramatically decreased risk of death from PCa (adjusted HR = 0.63; 95% CI = 0.51-0.77). This population-based cohort study demonstrated that statin use significantly decreased the mortality of PCa patients, and that this risk was inversely associated with the cumulative DDD of simvastatin therapy. The results of this study revealed that statins may be used for drug repositioning and in the development of a feasible approach to prevent death from PCa.

[30] *Masaki N, Kumagai K, Sasaki K et al. Suppressive effect of pitavastatin on aortic arch dilatation in acute stanford type B aortic dissection: analysis of STANP trial. General thoracic and cardiovascular surgery 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29626287>

ABSTRACT

OBJECTIVES: Medical therapy for patients with uncomplicated acute type B aortic dissection (ABAD) is essentially accepted for its excellent early outcome; however, long-term outcomes have not been satisfactory due to aorta-related complications. This trial was performed to investigate the efficacy of a statin as an additive that may enhance the effectiveness of conventional medical treatment in patients with ABAD. **METHODS:** This was a multi-center, prospective, and randomized comparative investigation of patients with uncomplicated ABAD. Fifty patients with ABAD compatible with inclusion criteria were randomly assigned to two groups and then received administration of pitavastatin (group P) or not (group C). We followed

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up the patients for 1 year from study onset. RESULTS: Two patients demised during the follow-up period (both were in group C). In addition, aorta-related interventions were performed in two patients (entry closure for aortic dissection by endovascular repair in one patient in each group). Aortic arch diameters at 1 year in group P tended to be smaller than in group C ($P = 0.17$), and the rate of change of the aortic arch diameters from onset to 1 year was significantly lower in group P ($P = 0.046$). Multivariate analysis identified patency of the false lumen was detected as a risk factor for aortic arch dilatation ($P = 0.02$), and pitavastatin intake was a negative risk factor ($P = 0.03$). CONCLUSIONS: Pitavastatin treatment, in addition to the standard antihypertensive therapy, may have a suppressive effect on aortic arch dilatation in patients with ABAD.

[31] *Ahmadi Y, Haghjoo AG, Dastmalchi S et al. Effects of Rosuvastatin on the expression of the genes involved in cholesterol metabolism in rat: Adaptive responses by extrahepatic tissues. Gene* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29605604>

ABSTRACT

BACKGROUND: Statins mostly target the liver; therefore, increase in the synthesis of cholesterol by extra-hepatic tissues and then transferring this cholesterol to the liver can be regarded as adaptive responses by these tissues. In addition to cholesterol, these adaptive responses can increase isoprenoid units as byproducts of the cholesterol biosynthesis pathway; isoprenoids play a key role in regulating cell signaling pathways and cancer development. Thus, there is a primary need for in vivo investigation of the effects of statins on the cholesterol metabolism in the extra-hepatic tissues. MATERIALS: Eighteen male Sprague-Dawley rats were randomly divided into control ($n=9$) and treatment ($n=9$) groups. The treatment group was orally given 10mg/kg/day of Rosuvastatin for 6weeks. Then, serum lipid profile, expression levels of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), ABCA1, ABCG1 and ApoA1, and activity of HMGCR were measured in the liver, intestine and adipose tissues. RESULTS: Rosuvastatin significantly reduced total cholesterol and LDL-C. The expression levels of ABCA1, ABCG1, and ApoA1 in the liver and HMGCR in both liver and intestine were significantly increased in the Rosuvastatin treated-group. However, in the intestine, there were no significant differences in the expression levels of ABCA1 and ABCG1 between the study groups. Rosuvastatin had no effect on the adipose tissue. The HMGCR activity was significantly increased in the liver and intestine of the Rosuvastatin-treated group. CONCLUSIONS: In spite of the adipose tissue, the intestine efficiently responds to the reduced levels of cholesterol and increases its cholesterologenesis capacity. However, adipose tissue seems to play a small role in correcting cholesterol deficiency during the course of statin therapy.

[32] *Kaasenbrood L, Ray KK, Boekholdt SM et al. Estimated individual lifetime benefit from PCSK9 inhibition in statin-treated patients with coronary artery disease. Heart* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29622600>

ABSTRACT

OBJECTIVE: In statin-treated patients with stable coronary artery disease (CAD), residual risk of cardiovascular events is partly explained by plasma levels of low-density lipoprotein cholesterol (LDL-C). This study aimed to estimate individual benefit of proprotein convertase

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subtilisin/kexin type 9 (PCSK9) inhibition in CAD patients already treated with high-dose statin. METHODS: Individual lifetime benefit was estimated in months gain free of stroke or myocardial infarction (MI) until age 80 years. Predictions were based on two competing risk models developed in data from 4853 patients with CAD originating from the atorvastatin 80 mg arm of the Treating to New Targets (TNT) trial. The relative effect of PCSK9 inhibition was added to the models and was assumed based on average estimates from large clinical trials. We accounted for individual LDL-C levels, assuming 50% LDL-C reduction by PCSK9 inhibition and 21% cardiovascular risk reduction per mmol/L (39 mg/dL) LDL-C lowering. RESULTS: Estimated individual gain was <6 months in 61% of the patients, 6-12 months in 28% of the patients and \geq 12 months in 10% of the patients (median 5, quartiles 2-8 months). Highest estimated benefit was observed in younger patients (aged 40-60 years) with high risk factor burden, particularly if LDL-C levels were >1.8 mmol/L (>70 mg/dL). Estimated benefit was lowest (\leq 5 months) in older patients (\geq 70 years), in particular if LDL-C and other risk factors levels were low. CONCLUSION: The individual estimated lifetime benefit from PCSK9 inhibition in patients with stable CAD on high-dose statin varied from <6 to \geq 12 months free of stroke or MI. Highest benefit is expected in younger patients (age 40-60 years) with high risk factor burden and relatively high LDL-C levels. TRIAL REGISTRATION NUMBER: NCT00327691; Post-results.

[33] *Prebble H, Cross S, Marks E et al. Induced macrophage activation in live excised atherosclerotic plaque. Immunobiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29605258>

ABSTRACT

Atherosclerotic plaques are complex tissues containing many different cell types. Macrophages contribute to inflammation, formation of the necrotic core, and plaque rupture. We examined whether macrophages in plaque can be activated and compared this to monolayer cells. The volume of calcium in the plaque was compared to the level of macrophage activation measured by total neopterin output. Carotid plaque samples were cut into 3mm sections and cultured for up to 96h. Live sections were stimulated with interferon-gamma, phytohaemagglutinin or phorbol 12-myristate 13-acetate. Macrophage activation and oxidative stress were monitored by total neopterin (oxidized and non-oxidized 7,8-dihydroneopterin) and neopterin levels every 24h for up to 4d. The calcium content of two plaques was investigated by spectral imaging. Direct stimulation of macrophages in plaque sections with interferon-gamma caused a sustained increase in neopterin ($p=.037$) and total neopterin ($p=.003$). The addition of phorbol 12-myristate 13-acetate to plaque had no significant effect on total neopterin production ($p=.073$) but increased neopterin ($p=.037$) whereas phytohaemagglutinin caused a significant increase in both neopterin and total neopterin ($p=.0279$ and $.0168$). There was an inverse association ($R(2)=0.91$) between the volume of calcium and macrophage activation as measured by total neopterin production in stimulated plaque tissue. Resident macrophages within excised carotid plaque activated either directly or indirectly generate the biomarkers 7,8-dihydroneopterin and neopterin. Macrophage activation rather than the oxidative environment is associated with plaque calcification.

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[34] Zhang M, Deng Q, Wang L et al. **Prevalence of dyslipidemia and achievement of low-density lipoprotein cholesterol targets in Chinese adults: A nationally representative survey of 163,641 adults.** *International journal of cardiology* 2018; 260:196-203.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29622441>

ABSTRACT

BACKGROUND: Elevated serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels are established risk factors for cardiovascular diseases, a leading cause of death in China. We sought to assess the latest levels of serum lipids, prevalence of dyslipidemia and achievement of LDL-C lowering targets among Chinese adults. METHODS: Data was obtained from a national representative survey recruited 163,641 adults aged >18years in mainland China between 2013 and 2014. Fasting serum total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by standard methods. Multiple logistic regression was performed to estimate potential risk factors for dyslipidemias. Proportion of residents not achieve the therapeutic goals for LDL-C by atherosclerotic cardiovascular diseases (ASCVD) risk stratification were evaluated. RESULTS: Nationally, the population-weighted means of TC, HDL-C, and LDL-C, and median of TG were 4.70, 1.35, 2.88, and 1.49mmol/L, respectively. The prevalence of high TC, high LDL-C, low HDL-C and high TG was 6.9%, 8.1%, 20.4% and 13.8%. Among individuals with high ASCVD risk, 74.5% had uncontrolled LDL-C levels (<2.6mmol/L) and 5.5% of them were treated. For very-high-risk individuals, 93.2% didn't achieve their LDL-lowering goals (<1.8mmol/L) and 14.5% of them were treated. CONCLUSIONS: Chinese adults currently experienced a high prevalence of abnormal serum lipid levels, more common in urban adults or those with obesity or central obesity. A significant proportion of people with high or very high ASCVD risk didn't meet LDL-C targets. Improvements in achievement of lipid-level targets and of LDL-lowering therapy rates based on ASCVD risk stratification were necessary.

[35] Engelbertsen D, Depuydt MAC, Verwilligen RAF et al. **IL-23R Deficiency Does Not Impact Atherosclerotic Plaque Development in Mice.** *Journal of the American Heart Association* 2018; 7.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29618473>

ABSTRACT

BACKGROUND: Interleukin-23 (IL-23) has been implicated in inflammatory and autoimmune diseases by skewing CD4(+) T helper cells towards a pathogenic Th17 phenotype. In this study we investigated the presence of IL-23 receptor (IL-23R)-expressing cells in the atherosclerotic aorta and evaluated the effect of IL-23R deficiency on atherosclerosis development in mice. METHODS AND RESULTS: We used heterozygous *Ldlr*(-/-)II23r(e)(GFP)(/)(WT) knock-in mice to identify IL-23R-expressing cells by flow cytometry and homozygous *Ldlr*(-/-)II23r(e)(GFP)(/)(eGFP) (*Ldlr*(-/-)II23r(-/-)) mice to investigate the effect of lack of IL-23R in atherosclerosis. We demonstrate the presence of relatively rare IL-23R-expressing cells in lymphoid tissue and aorta (approximately 0.1-1% IL23R(+) cells of all CD45(+) leukocytes). After 10 weeks on a high-fat diet, production of IL-17, but not interferon-gamma, by CD4(+) T cells and other lymphocytes was reduced in *Ldlr*(-/-)II23r(-/-) compared with *Ldlr*(-/-) controls. However, *Ldlr*(-/-) and *Ldlr*(-/-)II23r(-/-) mice had equivalent amounts of aortic sinus and descending aorta lesions. Adoptive transfer of IL-23R-deficient CD4(+) T cells to lymphopenic

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Ldlr(-/-)Rag1(-/-) resulted in dramatically reduced IL-17-producing T cells but did not reduce atherosclerosis, compared with transfer of IL-23R-sufficient CD4(+) T cells. CONCLUSIONS: These data demonstrate that loss of IL-23R does not affect development of experimental atherosclerosis in LDLr-deficient mice, despite a role for IL-23 in differentiation of IL-17-producing T cells.

[36] *Ako J, Hibi K, Kozuma K et al. Effect of alirocumab on coronary atheroma volume in Japanese patients with acute coronary syndromes and hypercholesterolemia not adequately controlled with statins: ODYSSEY J-IVUS rationale and design. J Cardiol* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29606415>

ABSTRACT

BACKGROUND: Serial intravascular ultrasound (IVUS) imaging can be used to evaluate the effect of cholesterol-lowering on coronary atheroma progression and plaque volume, with evidence of potential incremental effects with more aggressive lipid-lowering treatments. Alirocumab is a highly specific, fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9). This study will investigate the effect of alirocumab on coronary artery plaque volume in Japanese patients with a recent acute coronary syndrome (ACS) and hypercholesterolemia while on stable statin therapy. METHODS: ODYSSEY J-IVUS is a phase IV, open-label, randomized, blinded IVUS analysis, parallel-group, multicenter study in Japanese adults recently hospitalized for an ACS and who have elevated low-density lipoprotein cholesterol (LDL-C) values [≥ 100 mg/dL (2.6mmol/L)] at ACS diagnosis and suboptimal LDL-C control on stable statin therapy. Patients will be randomized (1:1) to receive alirocumab or standard-of-care (SOC). The alirocumab arm will receive alirocumab 75mg every 2 weeks (Q2W) added to statin therapy (atorvastatin ≥ 10 mg/day or rosuvastatin ≥ 5 mg/day), with a dose increase to 150mg Q2W in patients whose LDL-C value remains ≥ 100 mg/dL at week 12. The SOC arm will receive atorvastatin ≥ 10 mg/day or rosuvastatin ≥ 5 mg/day, with dose adjustment to achieve LDL-C < 100 mg/dL. Post-treatment IVUS imaging will be done at week 36 \pm 2. The primary objective is to compare the effect of alirocumab versus SOC on coronary atheroma progression (percent change in normalized total atheroma volume) after 9 months of treatment. CONCLUSION: ODYSSEY J-IVUS will provide insights into the effect of alirocumab on coronary atherosclerotic plaque volume in patients with a recent ACS and hypercholesterolemia while on stable statin therapy. ClinicalTrials.gov number: NCT02984982.

[37] *Holven KB, Narverud I, van Lennep JR et al. Sex differences in cholesterol levels from birth to 19 years of age may lead to increased cholesterol burden in females with FH. Journal of clinical lipidology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609857>

ABSTRACT

BACKGROUND: The increased risk of cardiovascular disease in familial hypercholesterolemia (FH) is caused by increased cholesterol burden from birth. Even small elevation in cholesterol level accumulates over time and aggravates atherosclerosis. OBJECTIVES: The aim of the present study was to describe the lipid profile across sex and age in a large cohort of untreated children and adolescents with FH, as this have not clearly been described. METHODS: FH children (438 girls, 452 boys) not receiving lipid-lowering therapy, aged 0 to 19 years were

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included and divided into 4 age groups (<5, 5-9, 10-14, and 15-19 years). Information was retrieved from the medical records. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL cholesterol (non-HDL-C) were studied in relation to sex and age by multiple linear regression analysis. RESULTS: Girls with FH as compared to boys had significantly higher TC, LDL-C, and non-HDL-C ($P < .001$ for all) levels with mean (95% confidence interval) differences of 0.48 mmol/L (0.28, 0.68) (18.6 g/dL), 0.39 mmol/L (0.19, 0.59) (15.08 mg/dL), and 0.42 mmol/L (0.22, 0.63) (16.24 mg/dL), respectively. These estimates did not change after adjustment for age. We also observed sex differences for HDL-C; girls had higher HDL-C in the youngest (<5 years, $P = .05$) and oldest age groups (15-19 years, $P < .001$). CONCLUSIONS: FH girls have higher levels of TC, LDL-C, and non-HDL-C levels than boys from birth up to 19 years of age. This may contribute significantly to the total lifelong cholesterol burden in FH women.

[38] *Rakovac Tisdall A, Crowley VEF, Crook MA. Undetectable high-density lipoprotein cholesterol in acute malaria. Journal of clinical lipidology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609858>

ABSTRACT

We report the case of a 39-year-old West African man in whom high-density lipoprotein cholesterol (HDL-C) was identified as undetectable at <0.08 mmol/L. Total cholesterol in the same sample was 2.85 mmol/L; triglycerides were only mildly elevated at 2.32 mmol/L. He was admitted with a 2-week history of polydipsia, polyuria, weight loss and hyperpyrexia. Dual malarial infection with *Plasmodium ovale* and *falciparum* was identified and attributed to a recent trip to Nigeria without chemoprophylaxis. Also, he was diagnosed with diabetes mellitus with random hyperglycemia of 39 mmol/L but no ketonemia. Subsequent investigation revealed a low apolipoprotein A1 of 0.38 g/L (1.04-2.02), confirming a true HDL-C deficit. On clinical examination, he had neither orange tonsils consistent with Tangier disease nor corneal opacification consistent with lecithin-cholesterol acyltransferase deficiency. The patient was an avid gym goer but denied anabolic steroid abuse, a fact supported by a transient primary testosterone deficiency at presentation (testosterone 6.56 nmol/L, RR 8.6-29; follicle-stimulating hormone high at 9.2 mU/L, luteinising hormone high at 11.9 mU/L). He was treated for malaria and started on metformin for diabetes. At 8-week follow-up, his HDL-C was entirely normal at 1.38 mmol/L. We believe this severe drop in HDL-C level to be due to acute inflammation caused by malaria. As extreme drops in HDL-C have been found to be associated with the poorest prognosis, prospective identification of HDL-C and prompt clinical liaison may be of benefit.

[39] *De Bortoli M, Taverna E, Maffioli E et al. Lipid accumulation in human breast cancer cells injured by iron depletors. Journal of experimental & clinical cancer research : CR* 2018; 37:75.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29615075>

ABSTRACT

BACKGROUND: Current insights into the effects of iron deficiency in tumour cells are not commensurate with the importance of iron in cell metabolism. Studies have predominantly focused on the effects of oxygen or glucose scarcity in tumour cells, while attributing insufficient emphasis to the inadequate supply of iron in hypoxic regions. Cellular responses to

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iron deficiency and hypoxia are interlinked and may strongly affect tumour metabolism. METHODS: We examined the morphological, proteomic, and metabolic effects induced by two iron chelators-deferoxamine (DFO) and di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT)-on MDA-MB-231 and MDA-MB-157 breast cancer cells. RESULTS: These chelators induced a cytoplasmic massive vacuolation and accumulation of lipid droplets (LDs), eventually followed by implosive, non-autophagic, and non-apoptotic death similar to methuosis. Vacuoles and LDs are generated by expansion of the endoplasmic reticulum (ER) based on extracellular fluid import, which includes unsaturated fatty acids that accumulate in LDs. Typical physiological phenomena associated with hypoxia are observed, such as inhibition of translation, mitochondrial dysfunction, and metabolic remodelling. These survival-oriented changes are associated with a greater expression of epithelial/mesenchymal transcription markers. CONCLUSIONS: Iron starvation induces a hypoxia-like program able to scavenge nutrients from the extracellular environment, and cells assume a hypertrophic phenotype. Such survival strategy is accompanied by the ER-dependent massive cytoplasmic vacuolization, mitochondrial dysfunctions, and LD accumulation and then evolves into cell death. LDs containing a greater proportion of unsaturated lipids are released as a consequence of cell death. The consequence of the disruption of iron metabolism in tumour tissue and the effects of LDs on intercellular communication, cancer-inflammation axis, and immunity remain to be explored. Considering the potential benefits, these are crucial subjects for future mechanistic and clinical studies.

[40] *Liu A, Frostegard J. PCSK9 plays a novel immunological role in the oxidized LDL-induced dendritic cell maturation and T cell activation from human blood and atherosclerotic plaque. Journal of internal medicine 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617044>

ABSTRACT

BACKGROUND: Activated T cells and dendritic cells (DCs) occur in atherosclerotic plaques. Proprotein convertase subtilisin kexin 9 (PCSK9) targets the LDL-receptor (LDLR), and results in increased LDL-levels. We here investigate immune effects of PCSK9 on OxLDL induced DC maturation and T cell activation. METHODS: T cells were isolated from carotid specimens of patients undergoing carotid endarterectomy, or from peripheral blood of healthy individuals. Human peripheral blood monocytes were differentiated into DCs. Naive T cells were co-cultured with pretreated DCs. The effects of PCSK9 and its inhibition by silencing were studied. RESULTS: OxLDL induced PCSK9 in DCs and promoted DC maturation with increased expression of CD80, CD83, CD86 and HLA-DR and the scavenger receptors LOX-1, CD36 and SR-A. T cells exposed to OxLDL-treated DCs proliferated and produced IFN-gamma and IL-17, thus with polarization to Th1 and/or Th17 subsets. Silencing of PCSK9 reversed the OxLDL effects on DCs and T cells. DC maturation was repressed and the production of TNF-alpha, IL-1beta and IL-6 was limited, while TGF-beta and IL-10 secretion and T regulatory cells were induced. OxLDL induced miRNA let-7c, miR-27a, miR-27b, miR-185. Silencing PCSK9 repressed miR-27a and to a lesser extent let-7c. PCSK9 silencing enhanced SOCS1 expression induced by OxLDL. Experiments on T cells from carotid atherosclerotic plaques or healthy individuals showed similar results. CONCLUSIONS: We demonstrate immunological effects of PCSK9 in relation to activation and maturation of DCs and plaque T cells by OxLDL, a central player in

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atherosclerosis. This may directly influence atherosclerosis and cardiovascular disease, independent of LDL-lowering. This article is protected by copyright. All rights reserved.

[41] *Albracht-Schulte K, Kalupahana NS, Ramalingam L et al. Omega-3 fatty acids in obesity and metabolic syndrome: a mechanistic update. The Journal of nutritional biochemistry* 2018; 58:1-16.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29621669>

ABSTRACT

Strategies to reduce obesity have become public health priorities as the prevalence of obesity has risen in the United States and around the world. While the anti-inflammatory and hypotriglyceridemic properties of long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) are well known, their antiobesity effects and efficacy against metabolic syndrome, especially in humans, are still under debate. In animal models, evidence consistently suggests a role for n-3 PUFAs in reducing fat mass, particularly in the retroperitoneal and epididymal regions. In humans, however, published research suggests that though n-3 PUFAs may not aid weight loss, they may attenuate further weight gain and could be useful in the diet or as a supplement to help maintain weight loss. Proposed mechanisms by which n-3 PUFAs may work to improve body composition and counteract obesity-related metabolic changes include modulating lipid metabolism; regulating adipokines, such as adiponectin and leptin; alleviating adipose tissue inflammation; promoting adipogenesis and altering epigenetic mechanisms.

[42] *Jain R, Austin Pickens C, Fenton JJ. The role of the lipidome in obesity-mediated colon cancer risk. The Journal of nutritional biochemistry* 2018; 59:1-9.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29605789>

ABSTRACT

Obesity is a state of chronic inflammation influenced by lipids such as fatty acids and their secondary oxygenated metabolites deemed oxylipids. Many such lipid mediators serve as potent signaling molecules of inflammation, which can further alter lipid metabolism and lead to carcinogenesis. For example, sphingosine-1-phosphate activates cyclooxygenase-2 in endothelial cells resulting in the conversion of arachidonic acid (AA) to prostaglandin E2 (PGE2). PGE2 promotes colon cancer cell growth. In contrast, the less studied path of AA oxygenation via cytochrome p450 enzymes produces epoxyeicosatetraenoic acids (EETs), whose anti-inflammatory properties cause shrinking of enlarged adipocytes, a characteristic of obesity, through the liberation of fatty acids. It is now thought that EET depletion occurs in obesity and may contribute to colon cell carcinogenesis. Meanwhile, gangliosides, a type of sphingolipid, are cell surface signaling molecules that contribute to the apoptosis of colon tumor cells. Many of these discoveries have been made recently and the mechanisms are still not fully understood, leading to an exciting new chapter of lipidomic research. In this review, mechanisms behind obesity-associated colon cancer are discussed with a focus on the role of small lipid signaling molecules in the process. Specifically, changes in lipid metabolite levels during obesity and the development of colon cancer, as well as novel biomarkers and targets for therapy, are discussed.

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[43] *Khokhar B, Simoni-Wastila L, Slejko JF et al. In-Hospital Mortality Following Traumatic Brain Injury Among Older Medicare Beneficiaries, Comparing Statin Users With Nonusers. The Journal of pharmacy technology : jPT : official publication of the Association of Pharmacy Technicians* 2017; 33:225-236.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29607441>

ABSTRACT

Background: Traumatic brain injury (TBI) is a significant public health concern for older adults. Small-scale human studies have suggested pre-TBI statin use is associated with decreased in-hospital mortality following TBI, highlighting the need for large-scale translational research. Objective: To investigate the relationship between pre-TBI statin use and in-hospital mortality following TBI. Methods: A retrospective study of Medicare beneficiaries 65 and older hospitalized with a TBI during 2006 to 2010 was conducted to assess the impact of pre-TBI statin use on in-hospital mortality following TBI. Exposure of interest included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Beneficiaries were classified as current, recent, past, and nonusers of statins prior to TBI. The outcome of interest was in-hospital mortality. Logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) comparing current, recent, and prior statin use to nonuse. Results: Most statin users were classified as current users (90%). Current atorvastatin (OR = 0.88; 95% CI 0.82, 0.96), simvastatin (OR = 0.84; 95% CI = 0.79, 0.91), and rosuvastatin (OR = 0.79; 95% CI = 0.67, 0.94) use were associated with a significant decrease in the risk of in-hospital mortality following TBI. Conclusions: In addition to being the most used statins, current use of atorvastatin, rosuvastatin, and simvastatin was associated with a significant decrease in in-hospital mortality following TBI among older adults. Future research must include clinical trials to help exclude the possibility of a healthy user effect in order to better understand the impact of statin use on in-hospital mortality following TBI.

[44] *Nguyen S, Chuah SY, Fontas E et al. Atorvastatin in Combination With Narrowband UV-B in Adult Patients With Active Vitiligo: A Randomized Clinical Trial. JAMA dermatology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29617528>

ABSTRACT

[45] *Kimak E, Zieba B, Duma D, Solski J. Myeloperoxidase level and inflammatory markers and lipid and lipoprotein parameters in stable coronary artery disease. Lipids in health and disease* 2018; 17:71.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29618370>

ABSTRACT

BACKGROUND: Myeloperoxidase (MPO) impairing endothelial functions. We investigated whether increasing concentration of myeloperoxidase (MPO) and inflammatory markers induce progression and incident acute coronary syndrome (ACS) in stable coronary artery disease (SCAD) patients. Therefore, the concentration of MPO, lipids, lipoproteins (apo(apolipoprotein) AI, apoB, lipoprotein associated phospholipase A2 (LpPLA2) level), inflammatory markers (high sensitivity C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-alpha), interleukine-6 (IL-6) concentration) were examined. METHODS: This study concerned 67 SCAD patients divided into groups: all patients, patients with MPO < 200 ng/ml, MPO 200-300 ng/ml, MPO > 300

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ng/ml concentration and 15 controls. ApoAI, apoB and hsCRP levels were examined using the immunonephelometric method, and MPO, LpPLA2, IL-6, TNF-alpha concentration was performed by using Quantikine ELISA kit R&D Systems. RESULTS: In the all patients, and in group with MPO 200-300 ng/ml TC, LDL-C, nonHDL-C, LpPLA2 concentration and TC/HDL-C, LDL-C/HDL-C ratios were insignificant, and significantly higher concentration of TG, apoB, MPO, inflammatory markers and TG/HDL-C, MPO/apoAI, MPO/HDL-C ratios but HDL-C, apoAI level and HDL-C/apoAI ratio were significantly reduced. In the group of patients with MPO < 200 ng/ml, level of TC, LDL-C, nonHDL-C, apoAI, apoAII, LpPLA2 and MPO and LDL-C/HDL-C ratio were in-significant, HDL-C was decreased but apoB, TG, inflammatory markers, apoB/apoAI, TG/HDL-C, MPO/apoAI, MPO/HDL-C ratio were significantly increased. In the group of patients with MPO > 300 ng/ml concentration of TC, LDL-C, nonHDL-C, apoAII, LpPLA2 and LDL-C/HDL-C ratios were not significant, but HDL-C and apoAI concentrations were significantly decreased. The concentrations of TG, apoB, MPO and inflammatory markers and TG/HDL-C, MPO/apoAI, MPO/HDL-C ratios were significantly increased compared to the controls. The apoAI concentration was significantly decreased and the concentration of MPO and hsCRP as well as MPO/apoAI and MPO/HDL-C ratios were significantly higher as compared to the group of patients with MPO < 200 ng/ml. Spearman's correlation test showed a positive correlation between MPO concentration and MPO/apoAI and MPO/HDL-C ratios in all patients and MPO < 200 ng/ml, MPO 200-300 ng/ml. The patients with MPO > 300 ng/ml showed a positive correlation between the concentration of MPO and the level of hsCRP and IL-6, and a negative correlation between MPO/apoAI ratio and the concentration of HDL-C, apoAI and apoAII. CONCLUSION: The results suggest that moderate dyslipidemia and dyslipoproteinemia deepening of inflammation, and inflammation slowly induce increase MPO concentration which decrease apoAI and HDL-C level and disturb HDLs function. The increasing MPO level and MPO/HDL-C, MPO/apoAI ratios can differentiate the SCAD patients at the risk of acute coronary syndrome (ACAD) and stroke.

[46] Wang D, Wang Y. **Fenofibrate monotherapy-induced rhabdomyolysis in a patient with hypothyroidism: A rare case report and literature review.** *Medicine (Baltimore)* 2018; 97:e0318.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29620657>

ABSTRACT

RATIONALE: Fenofibrate is a fibric acid derivative indicated for use in hypertriglyceridemia and mixed dyslipidemia treatment among adults. Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle contents into the systemic circulation, which is the most serious and fatal side effect of fenofibrate. The objective of this paper is to discuss fatal side effect of fenofibrate and keep safe medication. **PATIENT CONCERNS:** A patient with hypothyroidism who presented with rhabdomyolysis during fenofibrate monotherapy for hypertriglyceridemia was reported. **DIAGNOSES:** Fenofibrate Monotherapy Induced Rhabdomyolysis. **INTERVENTIONS:** Fenofibrate was stopped. Adequate fluid resuscitation, mannitol diuresis, myocardium protection, hepatoprotection and urine alkalinization with sodium bicarbonate were performed. **OUTCOMES:** Blood tests were normal and the patient was good and discharged 2 weeks later. **LESSONS:** 13 cases associated with fenofibrate monotherapy-induced rhabdomyolysis were reviewed, which had been published in the English

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literature. The severity of fenofibrate muscle toxicity may be the result of the combination of two rhabdomyolysis enhancers, such as hypothyroidism and female gender. To avoid it, strict clinical and laboratory monitoring should be maintained, particularly hypothyroidism. Patients should be informed of possible potentially irreversible effects after taking fibrates.

[47] *Bech AP, Wetzels JFM, Nijenhuis T. Effects of sildenafil, metformin, and simvastatin on ADH-independent urine concentration in healthy volunteers. Physiological reports 2018; 6:e13665.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29611351>

ABSTRACT

Nephrogenic diabetes insipidus (NDI) is a rare disorder characterized by resistance of the kidney to the action of antidiuretic hormone (ADH), resulting in a decrease in the capacity of the kidney to concentrate the urine. NDI can be inherited or acquired due to, for example, chronic lithium therapy. Current treatment options are limited to attempts to lower urine output by a low-solute diet and the use of diuretics or anti-inflammatory drugs. These measures are only partially effective. Recent reports suggested that sildenafil, metformin, and simvastatin might improve ADH-independent urine concentration. If confirmed, this would provide interesting additional therapeutic options for patients with NDI. We, therefore, tested the effect of these drugs on ADH-independent urine concentrating capacity in healthy volunteers. We included 36 healthy volunteers who received sildenafil 20 mg thrice daily, metformin 500 mg thrice daily or simvastatin 40 mg once daily during 1 week. At baseline and at the end of treatment, a water loading test was performed. No significant increase in lowest urine osmolality was seen after the use of metformin or sildenafil ($P = 0.66$ and $P = 0.09$ respectively). Lowest urine osmolality increased modestly but significantly after the use of simvastatin (70 mOsm/kg to 85 mOsm/kg, $P = 0.05$). Our data suggest that only simvastatin has an effect on urine osmolality in healthy volunteers. Validation studies are needed and, most importantly, these drugs should be tested in patients with NDI.

[48] *Zamora A, Masana L, Comas-Cufi M et al. Number of Patients Eligible for PCSK9 Inhibitors Based on Real-world Data From 2.5 Million Patients. Revista espanola de cardiologia (English ed.) 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29606363>

ABSTRACT

INTRODUCTION AND OBJECTIVES: PCSK9 inhibitors (PCSK9i) are safe and effective lipid-lowering drugs. Their main limitation is their high cost. The aim of this study was to estimate the number of patients eligible for treatment with PCSK9i according to distinct published criteria. **METHODS:** Data were obtained from the Information System for the Development of Research in Primary Care. Included patients were equal to or older than 18 years and had at least 1 low-density lipoprotein cholesterol measurement recorded between 2006 and 2014 ($n = 2\,500\,907$). An indication for treatment with PCSK9i was assigned according to the following guidelines: National Health System, Spanish Society of Arteriosclerosis, Spanish Society of Cardiology, National Institute for Health and Care Excellence, and the European Society of Cardiology/European Atherosclerosis Society Task Force. Lipid-lowering treatment was defined as optimized if it reduced low-density lipoprotein levels by $\geq 50\%$ and adherence was $> 80\%$.

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RESULTS: Among the Spanish population aged 18 years or older, the number of possible candidates to receive PCSK9i in an optimal lipid-lowering treatment scenario ranged from 0.1% to 1.7%, depending on the guideline considered. The subgroup of patients with the highest proportion of potential candidates consisted of patients with familial hypercholesterolemia, and the subgroup with the highest absolute number consisted of patients in secondary cardiovascular prevention. **CONCLUSIONS:** The number of candidates to receive PCSK9i in conditions of real-world clinical practice is high and varies widely depending on the recommendations of distinct scientific societies.

[49] *Enroth S, Maturi V, Berggrund M et al. Systemic and specific effects of antihypertensive and lipid-lowering medication on plasma protein biomarkers for cardiovascular diseases. Scientific reports* 2018; 8:5531.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29615742>

ABSTRACT

A large fraction of the adult population is on lifelong medication for cardiovascular disorders, but the metabolic consequences are largely unknown. This study determines the effects of common anti-hypertensive and lipid lowering drugs on circulating plasma protein biomarkers. We studied 425 proteins in plasma together with anthropometric and lifestyle variables, and the genetic profile in a cross-sectional cohort. We found 8406 covariate-protein associations, and a two-stage GWAS identified 17253 SNPs to be associated with 109 proteins. By computationally removing variation due to lifestyle and genetic factors, we could determine that medication, per se, affected the abundance levels of 35.7% of the plasma proteins. Medication either affected a single, a few, or a large number of protein, and were found to have a negative or positive influence on known disease pathways and biomarkers. Anti-hypertensive or lipid lowering drugs affected 33.1% of the proteins. Angiotensin-converting enzyme inhibitors showed the strongest lowering effect by decreasing plasma levels of myostatin. Cell-culture experiments showed that angiotensin-converting enzyme inhibitors reduced myostatin RNA levels. Thus, understanding the effects of lifelong medication on the plasma proteome is important both for sharpening the diagnostic precision of protein biomarkers and in disease management.

[50] *Lettiero B, Inasu M, Kimbung S, Borgquist S. Insensitivity to atorvastatin is associated with increased accumulation of intracellular lipid droplets and fatty acid metabolism in breast cancer cells. Scientific reports* 2018; 8:5462.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29615666>

ABSTRACT

Apart from the relevant lipid-lowering effects, statins have demonstrated significant, although heterogeneous, anti-tumor activities in preventing breast cancer (BC) progression. To characterize the critical pathways behind the diverse responses to therapy, we investigated statin-induced changes in regulation of lipid metabolism and abundance of neutral lipid-containing cytoplasmic lipid droplets (LDs) in BC cells displaying different sensitivity to atorvastatin. Following atorvastatin treatment, accumulated LD levels inversely mirrored the marginal anti-proliferative effects in a dose and time-dependent manner in the less-sensitive BC cells. Transcriptional profiling excluded dysregulation of lipid uptake and efflux as specific

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mechanisms associated with differences in LD accumulation and anti-proliferative effects of atorvastatin. Notably, significant upregulation of genes involved in unsaturated fatty acid metabolism [stearoyl-CoA desaturase (SCD)] and cholesterol biosynthesis [3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR)], were associated with atorvastatin insensitivity. Taken together, the increased ability to store neutral lipids in LDs as consequence of atorvastatin treatment likely confers a proliferative advantage to BC cells and may serve as potential biomarker of statin resistance in BC. Contributions of cholesterol biosynthesis and unsaturated fatty acid metabolism to LD formation should be thoroughly explored for better understanding of the molecular mechanisms underlying statin-induced effects against BC progression.

[51] *Can A, Castro VM, Dligach D et al. Lipid-Lowering Agents and High HDL (High-Density Lipoprotein) Are Inversely Associated With Intracranial Aneurysm Rupture. Stroke* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29622625>

ABSTRACT

BACKGROUND AND PURPOSE: Growing evidence from experimental animal models and clinical studies suggests the protective effect of statin use against rupture of intracranial aneurysms; however, results from large studies detailing the relationship between intracranial aneurysm rupture and total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and lipid-lowering agent use are lacking. **METHODS:** The medical records of 4701 patients with 6411 intracranial aneurysms diagnosed at the Massachusetts General Hospital and the Brigham and Women's Hospital between 1990 and 2016 were reviewed and analyzed. Patients were separated into ruptured and nonruptured groups. Univariable and multivariable logistic regression analyses were performed to determine the effects of lipids (total cholesterol, LDL, and HDL) and lipid-lowering medications on intracranial aneurysm rupture risk. Propensity score weighting was used to account for differences in baseline characteristics of the cohorts. **RESULTS:** Lipid-lowering agent use was significantly inversely associated with rupture status (odds ratio, 0.58; 95% confidence interval, 0.47-0.71). In a subgroup analysis of complete cases that includes both lipid-lowering agent use and lipid values, higher HDL levels (odds ratio, 0.95; 95% confidence interval, 0.93-0.98) and lipid-lowering agent use (odds ratio, 0.41; 95% confidence interval, 0.23-0.73) were both significantly and inversely associated with rupture status, whereas total cholesterol and LDL levels were not significant. A monotonic exposure-response curve between HDL levels and risk of aneurysmal rupture was obtained. **CONCLUSIONS:** Higher HDL values and the use of lipid-lowering agents are significantly inversely associated with ruptured intracranial aneurysms.

[52] *Huai J, Yang Z, Yi YH et al. [Regulation of pravastatin on long-chain fatty acid oxidative enzyme in pre-eclampsia-like mouse model]. Zhonghua fu chan ke za zhi* 2018; 53:183-189.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29609233>

ABSTRACT

Objective: To investigate the modulation of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) expression by pravastatin in pre-eclampsia-like mouse model. **Methods:** C57BL/6J mice were randomly injected with N-nitro-L-arginine methyl ester (L-NAME) as pre-eclampsia-like model group (PE) or saline as normal pregnancy control group (Con) respectively, from gestational the 7th to 18th day. For each group, pravastatin (PE+Pra, Con+Pra group) or saline

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(PE+N, Con+N Group) was given from the 8th to 18th day of gestation, respectively. Liver and placenta of pregnant mice were collected on gestational day 18. The LCHAD protein expression and mRNA levels of liver and placenta were detected through western blot, immunohistochemistry and real-time quantitative PCR. Results: (1) The average arterial pressure of pregnant mice increased gradually from the 8th to 18th day in PE+N group, but decreased in PE+Pra group from gestational 10th day, 24 hour urinary protein levels in PE+N group [(1 494 +/- 201) mug] were significantly higher than that in Con+N group [(935+/-128) mug, $P<0.01$], and also higher than that in PE+Pra group [(981+/-116) mug, $P<0.01$].(2) The results of western blot: the expression of LCHAD was significantly lower in PE+N group (liver: 0.64+/-0.11, placenta: 0.48+/-0.06) than that in Con+N group (liver: 1.06+/-0.10, placenta: 0.60+/-0.10), and lower than that in PE+Pra group (liver: 0.99+/-0.04, placenta: 0.60+/-0.08; all $P<0.01$). (3) The results of real-time quantitative PCR: the levels of LCHAD mRNA in liver and placenta in PE+N group (liver: 0.621+/-0.128, placenta: 0.646+/-0.129) were significantly decreased compared with Con+N group (liver: 1.007+/-0.130, placenta: 1.004+/-0.103; all $P<0.01$), but there was no significant difference between PE+Pra group (liver: 0.693+/-0.678, placenta: 0.662+/-0.183; $P>0.05$). (4) LCHAD protein was expressed widely and evenly in liver. The expression in placental cytotrophoblast and syncytial trophoblast cells located in outer layer of villous in labyrinth layer was the most. The expression of LCHAD was significantly lower in PE+N group (liver: 0.062+/-0.016, placenta: 0.147+/-0.018) than that in Con+N group (liver: 0.126+/-0.013, placenta: 0.183+/-0.024), and lower than that in PE+Pra group (liver: 0.111+/-0.017, placenta: 0.174+/-0.027; all $P<0.05$). Conclusion: Pravastatin could upregulate the LCHAD protein expression of liver and placenta in the pre-eclampsia-like mouse, which may be a mechanism to improve the clinical manifestations of pre-eclampsia.