Literature update week 12 (2018)

[1] *Chowaniec Z, Skoczynska A*. **Plasma lipid transfer proteins: The role of PLTP and CETP in atherogenesis**. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29558025
ABSTRACT
Cardiovascular diseases are still the main cause of death in Poland and throughout the world. Independent risk factors of cardiovascular disease, in addition to elevated LDL cholesterol, are both low HDL levels and high levels of non-HDL cholesterol. Plasma phospholipid-transfer protein (PLTP) and cholesteryl ester transfer protein (CETP) both play a major role in the metabolism of those lipoproteins. A lack of these proteins increases HDL and lowers LDL levels. In the light of current knowledge, it seems reasonable to search for compounds that may decrease the activity of CETP, and thus reduce the incidence of cardiovascular disease. Whereas on the one hand there are reports about the adverse effect of torcetrapib and the lack of therapeutic effects of dalcetrapib, on the other hand the question arises whether the CETP inhibitors that are currently in clinical trials will rise to the challenges before them. Currently, it is known that the activity of PLTP, while affecting the metabolism of lipoproteins, especially HDL, plays a major role in atherogenesis. Still, there are some contradictions and controversies about the effect of PLTP on reverse cholesterol transport (RCT). There are a number of studies about the role that PLTP plays in the pathogenesis of various diseases. Further studies are needed to clearly determine the impact of PLTP activity on the formation and development of pathological processes in the cardiovascular system.

[2] *Kim JK, Ailshire JA, Crimmins EM*. **Twenty-year trends in cardiovascular risk among men and women in the United States**. Aging clinical and experimental research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569117
ABSTRACT
BACKGROUND: Relative to men, women have experienced slower improvement in mortality in the US in recent decades. AIMS: We investigated 20-year trends in cardiovascular risk for men and women age 40 and over in the US to determine whether there was differential change in risk for men and women. METHODS: Using the National Health and Nutrition Examination Survey (NHANES), we estimated total cardiovascular risk, the prevalence of individual risk factors, and potential factors contributing to change in risk. RESULTS: Men showed steady reductions in cardiovascular risk over the 20 years; women experienced increased risk from 1990 to 2000, but decreased risk from 2000 to 2010. Sex differences in cardiovascular risk changed so that there was no significant difference by sex at any age over 50 in 2010. Large decreases in the prevalence of high risk lipids were important causes of reduction in risks for both sexes; changes in blood pressure were less important, except for women in the 2000-2010 period when they equaled the effect of changing lipids. Increasing medication usage and effectiveness drove improvements in blood pressure and total cholesterol for both sexes. In 2010 there was no difference between men and women in the use of antihypertensives or cholesterol-lowering medications. Metabolic risk, as indexed by obesity and HbA1c, increased over time and went against the trend in the summary measure. Diabetes, smoking, and hormone therapy use did not explain changes in high blood pressure or high total cholesterol

for either gender. CONCLUSIONS: Recent decreases in cardiovascular risk may lead to future reduction in cardiovascular events and mortality among both women and men.

[3] *Argaw A, Wondafrash M, Bouckaert KP et al.* **Effects of n-3 long-chain PUFA supplementation to lactating mothers and their breastfed children on child growth and morbidity: a 2 x 2 factorial randomized controlled trial in rural Ethiopia**. The American journal of clinical nutrition 2018; 107:454-464.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29566189
ABSTRACT
Background: Recurrent infections and inflammation contribute to growth faltering in low-income countries. n-3 (omega-3) Long-chain polyunsaturated fatty-acids (LC-PUFAs) may improve immune maturation, resistance to infections, and growth in young children who are at risk. Objective: We evaluated the independent and combined effects of fish oil (500 mg n-3 LC-PUFAs/d) supplementation to lactating mothers and their breastfed children, aged 6-24 mo, on child morbidity, systemic inflammation, and growth in southwest Ethiopia. Design: A 4-arm double-blind randomized controlled trial was conducted by enrolling 360 mother-infant pairs with infants 6-12 mo old. Study arms were both the lactating mother and child receiving fish oil intervention (MCI), only the lactating mother receiving fish oil intervention and child receiving placebo control (MI), only the child receiving intervention and mother receiving placebo control (CI), and both mother and child receiving a placebo supplement or control (C). The primary study outcome was linear growth using monthly changes in length-for-age z score. Anthropometric measurements were taken monthly, and hemoglobin, C-reactive protein, and blood LC-PUFAs were measured at baseline and after 6 and 12 mo of follow-up. Weekly morbidity surveillance was conducted throughout the study. Results: Fish-oil supplementation significantly increased blood n-3 LC-PUFA concentration ($P < 0.01$) and decreased the arachidonic acid:(docosahexaenoic acid + eicosapentaenoic acid) ratio ($P < 0.001$) in all intervention arms. No significant intervention effect was found on linear growth, morbidity, or systemic inflammation. Compared to the control group, a small positive effect on monthly changes in weight-for-length z scores was found in the CI arm (effect size: 0.022/mo; 95% CI: 0.005, 0.039/mo; $P = 0.012$) and the MCI arm (effect size: 0.018/mo; 95% CI: 0.001, 0.034/mo; $P = 0.041$). Conclusions: n-3 LC-PUFA supplementation of lactating mothers and children did not affect child linear growth and morbidity in a low-income setting. n-3 LC-PUFA supplementation given directly to children modestly increased relative weight gain. This trial was registered at clinicaltrials.gov as NCT01817634.

[4] *Martinez BK, White CM*. **The Emerging Role of Inflammation in Cardiovascular Disease**. The Annals of pharmacotherapy 2018:1060028018765939.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29557210
ABSTRACT
OBJECTIVE: To review the role of inflammatory suppression in patients with atherosclerotic cardiovascular disease (ASCVD) with a focus on the interleukin-1beta blocker canakinumab. DATA SOURCES: An Ovid MEDLINE literature search (1946 to February 2018) was performed using search terms inflammation, ASCVD, atherosclerosis, C-reactive protein, canakinumab. Additional references were identified from a review of literature citations. STUDY SELECTION

AND DATA EXTRACTION: English-language studies assessing the impact of pharmacological agents, including canakinumab, on inflammation as measured by high-sensitivity C-reactive protein (hsCRP) and the association with reducing ASCVD events were evaluated. DATA SYNTHESIS: Nine studies were included to describe the effect of ASCVD drugs on hsCRP. Aspirin, angiotensin-converting enzyme inhibitors, gemfibrozil, and statins exhibit varying degrees of hsCRP reduction and are associated with a reduction of ASCVD events. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), showed a significant reduction of ASVCD events in patients with elevated baseline hsCRP levels without affecting cholesterol. CONCLUSIONS: Patients with elevated inflammatory markers such as hsCRP are at risk for ASVCD events. Several drug classes have shown the ability to decrease hsCRP levels, but the extent to which this reduces ASCVD events in lieu of other drug mechanisms was not clear. Canakinumab specifically targets the inflammatory process in ASCVD and was proven to be effective in preventing ASCVD events in patients with elevated hsCRP levels.

[5] *Lorenzo A, Silva J, James CE et al.* **Clinical, Anthropometric and Biochemical Characteristics of Patients with or without Genetically Confirmed Familial Hypercholesterolemia**. Arquivos brasileiros de cardiologia 2018; 110:119-123.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29561990
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is a common autosomal dominant disorder, characterized by a high level of low-density lipoprotein cholesterol (LDL-C) and a high risk of premature cardiovascular disease. OBJECTIVE: To evaluate clinical and anthropometric characteristics of patients with the familiar hypercholesterolemia (FH) phenotype, with or without genetic confirmation of FH. METHODS: Forty-five patients with LDL-C > 190 mg/dl were genotyped for six FH-related genes: LDLR, APOB, PCSK9, LDLRAP1, LIPA and APOE. Patients who tested positive for any of these mutations were considered to have genetically confirmed FH. The FH phenotype was classified according to the Dutch Lipid Clinic Network criteria. RESULTS: Comparing patients with genetically confirmed FH to those without it, the former had a higher clinical score for FH, more often had xanthelasma and had higher LDL-C and apo B levels. There were significant correlations between LDL-C and the clinical point score for FH (R = 0.382, p = 0.037) and between LDL-C and body fat (R = 0.461, p = 0.01). However, patients with mutations did not have any correlation between LDL-C and other variables, while for those without a mutation, there was a correlation between LDL-C and the clinical point score. CONCLUSIONS: LDL-C correlated with the clinical point score and with body fat, both in the overall patient population and in patients without the genetic confirmation of FH. In those with genetically confirmed FH, there were no correlations between LDL-C and other clinical or biochemical variables in patients.

[6] *Erhart G, Lamina C, Lehtimaki T et al.* **Genetic Factors Explain a Major Fraction of the 50% Lower LPA (Lipoprotein[a]) Concentrations in Finns**. Arteriosclerosis, thrombosis, and vascular biology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29567679
ABSTRACT

OBJECTIVE: Lp(a) (lipoprotein[a]) concentrations are widely genetically determined by the LPA isoforms and show </=5-fold interpopulation differences. Two- to 3-fold differences have been reported even within Europe. Finns represent a distinctive population isolate within Europe and have been repeatedly reported to present lower Lp(a) concentrations than Central Europeans. The significance of this finding was unclear for a long time because of the difficult comparability of Lp(a) assays. Recently, a large standardized study in >50 000 individuals from 7 European populations confirmed this observation but could not provide insights into the causes. APPROACH AND RESULTS: We investigated Lp(a) concentrations, LPA isoforms, and genotypes of established genetic variants affecting Lp(a) concentrations (LPA variants, APOE isoforms, and PCSK9 R46L) in the Finnish YFS (Cardiovascular Risk in Young Finns Study) population (n=2281) and 3 Non-Finnish Central European populations (n=10 003). We observed approximately 50% lower Lp(a) concentrations in Finns. The isoform distribution was shifted toward longer isoforms, and the percentage of low-molecular-weight isoform carriers was reduced. Most interestingly, however, Lp(a) was reduced in each single-isoform group. In contrast to the known inverse relationship between LPA isoforms and Lp(a) concentrations, especially short isoforms presented unexpectedly low Lp(a) concentrations in Finns. The investigated genetic variants, as well as age, sex, and renal function, explained 71.8% of the observed population differences. CONCLUSIONS: The population differences in Lp(a) concentrations between Finnish and Central European populations originate not only from a different LPA isoform distribution but suggest the existence of novel functional variation in the small-isoform range.

[7] *Soderstrom LA, Tarnawski L, Olofsson PS*. **CD137: A checkpoint regulator involved in atherosclerosis**. Atherosclerosis 2018; 272:66-72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29571029
ABSTRACT
Inflammation is associated with atherosclerotic plaque development and precipitation of myocardial infarction and stroke, and anti-inflammatory therapy may reduce disease severity. Costimulatory molecules are key regulators of immune cell activity and inflammation, and are associated with disease development in atherosclerosis. Accumulating evidence indicates that a costimulatory molecule of the Tumor Necrosis Factor Receptor superfamily, the checkpoint regulator CD137, promotes atherosclerosis and vascular inflammation in experimental models. In light of the burgeoning consideration of CD137-targeted therapy in the clinic, it will be important to better understand costimulator immunobiology in development of cardiovascular disease. Here, we review available data on the costimulator CD137 and its potential role in atherosclerosis.

[8] *Zhang M, Zhao GJ, Yao F et al.* **AIBP reduces atherosclerosis by promoting reverse cholesterol transport and ameliorating inflammation in apoE(-/-) mice**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29555084
ABSTRACT
BACKGROUND AND AIMS: ApoA-1 binding protein (AIBP) is a secreted protein that interacts with apoA-I and accelerates cholesterol efflux from cells. We have recently reported that AIBP promotes apoA-1 binding to ABCA1 in the macrophage cell membrane, partially through 115-123 amino acids. However, the effects of AIBP on the development of atherosclerosis in vivo

remain unknown. METHODS: ApoE(-/-) mice with established atherosclerotic plaques were infected with rAAV-AIBP or rAAV-AIBP(Delta115-123), respectively. RESULTS: AIBP-treated mice showed reduction of atherosclerotic lesion formation, increase in circulating HDL levels and enhancement of reverse cholesterol transport to the plasma, liver, and feces. AIBP increased ABCA1 protein levels in aorta and peritoneal macrophages. Furthermore, AIBP could diminish atherosclerotic plaque macrophage content and the expression of chemotaxis-related factors. In addition, AIBP prevented macrophage inflammation by inactivating NF-kappaB and promoted the expression of M2 markers like Mrc-1 and Arg-1. However, lack of 115-123 amino acids of AIBP(Delta115-123) had no such preventive effects on the progression of atherosclerosis. CONCLUSIONS: Our observations demonstrate that AIBP inhibits atherosclerosis progression and suggest that it may be an effective target for prevention of atherosclerosis.

[9] *Pelcl T, Skrha J, Jr., Prazny M et al.* **Diabetes, cardiovascular disorders and 2,3,7,8-TCDD body burden In Czech patients 50 years after the intoxication**. Basic & clinical pharmacology & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569337
ABSTRACT
The correlation between 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD) intoxication and the parameters of metabolic impairment were examined in the last 8 male survivors out of 80 workers exposed to TCDD during the production of herbicides in a chemical factory in 1965-1967. Their median TCDD blood level was 112 (46-390) pg/g lipids and the median TCDD body deposit was 3.9 (0.8-11.7) mug. This puts these patients into the most severely intoxicated group of subjects, according to back-calculated levels of TCDD. The median TCDD blood level in 8 controls was 12 pg/g (<0.10 to 22.2 pg/g). Markers of metabolic impairment - diabetes, dyslipidaemia, arterial hypertension, carotid artery plaque, skin microvascular reactivity, eye-fundus hypertensive angiopathy and history of coronary heart disease were assessed and compared to a general male population of comparable age. Measured parameters compared with a population of comparable age were as follows: prevalence of diabetes (62.5% versus 17.6%), arterial hypertension (87.5% versus 71.8%), dyslipidaemia (87.5% versus 88.8%), history of coronary heart disease (62.5% versus 26.0%), eye-fundus hypertension angiopathy (50% versus 14%). All 8 patients (100% versus 43%) developed plaques in carotid arteries, 6 had stenosis >50%, and 2 had a carotid intervention (stenting or endarterectomy). Total cholesterol levels decreased compared to the earlier study this patient group in 2008, most likely due to a more intensive use of lipid-lowering drugs. Several metabolic parameters were higher (diabetes as much as 3.5-fold) in the group of severely TCDD intoxicated subjects than in a general population of comparable age. This suggests that TCDD plays a role in the development of metabolic impairment and vascular changes.

[10] *Chen Y, Li M, Zhang Y et al.* **Traditional Chinese medication Tongxinluo attenuates apoptosis in ox-LDL-stimulated macrophages by enhancing Beclin-1-induced autophagy**. Biochem Biophys Res Commun 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29550482

ABSTRACT
In advanced atherosclerosis, a large number of necrotic core increases plaque vulnerability, which leads to the occurrence of acute atherothrombotic cardiovascular events. Macrophage apoptosis plays an important role in secondary necrosis. The present study aimed to examine and describe the effect of the traditional Chinese medication Tongxinluo (TXL) on macrophage apoptosis in advanced atherosclerotic plaques and to explore its mechanism. By observing the effect of TXL on ox-LDL-stimulated macrophage apoptosis, it was shown that TXL significantly inhibited ox-LDL-induced apoptosis of macrophages by enhancing autophagy. Therapeutic mechanism of TXL included increasing the expression of Beclin-1 and improving the dissociation of Bcl-2-Beclin-1 Complex. Apolipoprotein E knockout (apoE-/-) mice with a high fat diet were divided into four groups: saline group (Saline gavage), low dose TXL group (0.38g/kg/d, gavage), medium dose TXL group (0.75g/kg/day, gavage), and high dose TXL group (1.5g/kg/day, gavage). 4 weeks after carotid-artery surgery, lentiviral of Beclin-1 silencing was injected through the tail vein. TXL treatment significantly reduced macrophage apoptosis dose-dependently and the result was blocked by Beclin-1 silencing. In addition, the increased Lc3b dots by TXL almost localized to macrophages in advanced atherosclerotic plaque. Compared with the same dose of TXL shBeclin-1 group, plaque area and vulnerability index of TXL groups decreased. The anti-apoptosis effects of TXL on atherosclerosis was related to the improvement of autophagy via Beclin-1.

[11] *Wang Q, Meng Y, Cao W et al.* **Association of monocyte to high-density lipoprotein cholesterol ratio with carotid artery intima-media thickness in patients with systemic lupus erythematosus**. Biomarkers in medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569475

ABSTRACT
AIM: The purpose of this study was to evaluate the relationship between Monocyte to high-density lipoprotein cholesterol ratio (MHR) and carotid atherosclerostic plaque in patients with systemic lupus erythematosus (SLE). METHODS: A total of 214 SLE patients were divided into two groups according to the results of ultrasonic examination: carotid arterial atherosclerotic plaque groups and noncarotid arterial atherosclerosis groups. RESULTS: The values of monocyte to high-density lipoprotein-cholesterol ratio (MHR) increase in carotid arterial atherosclerotic plaque groups compared with noncarotid arterial atherosclerosis groups (0.32 +/- 0.18 vs 0.26 +/- 0.15; p = 0.015). There was a significant correlation between MHR and carotid artery intima-media thickness (r = 0.228; p = 0.001) in patients with SLE. CONCLUSION: Our study suggests that the values of MHR could be a marker to assess carotid artery intima-media thickness in patients with SLE.

[12] *Melo AC, Cattani-Cavalieri I, Barroso MV et al.* **Atorvastatin dose-dependently promotes mouse lung repair after emphysema induced by elastase**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 102:160-168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29554594

ABSTRACT
Emphysema results in a proteinase - antiproteinase imbalance, inflammation and oxidative stress. Our objective was to investigate whether atorvastatin could repair mouse lungs after

elastase-induced emphysema. Vehicle (50muL) or porcine pancreatic elastase (PPE) was administered on day 1, 3, 5 and 7 at 0.6U intranasally. Male mice were divided into a control group (sham), PPE 32d (sacrificed 24h after 32 days), PPE 64d (sacrificed 24h after 64 days), and atorvastatin 1, 5 and 20mg treated from day 33 until day 64 and sacrificed 24h later (A1mg, A5mg and A20mg, respectively). Treatment with atorvastatin was performed via inhalation for 10min once a day. We observed that emphysema at day 32 was similar to emphysema at day 64. The mean airspace chord length (Lm) indicated a recovery of pulmonary morphology in groups A5mg and A20mg, as well as recovery of collagen and elastic fibers in comparison to the PPE group. Bronchoalveolar lavage fluid (BALF) leukocytes were reduced in all atorvastatin-treated groups. However, tissue macrophages were reduced only in the A20mg group compared with the PPE group, while tissue neutrophils were reduced in the A5mg and A20mg groups. The redox balance was restored mainly in the A20mg group compared with the PPE group. Finally, atorvastatin at doses of 5 and 20mg reduced nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and matrix metalloproteinase-12 (MMP-12) compared with the PPE group. In conclusion, atorvastatin was able to induce lung tissue repair in emphysematous mice.

[13] *Liu B, Chen Z, Dong X, Qin G*. **Association of prehypertension and hyperhomocysteinemia with subclinical atherosclerosis in asymptomatic Chinese: a cross-sectional study**. BMJ open 2018; 8:e019829.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29555791
ABSTRACT
OBJECTIVES: Comorbid hypertension and hyperhomocysteinemia is an important risk factor for carotid atherosclerotic plaque formation. We put forward the hypothesis that the subjects with comorbid prehypertension and hyperhomocysteinemia also had an increased risk of subclinical atherosclerosis, using carotid intima-media thickness (CIMT) as the marker of the atherosclerotic process. METHODS: A total of 4102 asymptomatic Chinese subjects aged 18-60 years were divided into four groups according to blood pressure (BP) and homocysteine (HCY) level: the control group without prehypertension or hyperhomocysteinemia, isolated prehypertension group, simple hyperhomocysteinemia group and prehypertension with hyperhomocysteinemia group. Serum lipids, fasting blood glucose (FBG), HCY and CIMT were measured. RESULTS: There was significant difference in the positive rates of increased CIMT among four groups. Compared with the controls, the subjects in the other three groups had a higher risk of increased CIMT (isolated prehypertension group, OR 2.049, 95% CI 1.525 to 2.754; simple hyperhomocysteinemia group, OR 2.145, 95% CI 1.472 to 3.125; prehypertension and hyperhomocysteinemia group, OR 3.199, 95% CI 2.362 to 4.332). However, by multiple logistic regression analysis, only comorbid prehypertension and hyperhomocysteinemia was independently associated with increased CIMT (OR 1.485, 95% CI 1.047 to 2.108, P<0.05). CONCLUSIONS: Comorbid prehypertension and hyperhomocysteinemia was an independent risk factor of subclinical atherosclerosis in asymptomatic Chinese, but isolated prehypertension or hyperhomocysteinemia was not. Therefore, combined intervention for prehypertension and hyperhomocysteinemia may contribute to decrease the incident of cardiovascular disease.

[14] *Safai N, Carstensen B, Vestergaard H, Ridderstrale M*. **Impact of a multifactorial treatment programme on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialised diabetes centre in Denmark**. BMJ open 2018; 8:e019214.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29550776

ABSTRACT

OBJECTIVES: To investigate the impact of a multifactorial treatment programme in a real-life setting on clinical outcomes and estimated cardiovascular disease (CVD) risk. DESIGN: A retrospective observational cohort study, using data from the electronic medical records and national registers. SETTING: Tertiary diabetes centre in Denmark. PARTICIPANTS: Patients with type 2 diabetes (n=4299) referred to a programme with focus on treatment of hyperglycaemia, hypertension and dyslipidaemia between 1 January 2001 and 1 April 2016. OUTCOMES: Primary outcomes were changes in haemoglobin A1c (HbA1c), blood pressure (BP) and low-density lipoprotein (LDL) cholesterol as well as proportion reaching treatment targets. Our secondary outcome was to investigate changes in antidiabetic, antihypertensive and lipid-lowering treatment, together with the impact on estimated CVD risk. Linear mixed model for repeated measurements were used for continuous variables and logistic regression for dichotomous variables. RESULTS: The patients achieved a mean+/-SD decrease in HbA1c, systolic and diastolic BP and LDL cholesterol of 1.0%+/-0.04% (10.6+/-0.4 mmol/mol), 6.3+/-0.4 mm Hg, 2.7+/-0.2 mm Hg and 0.32+/-0.02 mmol/L, respectively (p<0.0001). The proportion of patients who met the treatment goal for HbA1c (<7% (<53 mmol/mol)) increased from 31% to 58% (p<0.0001); for BP (<130/80 mm Hg) from 24% to 34% (p<0.0001), and for LDL cholesterol (<2.5 mmol/L (patients without previous CVD) or <1.8 mmol/L (patients with previous CVD)) from 52% to 65%. Those reaching all three guideline treatment targets increased from 4% to 15% (p<0.0001), and when relaxing the BP target to <140/85 from 8% to 24%. The estimated CVD risk was relatively reduced by 15.2% using the Swedish National Diabetes Register risk engine and 30.9% using the UK Prospective Diabetes Study risk engine. CONCLUSIONS: Our data support that short-term multifactorial treatment of patients with glycaemic dysregulation in a specialist outpatient setting is both achievable and effective, and associated with a clinically meaningful improvement in CVD risk.

[15] *Wang J, Tan M, Ge J et al.* **Lysosomal acid lipase promotes cholesterol ester metabolism and drives clear cell renal cell carcinoma progression**. Cell proliferation 2018:e12452.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569766

ABSTRACT

OBJECTIVES: Clear cell renal cell carcinoma (ccRCC) is characterized histologically by accumulation of cholesterol esters, cholesterol and other neutral lipids. Lysosomal acid lipase (LAL) is a critical enzyme involved in the cholesterol ester metabolism. Here, we sought to determine whether LAL could orchestrate metabolism of cholesterol esters in order to promote ccRCC progression. MATERIALS AND METHODS: Quantitative reverse-transcription PCR and western blots were conducted to assess the expression of LAL in human ccRCC tissues. We analysed the relationship between LAL levels and patient survival using tissue microarrays. We used cell proliferation assays, colony formation assays, cell death assays, metabolic assays and xenograft tumour models to evaluate the biological function and underlying mechanisms. RESULTS: LAL was up-regulated in ccRCC tissue. Tissue microarray analysis revealed higher

levels of LAL in advanced grades of ccRCC, and high LAL expression indicated lower patient survival. Suppressing LAL expression not only blocked the utilization of cholesterol esters but also impaired proliferation and cellular survival. Furthermore, immunohistochemistry staining showed that LAL expression was correlated with Akt phosphorylation. Suppressing LAL expression decreased the phosphorylation level of Akt and Src and reduced the level of 14,15-epoxyeicosatrienoic acids in ccRCC cells. Supplement of 14,15-epoxyeicosatrienoic acids rescued proliferation in vitro and in vivo. CONCLUSIONS: LAL promoted cell proliferation and survival via metabolism of epoxyeicosatrienoic acids and activation of the Src/Akt pathway.

[16] *Marmontel O, Charriere S, Simonet T et al.* **Single, short in-del, and copy number variations detection in monogenic dyslipidemia using an NGS strategy**. Clinical genetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29572815
ABSTRACT
Optimal molecular diagnosis of primary dyslipidemia is challenging to confirm the diagnosis, test and identify at risk relatives. The aim of this study was to test the application of a single targeted next-generation sequencing (NGS) panel for hypercholesterolemia, hypocholesterolemia, and hypertriglyceridemia molecular diagnosis. NGS workflow based on a custom AmpliSeq panel was designed for sequencing the most prevalent dyslipidemia causing genes (ANGPTL3, APOA5, APOC2, APOB, GPIHBP1, LDLR, LMF1, LPL, PCSK9) on the Ion PGM Sequencer. One hundred and forty patients without molecular diagnosis were studied. In silico analyses were performed using the NextGENe(R) software and homemade tools for detection of copy number variations (CNV). All mutations were confirmed using appropriate tools. Eighty seven variations and 4 CNV were identified, allowing a molecular diagnosis for 40/116 hypercholesterolemic patients, 5/13 hypocholesterolemic patients, and 2/11, hypertriglyceridemic patients respectively. This workflow allowed the detection of CNV contrary to our previous strategy. Some variations were found in previously unexplored regions providing an added value for genotype-phenotype correlation and familial screening. In conclusion, this new NGS process is an effective mutation detection method and allows better understanding of phenotype. Consequently this assay meets the medical need for individualized diagnosis of dyslipidemia.

[17] *Maki KC, Dicklin MR*. **Assessing Cardiovascular Disease Risk and Responses to Preventive Therapies in Clinical Practice**. Current atherosclerosis reports 2018; 20:23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29556802
ABSTRACT
PURPOSE OF REVIEW: The aims of this review are to provide perspective on evaluation of relative and absolute cardiovascular disease (CVD) risk reductions for assessing the efficacy of preventive therapies and to summarize methods for evaluation of CVD risk in clinical practice. RECENT FINDINGS: Major CVD risk factors can be used to stratify patients into risk categories. Results from recent trials reinforce the view that benefits of preventive therapies will be greatest in those with the highest absolute risk and in those with the most severe disturbance in the risk factor targeted. In evaluating clinical utility, it is necessary to assess the impact of an intervention on both relative and absolute risk. Quantitative risk scoring using major CVD risk factors is effective for identifying those at low, moderate, and high CVD risk. When there is

uncertainty about the appropriate treatment strategy, additional testing may be used to refine risk assessment. This may include measurement of inflammatory markers, subclinical indicators of atherosclerosis (e.g., coronary artery calcium and ankle brachial index), urinary albumin/creatinine ratio, and the level of lipoprotein (a). The benefit of a preventive therapy will generally be the greatest in those with the highest absolute risk and in those with the most severe disturbance in the risk factor targeted. Quantitative risk scoring with major CVD risk factors can be supplemented with additional testing for refinement of risk assessment in patients for whom decisions about pharmacotherapy, or the intensity of therapy, for risk factor modification are uncertain.

[18] *Stoekenbroek RM, Kastelein JJP*. **Proprotein convertase subtilisin/kexin type 9: from genetics to clinical trials**. Current opinion in cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29561319
ABSTRACT
PURPOSE OF REVIEW: This review describes the pivotal role of genetic insights and technologies in the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the rapid development of PCSK9 inhibitors - a revolutionary new class of lipid-lowering agents. RECENT FINDINGS: PCSK9 was discovered as a the third gene implicated in familial hypercholesterolemia. Population genetics studies, enabled by technological advances, were instrumental in validating PCSK9 as a therapeutic target. Monoclonal antibodies against PCSK9 were introduced in the clinic after an unprecedently rapid development path, in which clinical trial results confirmed that these drugs robustly lower cholesterol and improve clinical outcomes regardless of disease indication or background therapy. New strategies to PCSK9 inhibition are underway and have delivered promising preliminary results, including inhibition of PCSK9 synthesis by targeting the cellular gene expression machinery and vaccination. The future will tell whether directly targeting the genome through editing techniques will ultimately enable us to virtually eliminate many of the traditional CVD risk factors. SUMMARY: The extraordinary PCSK9 narrative highlights the opportunities offered by genetics-driven drug development and holds valuable lessons for future development programs.

[19] *Wierzbicki AS, Reynolds TM, Viljoen A*. **An update on trials of novel lipid-lowering drugs**. Current opinion in cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29561321
ABSTRACT
PURPOSE OF REVIEW: A number of novel trials have assessed the efficacy of new lipid-lowering therapies in cardiovascular disease (CVD). RECENT FINDINGS: Proprotein convertase subtilisin kexin-9 inhibitors reduce low-density lipoprotein cholesterol (LDL-C) by 50-55%. A CVD outcome trial in patients with acute coronary syndromes with evolocumab achieved a LDL-C of 0.8 mmol/l (31 mg/dl) and a 20% relative risk reduction in CVD events in 2.2 years. Cholesterol ester transfer protein inhibitors raise high-density lipoprotein cholesterol and can lower LDL-C. Anacetrapib reduced coronary artery disease events by 7%, but not wider composite CVD outcomes, in a population with chronic CVD with pretreatment LDL-C of 1.6 mmol/l (62 mg/dl). The conflicting outcomes of cholesterol ester transfer protein inhibitor trials means these compounds are not being developed further. Trials using lipid drugs targeting inflammation

have previously been generally unsuccessful, but recent data on the interleukin-1B receptor antagonist canakinumab has proven the concept of intervention on inflammation in atherosclerosis by showing a reduction in acute coronary interventions, but at the predictable cost of increased infections. SUMMARY: Despite the success of proprotein convertase subtilisin kexin-9 inhibition, the ability to achieve low LDL-C with off-patent medications and the costs of novel therapies will limit their use even in high-risk patients and confine them to the highest-risk sub-groups of patients.

[20] *Yvan-Charvet L, Cariou B*. **Poststatin era in atherosclerosis management: lessons from epidemiologic and genetic studies**. Current opinion in lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29553996
ABSTRACT
PURPOSE OF REVIEW: Cardiovascular diseases (CVD) are the leading cause of death worldwide with over 17 million deaths every year and represent a major public health challenge. The last decade has seen the emergence of novel antiatherogenic therapies. RECENT FINDINGS: Despite intensive lipid and blood pressure interventions, the burden of CVD is expected to markedly progress because of the global aging of the population and increasing exposure to detrimental lifestyle-related risk. Epidemiologic and genetic studies helped to better apprehend the biology of atherosclerosis and allowed pharmaceutical innovation and recent translational successes. This includes the development of novel lipid and glucose-lowering therapies and the leverage of anti-inflammatory therapies. SUMMARY: Here, we discuss promises and expectations of emerging scientific and pharmaceutical innovations and translational successes to meet the global therapeutic demand.

[21] *Cao YX, Li JJ*. **Comment on de Carvalho et al. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors and Incident Type 2 Diabetes: A Systematic Review and Meta-analysis With Over 96,000 Patient-Years. Diabetes Care 2018;41:364-367**. Diabetes Care 2018; 41:e69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29559466
ABSTRACT

[22] *de Carvalho LSF, Campos AM, Sposito AC*. **Response to Comment on de Carvalho et al. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors and Incident Type 2 Diabetes: A Systematic Review and Meta-analysis With Over 96,000 Patient-Years. Diabetes Care 2018;41:364-367**. Diabetes Care 2018; 41:e70-e71.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29559467
ABSTRACT

[23] *Ciccarelli G, D'Elia S, De Paulis M et al.* **Lipid Target in Very High-Risk Cardiovascular Patients: Lesson from PCSK9 Monoclonal Antibodies**. Diseases (Basel, Switzerland) 2018; 6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29562587
ABSTRACT
The role of low-density lipoproteins (LDLs) as a major risk factor for cardiovascular disease has been demonstrated by several epidemiological studies. The molecular basis for LDLs in atherosclerotic plaque formation and progression is not completely unraveled yet.

Pharmacological modulation of plasma LDL-C concentrations and randomized clinical trials addressing the impact of lipid-lowering interventions on cardiovascular outcome have clearly shown that reducing plasma LDL-C concentrations results in a significant decrease in major cardiovascular events. For many years, statins have represented the most powerful pharmacological agents available to lower plasma LDL-C concentrations. In clinical trials, it has been shown that the greater the reduction in plasma LDL-C concentrations, the lower the rate of major cardiovascular events, especially in high-risk patients, because of multiple risk factors and recurrent events. However, in a substantial number of patients, the recommended LDL target is difficult to achieve because of different factors: genetic background (familial hypercholesterolemia), side effects (statin intolerance), or high baseline plasma LDL-C concentrations. In the last decade, our understanding of the molecular mechanisms involved in LDL metabolism has progressed significantly and the key role of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged. This protein is an enzyme able to bind the LDL receptors (LDL-R) on hepatocytes, favoring their degradation. Blocking PCSK9 represents an intriguing new therapeutic approach to decrease plasma LDL-C concentrations, which in recent studies has been demonstrated to also result in a significant reduction in major cardiovascular events.

[24] *Elkind-Hirsch KE, Paterson MS, Shaler D, Gutowski HC*. **SHORT-TERM SITAGLIPTIN-METFORMIN THERAPY IS MORE EFFECTIVE THAN METFORMIN OR PLACEBO IN PRIOR GESTATIONAL DIABETIC WOMEN WITH IMPAIRED GLUCOSE REGULATION**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29561188

ABSTRACT

OBJECTIVE: Our pilot study examined the effectiveness of sitagliptin-metformin (SITA-MET), metformin (MET), and placebo (P) therapy on fasting and post-glucose challenge glucose levels in postpartum women with prior gestational diabetes mellitus (GDM) and impaired glucose regulation. METHODS: Prediabetic women (N = 36, age 18 to 42 years) with recent GDM were randomized to P (one pill twice a day), MET (1,000 mg twice a day), or SITA-MET (50 mg SITA, 1,000 mg MET twice a day) for 16 weeks in a single-blind fashion. An individualized diet and exercise plan were provided to all participants. At baseline and 16 weeks, oral glucose tolerance tests were performed to assess glycemia, mean blood glucose (MBG), and calculate insulin sensitivity (IS) and secretion (SI) indexes. Lipid profile, thyroid-stimulating hormone level, and pregnancy test were performed in the baseline sample. RESULTS: Thirty-three (92%) participants completed the study. At study end, 15 participants had normal glycemia (SITA-MET vs. MET, P; P = .035). MBG, IS, IS-SI index, and waist to height ratio were significantly improved with SITA-MET compared with MET and P treatment. SITA-MET therapy was more effective in lowering body mass index and waist circumference compared to P treatment. CONCLUSION: Our pilot study is the first to evaluate the use of a dipeptidyl peptidase 4 inhibitor combined with MET in glucose-impaired women with a history of GDM. In this investigation, combination SITA-MET was found to be superior to MET and P in improving glycemia and metabolic measures in this prediabetic population. ABBREVIATIONS: BID = twice a day; BMI = body mass index; BP = blood pressure; BW = body weight; CHOL = cholesterol; DI = disposition index; DM =

diabetes mellitus; DPP-4i = dipeptidyl peptidase 4 inhibitor; FBG = fasting blood glucose; GDM = gestational diabetes mellitus; GLP-1 = glucagon-like peptide 1; HDL-C = high-density-lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; IGI = insulinogenic index; IGR = impaired glucose regulation; IGT = impaired glucose tolerance; IR = insulin resistance; IS = insulin sensitivity; LDL-C = low-density-lipoprotein cholesterol; MBG = mean blood glucose; MET = metformin; OGTT = oral glucose tolerance test; P = placebo; SI = insulin secretion; SIogtt = Matsuda's insulin sensitivity index; TRG = triglycerides; WC = waist circumference; WHR = waist to hip ratio; WHtR = waist to height ratio.

[25] *Tomas L, Edsfeldt A, Mollet IG et al.* **Altered metabolism distinguishes high-risk from stable carotid atherosclerotic plaques**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29562241
ABSTRACT
Aims: Identification and treatment of the rupture prone atherosclerotic plaque remains a challenge for reducing the burden of cardiovascular disease. The interconnection of metabolic and inflammatory processes in rupture prone plaques is poorly understood. Herein, we investigate associations between metabolite profiles, inflammatory mediators and vulnerability in carotid atherosclerotic plaques. Methods and results: We collected 159 carotid plaques from patients undergoing endarterectomy and measured 165 different metabolites in a targeted metabolomics approach. We identified a metabolite profile in carotid plaques that associated with histologically evaluated vulnerability and inflammatory mediators, as well as presence of symptoms in patients. The distinct metabolite profiles identified in high-risk and stable plaques were in line with different transcription levels of metabolic enzymes in the two groups, suggesting an altered metabolism in high-risk plaques. The altered metabolic signature in high-risk plaques was consistent with a change to increased glycolysis, elevated amino acid utilization and decreased fatty acid oxidation, similar to what is found in activated leucocytes and cancer cells. Conclusion: These results highlight a possible key role of cellular metabolism to support inflammation and a high-risk phenotype of atherosclerotic plaques. Targeting the metabolism of atherosclerotic plaques with novel metabolic radiotracers or inhibitors might therefore be valid future approaches to identify and treat the high-risk atherosclerotic plaque.

[26] *Watts GF, Chan DC, Somaratne R et al.* **Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29566128
ABSTRACT
Aims: Lipoprotein(a) [Lp(a)], a low-density lipoprotein (LDL) particle covalently bound to apolipoprotein(a) [apo(a)], is a potentially potent heritable risk factor for cardiovascular disease. We investigated the mechanism whereby evolocumab, a monoclonal antibody against proprotein convertase subtilisin-kexin type 9 (PCSK9), lowers Lp(a). Methods and results: We studied the kinetics of Lp(a) particles in 63 healthy men, with plasma apo(a) concentration >5 nmol/L, participating in an 8-week factorial trial of the effects of evolocumab (420 mg every 2 weeks) and atorvastatin (80 mg daily) on lipoprotein metabolism. Lipoprotein(a)-apo(a) kinetics were studied using intravenous D3-leucine administration, mass spectrometry, and

compartmental modelling; Lp(a)-apoB kinetics were also determined in 16 subjects randomly selected from the treatment groups. Evolocumab, but not atorvastatin, significantly decreased the plasma pool size of Lp(a)-apo(a) (-36%, P < 0.001 for main effect). As monotherapy, evolocumab significantly decreased the production of Lp(a)-apo(a) (-36%, P < 0.001). In contrast, in combination with atorvastatin, evolocumab significantly increased the fractional catabolism of Lp(a)-apo(a) (+59%, P < 0.001), but had no effect on the production of Lp(a)-apo(a). There was a highly significant association between the changes in the fractional catabolism of Lp(a)-apo(a) and Lp(a)-apoB in the substudy of 16 subjects (r = 0.966, P < 0.001). Conclusions: Evolocumab monotherapy lowered the plasma Lp(a) pool size by decreasing the production of Lp(a) particles. In combination with atorvastatin, evolocumab lowered the plasma Lp(a) pool size by accelerating the catabolism of Lp(a) particles. This dual mechanism may relate to an effect of PCSK9 inhibition on Lp(a)-apo(a) production and to marked up-regulation of LDL receptor activity on Lp(a) holoparticle clearance. Clinical Trial Registration Information: NCT02189837.

[27] *Ko HHT, Lareu RR, Dix BR, Hughes JD*. **In vitro antibacterial effects of statins against bacterial pathogens causing skin infections**. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569046

ABSTRACT

With financial considerations impeding research and development of new antibiotics, drug repurposing (finding new indications for old drugs) emerges as a feasible alternative. Statins are extensively prescribed around the world to lower cholesterol, but they also possess inherent antimicrobial properties. This study identifies statins with the greatest potential to be repurposed as topical antibiotics and postulates a mechanism of action for statins' antibacterial activity. Using broth microdilution, the direct antibacterial effects of all seven parent statins currently registered for human use and three selected statin metabolites were tested against bacterial skin pathogens Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Serratia marcescens. Simvastatin and pitavastatin lactone exerted the greatest antibacterial effects (minimum inhibitory concentrations of 64 and 128 mug/mL, respectively) against S. aureus. None of the statins tested were effective against E. coli, P. aeruginosa, or S. marcescens, but simvastatin hydroxy acid acid might be active against S. aureus, E. coli, and S. marcescens at drug concentrations > 256 mug/mL. It was found that S. aureus may exhibit a paradoxical growth effect when exposed to simvastatin; thus, treatment failure at high drug concentrations is theoretically probable. Through structure-activity relationship analysis, we postulate that statins' antibacterial action may involve disrupting the teichoic acid structures or decreasing the number of alanine residues present on Gram-positive bacterial cell surfaces, which could reduce biofilm formation, diminish bacterial adhesion to environmental surfaces, or impede S. aureus cell division.

[28] *Khan SU, Talluri S, Riaz H et al.* **A Bayesian network meta-analysis of PCSK9 inhibitors, statins and ezetimibe with or without statins for cardiovascular outcomes**. European journal of preventive cardiology 2018:2047487318766612.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569492

ABSTRACT
Background The comparative effects of statins, ezetimibe with or without statins and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors remain unassessed. Design Bayesian network meta-analysis was conducted to compare treatment groups. Methods Thirty-nine randomized controlled trials were selected using MEDLINE, EMBASE, and CENTRAL (inception - September 2017). Results In network meta-analysis of 189,116 patients, PCSK9 inhibitors were ranked as the best treatment for prevention of major adverse cardiovascular events (Surface Under Cumulative Ranking Curve (SUCRA), 85%), myocardial infarction (SUCRA, 84%) and stroke (SUCRA, 80%). PCSK9 inhibitors reduced the risk of major adverse cardiovascular events compared with ezetimibe + statin (odds ratio (OR): 0.72; 95% credible interval (CrI), 0.55-0.95; Grading of Recommendation Assessment, Development and Evaluation (GRADE) criteria: moderate), statin (OR: 0.78; 95% CrI: 0.62-0.97; GRADE: moderate) and placebo (OR: 0.63; 95% CrI: 0.49-0.79; GRADE: high). The PCSK9 inhibitors were consistently superior to groups for major adverse cardiovascular event reduction in secondary prevention trials (SUCRA, 95%). Statins had the highest probability of having lowest rates of all-cause mortality (SUCRA, 82%) and cardiovascular mortality (SUCRA, 84%). Compared with placebo, statins reduced the risk of all-cause mortality (OR: 0.88; 95% CrI: 0.83-0.94; GRADE: moderate) and cardiovascular mortality (OR: 0.84; 95% CrI: 0.77-0.90; GRADE: high). For cardiovascular mortality, PCSK9 inhibitors were ranked as the second best treatment (SUCRA, 78%) followed by ezetimibe + statin (SUCRA, 50%). Conclusion PCSK9 inhibitors were ranked as the most effective treatment for reducing major adverse cardiovascular events, myocardial infarction and stroke, without having major safety concerns. Statins were ranked as the most effective therapy for reducing mortality.

[29] *Katsuumi G, Shimizu I, Yoshida Y, Minamino T*. **Vascular Senescence in Cardiovascular and Metabolic Diseases**. Frontiers in cardiovascular medicine 2018; 5:18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29556500

ABSTRACT
In mammals, aging is associated with accumulation of senescent cells. Stresses such as telomere shortening and reactive oxygen species induce "cellular senescence", which is characterized by growth arrest and alteration of the gene expression profile. Chronological aging is associated with development of age-related diseases, including heart failure, diabetes, and atherosclerotic disease, and studies have shown that accumulation of senescent cells has a causative role in the pathology of these age-related disorders. Endothelial cell senescence has been reported to develop in heart failure and promotes pathologic changes in the failing heart. Senescent endothelial cells and vascular smooth muscle cells are found in atherosclerotic plaque, and studies indicate that these cells are involved in progression of plaque. Diabetes is also linked to accumulation of senescent vascular endothelial cells, while endothelial cell senescence per se induces systemic glucose intolerance by inhibiting skeletal muscle metabolism. A close connection between derangement of systemic metabolism and cellular senescence is also well recognized. Aging is a complex phenomenon, and there is no simple approach to understanding the whole process. However, there is accumulating evidence that cellular senescence has a central role in the development and progression of various undesirable aspects of aging. Suppression of cellular senescence or elimination of senescent

cells reverses phenotypic changes of aging in several models, and proof-of-concept has been established that inhibiting accumulation of senescent cells could become a next generation therapy for age-related disorders. It is clear that cellular senescence drives various pathological changes associated with aging. Accordingly, further investigation into the role of this biological process in age-related disorders and discovery of senolytic compounds are important fields for future exploration.

[30] *Badimon L, Pena E, Arderiu G et al.* **C-Reactive Protein in Atherothrombosis and Angiogenesis**. Frontiers in immunology 2018; 9:430.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29552019
ABSTRACT
C-reactive protein (CRP) is a short pentraxin mainly found as a pentamer in the circulation, or as non-soluble monomers CRP (mCRP) in tissues, exerting different functions. This review is focused on discussing the role of CRP in cardiovascular disease, including recent advances on the implication of CRP and its forms specifically on the pathogenesis of atherothrombosis and angiogenesis. Besides its role in the humoral innate immune response, CRP contributes to cardiovascular disease progression by recognizing and binding multiple intrinsic ligands. mCRP is not present in the healthy vessel wall but it becomes detectable in the early stages of atherogenesis and accumulates during the progression of atherosclerosis. CRP inhibits endothelial nitric oxide production and contributes to plaque instability by increasing endothelial cell adhesion molecules expression, by promoting monocyte recruitment into the atheromatous plaque and by enzymatically binding to modified low-density lipoprotein. CRP also contributes to thrombosis, but depending on its form it elicits different actions. Pentameric CRP has no involvement in thrombogenesis, whereas mCRP induces platelet activation and thrombus growth. In addition, mCRP has apparently contradictory pro-angiogenic and anti-angiogenic effects determining tissue remodeling in the atherosclerotic plaque and in infarcted tissues. Overall, CRP contributes to cardiovascular disease by several mechanisms that deserve an in-depth analysis.

[31] *Das EK, Lai PY, Robinson AT et al.* **Regular Aerobic, Resistance, and Cross-Training Exercise Prevents Reduced Vascular Function Following a High Sugar or High Fat Mixed Meal in Young Healthy Adults**. Front Physiol 2018; 9:183.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29568273
ABSTRACT
The postprandial state can negatively influence flow mediated dilation (FMD), a predictor of atherosclerosis and cardiovascular disease. This investigation was designed to determine the effect of regular aerobic and/or resistance exercise on postprandial FMD after a high sugar or high fat mixed meal. Forty-five healthy participants were recruited from one of four groups: lean sedentary (SED), runners, weight lifters, and cross-trainers. Participants were randomly crossed over to a high sugar meal (HSM) and a high fat mixed meal (HFMM; both fat and carbohydrate). Pre-and postprandial endothelial function was assessed for both meals using brachial artery FMD. Plasma lipids, insulin, glucose, hs-CRP, and SOD were also measured with both meals. Endothelium-independent dilation was determined via sublingual nitroglycerin. Brachial artery FMD was reduced in SED following the HSM (9.9 +/- 0.9% at baseline, peak

reduction at 60 min 6.5 +/- 1.0%) and the HFMM (9.4 +/- 0.9% at baseline, peak reduction at 120 min 5.9 +/- 1.2%; P < 0.05 for both, Mean +/- SEM). There was no change in FMD after either HSM or HFMM in runners, weight lifters, and cross-trainers. Post-prandial increases in blood glucose, insulin and triglycerides were less pronounced in the exercisers compared to SED. In addition, exercisers presented lower baseline plasma hs-CRP and higher SOD activity. Nitroglycerin responses were similar among groups. These results suggest that endothelial function is reduced in sedentary adults after a HSM or HFMM, but not in regular aerobic or resistance exercisers. This response may be due to favorable postprandial metabolic responses or lower postprandial levels of inflammation and oxidative stress. These findings may help to explain the cardioprotective effect of exercise.

[32] *Windler E, Beil FU, Klose G, Thiery J*. **[Lipid-lowering therapy in the elderly : Who profits from which target values?]**. Herz 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29569148
ABSTRACT
Lowering low-density lipoprotein (LDL) cholesterol levels has been proven to reduce the incidence of cardiovascular and cerebrovascular events and mortality. So far recommendations have not provided information as to a meaningful duration of cholesterol-lowering therapy and were largely guided by economic constraints and limited therapeutic options. In light of the decline in the price of statins, the essential therapeutic agent and the increased efficacy of therapeutic options, treatment can nowadays be geared to target values that can be expected to have an optimal effect even in old age. The most favorable level of LDL-cholesterol for primary prevention is around and below 100mg/dl, provided continuous adherence to these low levels from adolescence onwards. With later onset of cholesterol reduction the existence of initial atheromatous deposits must be expected. Therefore, with age and the manifestation of other risk factors the optimal treatment targets increasingly converge to those for which experience has been gained from secondary prevention. Both measurements of the effect of cholesterol lowering on the volume of atheromatous plaques and of the incidence of vascular events indicate a target for LDL-cholesterol well below 70mg/dl and in the range 50-60mg/dl. At the onset of cholesterol lowering in advanced age, a smaller effect has to be expected but due to the increasing incidence rate of vascular events a higher number of events may be avoided; thus, the efficiency does not necessarily decrease; however, long-term studies indicate that earlier cholesterol lowering provides an advantage for more than a decade, in terms of preventing vascular disease, which tends to increase. Therefore, optimal cardiovascular prevention involves moderate measures to maintain the LDL-cholesterol below 100mg/dl lifelong from childhood on.

[33] *Yin X, Xu R, Wang Y et al.* **Implication of coronary CT angiography combined with four-dimensional speckle tracking echocardiography for predicting major adverse cardiac events**. The international journal of cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29564584
ABSTRACT
Coronary computed tomography angiography (CCTA) can provide abundant information about the anatomy of the coronary artery. However, this modality is limited in evaluation of

myocardial function. Four-dimensional speckle tracking echocardiography (4DSTE) is a novel and sensitive technique for quantitative evaluation of myocardial deformation. We estimated the value of these imaging modalities to predict the risk of MACE in 209 patients with suspected coronary artery disease(CAD) after a median follow-up of 727 days. Three models were established: (1) CCTA alone, (2) CCTA combined with 4DSTE, and (3) CCTA combined with 4DSTE and clinical risk factors. Forty-six (22.0%) patients developed MACE. The hazard ratio (HR) of CCTA classification to predict the risk of MACE was greater (HR = 4.86) than for other parameters, including B-type natriuretic peptide (BNP) (HR = 2.44) and left ventricular ejection fraction (LVEF) (HR = 0.40). The area under the curve of models 2 and 3 to predict MACE was significantly greater than that of model 1 (0.92 and 0.93 vs. 0.84, respectively, $p < 0.001$). We conclude that there is direct relationship between CCTA classification and MACE risk. CCTA combined with 4DSTE can improve the ability of CCTA to predict the risk of MACE. This approach provides cardiologists a noninvasive, objective, and efficient method to predict MACE.

[34] *Yang C, Zhao D, Liu G et al.* **Atorvastatin Attenuates Metabolic Remodeling in Ischemic Myocardium through the Downregulation of UCP2 Expression**. International journal of medical sciences 2018; 15:517-527.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29559841
ABSTRACT
Uncoupling protein 2 (UCP2) is primarily expressed in the myocardium and is closely related to myocardial ischemia/reperfusion injury and myocardial metabolism. To explore the effects and the mechanisms of UCP2 on atorvastatin-mediated myocardium protection, the rat model of myocardial ischemia was established by ligation of the left anterior descending coronary arteries (LADs). The rats were divided into the sham operation (SO) group, myocardial infarction (MI) group and MI-atorvastatin group. The study that atorvastatin reduced myocardial remodeling and improved the disturbed myocardial energy metabolism after MI. Furthermore, the mechanisms of myocardial metabolic remodeling affected by atorvastatin were explored. The atorvastatin group showed a significantly decreased expression of UCP2 mRNA and protein. Furthermore, the primary rat cardiomyocytes were cultured and treated with angiotensin II (Ang II) to induce cardiomyocyte hypertrophy. The results showed that in the atorvastatin group, the surface area of the cardiomyocytes, the total protein content per unit of cells, and the expression of the UCP2 protein were significantly decreased. These data suggested that atorvastatin significantly attenuated the myocardial remodeling by downregulating the expression of UCP2 that was found to improve the myocardial energy metabolism, inhibit myocardial hypertrophy, and eventually reduce myocardial remodeling.

[35] *Yu Y, Jin L, Zhuang Y et al.* **Cardioprotective effect of rosuvastatin against isoproterenol-induced myocardial infarction injury in rats**. International journal of molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29568858
ABSTRACT
Rosuvastatin, a member of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, exerts various pharmacological activities. This study evaluated the cardioprotective effect of rosuvastatin on isoproterenol-induced myocardial infarction injury in rats. A rat model of

myocardial infarction injury was induced by isoproterenol (ISO) for 2 consecutive days, rosuvastatin was administered for 8 weeks. The levels of myocardial infarct size, aspartate transaminase (AST), alanine transaminase (ALT), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH) activities, as well as malondialdehyde (MDA) levels, superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT) activities and reduced glutathione (GSH) concentrations were determined. Hematoxylin and eosin staining was used to observe cardiac histological changes. Interleukin-1beta (IL-1beta) and IL-18 levels in heart tissues were detected with ELISA kits. The mRNA and protein levels of NOD-like receptor superfamily, pyrin domain containing 3 (NLRP3) inflammasome were measured by qRT-PCR and western blot analysis, respectively. Our results showed that treatment with rosuvastatin reduced myocardial infract area, ameliorated histopathological alterations in myocardium, and decreased activities of myocardial injury marker enzymes in ISO-induced rats. In addition, rosuvastatin remarkably restored ISO-induced elevation of lipid peroxidation and decrease of antioxidants, significantly reduced myocardial pro-inflammatory cytokines concentrations in this animal model. Furthermore, rosuvastatin significantly inhibited the activation of NLRP3 inflammasome in this animal model. This study demonstrates that rosuvastatin significantly alleviates ISO-induced myocardial infarction injury. The mechanism is associated with attenuation of oxidative stress and inflammation, via the inhibition of NLRP3 inflammasome.

[36] *Xu N, Chu J, Wang M et al.* **Large yellow tea attenuates macrophage-related chronic inflammation and metabolic syndrome in high-fat diet treated mice**. Journal of agricultural and food chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29553261
ABSTRACT
Large yellow tea is a traditional beverage in China with unique toasty flavor. Preliminary study using 3T3-L1 cells indicted that large yellow tea, possessed more potent lipid-lowering efficacy than green, black, dark and white teas. In the present study we further investigated its influence on metabolic syndrome in high-fat diet (HFD) mouse model with an emphasis on dose response. Thirty-two C57BL/6 male mice were randomly divided into 4 groups: low-fat diet (LFD), HFD, HFD+2.5% large yellow tea hot-water extract (YT, equivalent to 10 cups of tea daily for humans), HFD+0.5% YT. Our data indicated that YT treatment for 12 weeks significantly reduced body weight, liver weight, and adipose tissues weight of the mice; lowered serum insulin and leptin; raised serum adiponectin with dose effect. H&E staining showed that HFD group exhibited significant enlargement of adipose cell sizes and the corresponding decrease of adipose cell numbers, which were dose-dependently attenuated in both YT groups. IHC results revealed that YT decreased macrophage recruitment in the liver, epididymal adipose tissue and subcutaneous adipose tissue, and depressed serum inflammatory cytokines including TNF-alpha, MCP-1, IFN-gamma, IL-6 and IL-1beta, in a dose-dependent manner. In addition, YT decreased serum glucose, TC, TG, LDL-C and HDL-C; as well as ameliorated glucose intolerance and insulin resistance independent of dose. Overall, YT would be a unique tea with dose-independent anti-hyperglycemic and robust lipid-lowering efficacies.

Literature update week 12 (2018)

[37] *Courtemanche H, Bigot E, Pichelin M et al.* **PCSK9 Concentrations in Cerebrospinal Fluid Are Not Specifically Increased in Alzheimer's Disease**. Journal of Alzheimer's disease : JAD 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29562508
ABSTRACT
The role of PCSK9 in Alzheimer's disease (AD) is controversial. We compared cerebrospinal fluid (CSF) PCSK9 concentrations in 36 AD and 31 non-AD patients. CSF PCSK9 levels did not differ between AD and non-AD groups (2.80 versus 2.62 ng/mL). However, PCSK9 CSF levels were increased in AD and non-AD patients with other neurodegenerative process (non-AD ND, n = 20) compared to patients without neurodegenerative disorders (non-ND, n = 11): 2.80 versus 2.30 ($p < 0.005$) and 2.83 versus 2.30 ng/mL (p = NS), respectively. CSF PCSK9 were positively correlated with AD biomarkers (Abeta1-42, T-tau, and P-tau). PCSK9 concentrations in CSF are increased in neurodegenerative disorders rather than specifically in AD.

[38] *Yuan F, Guo L, Park KH et al.* **Ossabaw Pigs With a PCSK9 Gain-of-Function Mutation Develop Accelerated Coronary Atherosclerotic Lesions: A Novel Model for Preclinical Studies**. Journal of the American Heart Association 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29572319
ABSTRACT
BACKGROUND: Ossabaw pigs are unique miniature swine with genetic predisposition to develop metabolic syndrome and coronary atherosclerosis after extended periods receiving atherogenic diets. We have hypothesized that transgenic Ossabaw swine expressing chimp PCSK9 (proprotein convertase subtilisin-like/kexin type 9) containing the D374Y gain of function would develop familial hypercholesterolemia and coronary artery plaques more rapidly than Landrace swine with the same transgene. METHODS AND RESULTS: Ossabaw and Landrace PCSK9 gain-of-function founders were generated by Sleeping Beauty transposition and cloning. Histopathologic findings in the Ossabaw founder animal showed more advanced plaques and higher stenosis than in the Landrace founder, underscoring the Ossabaw genetic predisposition to atherosclerosis. We chose to further characterize the Ossabaw PCSK9 gain-of-function animals receiving standard or atherogenic diets in a 6-month longitudinal study using computed tomography, magnetic resonance (MR) imaging, intravascular ultrasound, and optical coherence tomography, followed by pathological analysis of atherosclerosis focused on the coronary arteries. The Ossabaw model was consistently hypercholesterolemic, with or without dietary challenge, and by 6 months had consistent and diffuse fibrofatty or fibroatheromatous plaques with necrosis, overlying fibrous caps, and calcification in up to 10% of coronary plaques. CONCLUSIONS: The Ossabaw PCSK9 gain-of-function model provides consistent and robust disease development in a time frame that is practical for use in preclinical therapeutic evaluation to drive innovation. Although no animal model perfectly mimics the human condition, this genetic large-animal model is a novel tool for testing therapeutic interventions in the context of developing and advanced coronary artery disease.

[39] *Anand TN, Joseph LM, Geetha AV et al.* **Task-sharing interventions for cardiovascular risk reduction and lipid outcomes in low- and middle-income countries: A systematic review and meta-analysis**. Journal of clinical lipidology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29559305

ABSTRACT

BACKGROUND: One of the potential strategies to improve health care delivery in understaffed low- and middle-income countries (LMICs) is task sharing, where specific tasks are transferred from more qualified health care cadre to a lesser trained cadre. Dyslipidemia is a major risk factor for cardiovascular disease but often it is not managed appropriately. OBJECTIVE: We conducted a systematic review with the objective to identify and evaluate the effect of task sharing interventions on dyslipidemia in LMICs. METHODS: Published studies (randomized controlled trials and observational studies) were identified via electronic databases such as PubMed, Embase, Cochrane Library, PsycINFO, and CINAHL. We searched the databases from inception to September 2016 and updated till 30 June 2017, using search terms related to task shifting, and cardiovascular disease prevention in LMICs. All eligible studies were summarized narratively, and potential studies were grouped for meta-analysis. RESULTS: Although our search yielded 2938 records initially and another 1628 in the updated search, only 15 studies met the eligibility criteria. Most of the studies targeted lifestyle modification and care coordination by involving nurses or allied health workers. Eight randomized controlled trials were included in the meta-analysis. Task sharing intervention were effective in lowering low-density lipoprotein cholesterol (-6.90 mg/dL; 95% CI -11.81 to -1.99) and total cholesterol (-9.44 mg/dL; 95% CI -17.94 to -0.93) levels with modest effect size. However, there were no major differences in high-density lipoprotein cholesterol (-0.29 mg/dL; 95% CI -0.88 to 1.47) and triglycerides (-14.31 mg/dL; 95% CI -33.32 to 4.69). The overall quality of evidence based on Grading of Recommendations Assessment, Development and Evaluation was either "low" or "very low". CONCLUSION: Available data are not adequate to make recommendations on the role of task sharing strategies for the management of dyslipidemia in LMICs. However, the studies conducted in LMICs demonstrate the potential use of this strategy especially in terms of reduction in low-density lipoprotein cholesterol and total cholesterol levels. Our review calls for the need of well-designed and large-scale studies to demonstrate the effect of task-sharing strategy on lipid management in LMICs.

[40] *Paquette M, Saavedra YGL, Poirier J et al.* **Loss-of-Function PCSK9 Mutations Are Not Associated With Alzheimer Disease**. Journal of geriatric psychiatry and neurology 2018:891988718764330.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29562810

ABSTRACT

BACKGROUND: Hypercholesterolemia is a major risk factor for the late-onset form of Alzheimer disease (AD). Loss-of-function (LOF) mutations of PCSK9 and PCSK9 inhibitors lower low-density lipoprotein cholesterol (LDL-C) and have been associated with a reduced risk of cardiovascular disease. The aim of this study was to examine the effect of PCSK9 LOF variants on risk and age of onset of AD. METHODS: A total of 878 participants (410 controls and 468 AD cases) from the Quebec Founder Population were included in the study. RESULTS: Fifty-four (6.2%) participants carried the R46L mutation, whereas 226 (26.2%) participants carried the InsLEU mutation. There was no protective or no deleterious effect of carrying PCSK9 LOF mutations on AD prevalence nor on age of onset, even when stratified by apolipoprotein E epsilon 4 genotype or

by gender. CONCLUSION: Our data indicate that carrying PCSK9 LOF mutations has a neutral effect on neurocognitive health and the prevalence of AD.

[41] *Dezsi CA*. **Treatment with triple combination of atorvastatin, perindopril, and amlodipine in patients with stable coronary artery disease: A subgroup analysis from the PAPA-CAD study**. J Int Med Res 2018:300060518760158.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29557300
ABSTRACT
Background In patients with stable coronary artery disease, aspirin, a statin, and an angiotensin-converting enzyme inhibitor are recommended as first-line agents for secondary prevention. Subgroup analyses of the previously published Hungarian Perindopril plus Amlodipine in PAtients with Coronary Artery Disease (PAPA-CAD) non-interventional trial demonstrated that the addition of the metabolically beneficial, fixed combination of perindopril + amlodipine to atorvastatin further improves the patient's lipid profile. Methods The PAPA-CAD study, a 6-month open-label, prospective, multicenter, observational/non-interventional survey evaluated data accumulated from patients with hypertensive patients with stable coronary artery disease. The herein-reported subgroup analysis was conducted using the findings from those 1130 patients, who were taking atorvastatin in addition to the fixed combination of perindopril + amlodipine at the time of all four study visits (i.e., at baseline and 1, 3, and 6 months later). Results In the subgroup of patients taking atorvastatin as an add-on agent, 82.5% reached the target blood pressure of 140/90 mmHg compared with 78.8% of those not taking a statin. The addition of atorvastatin to the fixed combination of perindopril + amlodipine resulted in further significant improvements of key metabolic parameters. Conclusion This subgroup analysis confirmed that favorable synergism exists among perindopril, amlodipine, and atorvastatin.

[42] *Kotyla PJ*. **Short course of simvastatin has no effect on markers of endothelial activation in normolipidemic patients with systemic sclerosis**. J Int Med Res 2018:300060518762681.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29557229
ABSTRACT
Objective Statins, a class of 3-hydroxy-3 methyl-glutaryl-coenzyme A reductase inhibitors, are widely used for the treatment of atherosclerosis. Less is known about the role of statins in the treatment of vascular complication in systemic sclerosis (SSc). We therefore performed a short-term interventional study with simvastatin in patients with the diffuse variant of SSc and normal lipid profiles. Methods Twenty-five patients with diffuse SSc were enrolled and received simvastatin at a daily dose of 20 mg for 28 days. Soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble P-, E- and L-selectins were assessed by ELISA prior to treatment and at day 28. Results No statistically significant changes in the levels of adhesion molecules were observed: sICAM-1 1011 vs. 1032 ng/mL, sVCAM-1 1225 vs. 1570 ng/mL, sP-selectin 66.7 vs. 66.0 ng/mL, sE-selectin 276 vs. 253 ng/mL and sL-selectin 887 vs. 927 ng/mL prior to treatment and at day 28, respectively. Conclusions Markers characterizing vascular activation were not affected by short treatment with low-dose simvastatin in SSc patients, indicating that the endothelial-protective effect of statins may be related to treatment duration and dose.

[43] *Gajzlerska-Majewska W, Bomba-Opon DA, Wielgos M*. **Is pravastatin a milestone in the prevention and treatment of preeclampsia?** Journal of perinatal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29570452
ABSTRACT

[44] *Aryal B, Singh AK, Zhang X et al.* **Absence of ANGPTL4 in adipose tissue improves glucose tolerance and attenuates atherogenesis**. JCI insight 2018; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29563332
ABSTRACT
Alterations in ectopic lipid deposition and circulating lipids are major risk factors for developing cardiometabolic diseases. Angiopoietin-like protein 4 (ANGPTL4), a protein that inhibits lipoprotein lipase (LPL), controls fatty acid (FA) uptake in adipose and oxidative tissues and regulates circulating triacylglycerol-rich (TAG-rich) lipoproteins. Unfortunately, global depletion of ANGPTL4 results in severe metabolic abnormalities, inflammation, and fibrosis when mice are fed a high-fat diet (HFD), limiting our understanding of the contribution of ANGPTL4 in metabolic disorders. Here, we demonstrate that genetic ablation of ANGPTL4 in adipose tissue (AT) results in enhanced LPL activity, rapid clearance of circulating TAGs, increased AT lipolysis and FA oxidation, and decreased FA synthesis in AT. Most importantly, we found that absence of ANGPTL4 in AT prevents excessive ectopic lipid deposition in the liver and muscle, reducing novel PKC (nPKC) membrane translocation and enhancing insulin signaling. As a result, we observed a remarkable improvement in glucose tolerance in short-term HFD-fed AT-specific Angptl4-KO mice. Finally, lack of ANGPTL4 in AT enhances the clearance of proatherogenic lipoproteins, attenuates inflammation, and reduces atherosclerosis. Together, these findings uncovered an essential role of AT ANGPTL4 in regulating peripheral lipid deposition, influencing whole-body lipid and glucose metabolism and the progression of atherosclerosis.

[45] *Waters DD, Vogt L*. **Lipids, inflammation, and chronic kidney disease: a SHARP perspective**. Kidney international 2018; 93:784-786.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29571452
ABSTRACT
Accumulating evidence indicates that inflammation plays a role in the initiation and progression of chronic kidney disease. In the Study of Heart and Renal Protection (SHARP) trial, higher baseline C-reactive protein and higher baseline low-density lipoprotein cholesterol levels were both associated with a higher risk of cardiovascular events, but higher baseline C-reactive protein levels were also associated with a higher risk of nonvascular events. Simvastatin/ezetimibe reduced cardiovascular events independent of baseline C-reactive protein levels. However, this observation does not exclude inflammation as a causal factor for cardiovascular disease development in chronic kidney disease patients.

[46] *Lee HY, Jun DW, Kim HJ et al.* **Ezetimibe decreased nonalcoholic fatty liver disease activity score but not hepatic steatosis**. The Korean journal of internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29551054
ABSTRACT

Background/Aims: A number of clinical trials reported varying effects of cholesterol lowering agents in nonalcoholic fatty liver disease (NAFLD) patients. We, therefore, assessed the changes in hepatic steatosis and NAFLD activity score (NAS) after treatment with cholesterol lowering agents in NAFLD patients by metaanalysis. Methods: The Cochrane Library, the MEDLINE, and the Embase databases were searched until May 2015, without any language restrictions, for randomized controlled trials (RCTs) and nonrandomized studies (NRSs). Additional references were obtained from review of bibliography of relevant articles. The quality of evidence was assessed using the grading of recommendations assessment, development and evaluation guidelines. Results: Three RCTs (n = 98) and two NRSs (n = 101) met our study inclusion criteria (adult, NAFLD, liver biopsy). Liver biopsy was performed in all five studies, but only the three studies reported NAS. Ezetimibe significantly decreased NAS (standardized mean difference [SMD], -0.30; 95% confidence interval [CI], -0.57 to -0.03) but not hepatic steatosis in RCT (SMD, -0.1; 95% CI, -0.53 to 0.32), while the effect was significant for both NAS and intrahepatic content in NRSs (SMD, -3.0; 95% CI, -6.9 to 0.91). Conclusions: Ezetimibe decreased NAS without improving hepatic steatosis.

[47] *Liu X, Yang R, Dai B et al.* **Nicotinic acid and related compounds: A meta-analysis of their use for hyperphosphatemia in dialysis patients**. Medicine (Baltimore) 2018; 97:e0117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29561409

ABSTRACT

BACKGROUND: Studies indicate that nicotinic acid and related compounds may decrease phosphorus concentrations effectively by reducing the absorption in the gastrointestinal tract. However, the efficacy and safety of oral niacin treatments have only been investigated in a limited number of small-scale studies. METHODS: We performed this meta-analysis by pooling 12 qualified relevant preclinical and clinical trials to evaluate the association of nicotinic acid (and its related compounds) treatment and hyperphosphatemia among dialysis patients. Baseline and after treatment data were collected from the studies to evaluate drug efficacy, effect on lipid profile, and drug safety. To evaluate drug efficacy, subgroups were created based on different exposure time (i.e., 4 wks, 8 wks, 12 wks, and 24 wks) and each subgroup was compared against baseline data. In the assessment of lipid profile and drug safety, results of 8-week treatment were compared against baseline data. RESULTS: Our study showed that in the efficacy assessment of drug treatment, serum phosphorus concentration was only significantly reduced in the 4-week (SMD, 0.68; 95% CI, 0.40 to 0.97; P = .000; n = 8), and 8-week (SMD, 1.05; 95% CI, 0.68 to 1.42; P = .000; n = 10) treatment groups. The calcium x phosphorus product showed significantly reduced concentration in all the drug exposure time settings, and no rebound was detected (4-wk treatment: SMD, 0.61; 95% CI, 0.18 to 1.04; P = .005; n = 5; 8-wk treatment: SMD, 0.76; 95% CI, 0.32 to 1.18, P = .001; n = 8; and 12-wks treatment: SMD, 0.28, 95% CI, -0.06 to 0.61; P = .103; n = 3). Lipid profile monitoring showed that high-density lipoprotein (HDL) and triglycerides (TG) significantly changed after 8 weeks of treatment (HDL: SMD, -0.63; 95% CI, -1.03 to 0.24; P = .002; n = 5) and TG: SMD, 0.25; 95% CI, 0.02 to 0.49; P = .033; n = 5). Assessment of drug safety detected significant association for incidence of diarrhea (8% incidence rate; 95% CI, 4% to 12%; P = .001) and total adverse event (41% incidence rate, 95% CI: 12% to 69%, P = .001). CONCLUSION: Our study concludes that nicotinic acid and related compounds can significantly reduce serum phosphorus concentration with additive

antilipemic effects. We also recommend that the safety of this drug be further studied, as our results suggest significant incidence of adverse events.

[48] *Yamada K, Shiraishi H, Oki E et al.* **Open-label clinical trial of bezafibrate treatment in patients with fatty acid oxidation disorders in Japan**. Molecular genetics and metabolism reports 2018; 15:55-63.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29552494
ABSTRACT
Introduction: Fatty acid oxidation disorders (FAODs) are rare diseases caused by defects in mitochondrial fatty acid oxidation (FAO) enzymes. While the efficacy of bezafibrate, a peroxisome proliferator-activated receptor agonist, on the in vitro FAO capacity has been reported, the in vivo efficacy remains controversial. Therefore, we conducted a clinical trial of bezafibrate in Japanese patients with FAODs. Materials and methods: This trial was an open-label, non-randomized, and multicenter study of bezafibrate treatment in 6 patients with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and 2 patients with carnitine palmitoyltransferase-II (CPT-2) deficiency (median age, 8.2years; ranging from 5.8 to 26.4years). Bezafibrate was administered for 6months following a 6-month observation period. The primary endpoint was the frequency of myopathic attacks, and the secondary endpoints were serum acylcarnitines (ACs, C14:1 or C16+C18:1), creatine kinase (CK) levels, degree of muscle pain (VAS; visual analog scale) during myopathic attacks, and quality of life (QOL; evaluated using validated questionnaires). Results: The frequency of myopathic attacks after bezafibrate administration decreased in 3 patients, increased in 3, and did not change in 2. The CK, AC, and VAS values during attacks could be estimated in only three or four patients, but a half of the patients did not experience attacks before or after treatment. Changes in CK, AC, and VAS values varied across individuals. In contrast, three components of QOL, namely, physical functioning, role limitation due to physical problems (role physical), and social functioning, were significantly elevated. No adverse drug reactions were observed. Conclusion: In this study, the frequency of myopathic attacks and CK, AC, and VAS values during the attacks could not be evaluated due to several limitations, such as a small trial population. Our findings indicate that bezafibrate improves the QOL of patients with FAODs, but its efficacy must be examined in future investigations.

[49] *Roncero-Ramos I, Rangel-Zuniga OA, Lopez-Moreno J et al.* **Mediterranean Diet, Glucose Homeostasis and Inflammasome Genetic Variants: The CORDIOPREV Study**. Molecular nutrition & food research 2018:e1700960.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29573224
ABSTRACT
SCOPE: Insulin resistance (IR) and chronic low-grade inflammation are hallmarks of Type 2 Diabetes Mellitus (T2DM). The 'NOD-like receptor pyrin domain containing-3' (NLRP3) inflammasome component of innate immunity is a metabolic stress sensor modulated by dietary and genetics factors. The aim of this study was to evaluate the effects of the consumption of two diets for 3 years, Med and low-fat, on glucose homeostasis in the 1002 coronary heart disease patients of the CORDIOPREV study, according to a genetic variant of NLRP3 inflammasome. METHODS AND RESULTS: The study was conducted in the framework of

the CORDIOPREV study, a randomized dietary intervention with Mediterranean and low-fat diets. Single nucleotide polymorphisms (SNPs) located at inflammasome NLRP3 gene were genotyped by OpenArray platform. Non-diabetic CT+TT carriers of the rs4612666 SNP and AG+AA carriers of the rs10733113 SNP increased insulin sensitivity index (ISI) after three years of dietary intervention, whereas no effect was observed in diabetic patients. Further analysis by diet showed that the improvement of the ISI in non-diabetic rs10733113 AG+AA carriers was specific to the consumption of the Mediterranean diet. CONCLUSION: Our results show that the benefits associated with a Mediterranean diet regarding glucose homeostasis in non-T2DM patients depend on genetic variation in the inflammasome.

[50] *Li HH, Lin CL, Huang CN*. **Neuroprotective effects of statins against amyloid beta-induced neurotoxicity**. Neural regeneration research 2018; 13:198-206.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29557360
ABSTRACT
A growing body of evidence suggests that disruption of the homeostasis of lipid metabolism affects the pathogenesis of Alzheimer's disease (AD). In particular, dysregulation of cholesterol homeostasis in the brain has been reported to considerably increase the risk of developing AD. Thus, dysregulation of lipid homeostasis may increase the amyloid beta (Abeta) levels by affecting amyloid precursor protein (APP) cleavage, which is the most important risk factor involved in the pathogenesis of AD. Previous research demonstrated that Abeta can trigger neuronal insulin resistance, which plays an important role in response to Abeta-induced neurotoxicity in AD. Epidemiological studies also suggested that statin use is associated with a decreased incidence of AD. Therefore, statins are believed to be a good candidate for conferring neuroprotective effects against AD. Statins may play a beneficial role in reducing Abeta-induced neurotoxicity. Their effect involves a putative mechanism beyond its cholesterol-lowering effects in preventing Abeta-induced neurotoxicity. However, the underlying molecular mechanisms of the protective effect of statins have not been clearly determined in Abeta-induced neurotoxicity. Given that statins may provide benefits beyond the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, these drugs may also improve the brain. Thus, statins may have beneficial effects on impaired insulin signaling by activating AMP-activated protein kinase (AMPK) in neuronal cells. They play a potential therapeutic role in targeting Abeta-mediated neurotoxicity.

[51] *Lai SC, Phelps CA, Short AM et al.* **Thyroid transcription factor 1 enhances cellular statin sensitivity via perturbing cholesterol metabolism**. Oncogene 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29551766
ABSTRACT
We have discovered an unexpected connection between a critical lung development and cancer gene termed thyroid transcription factor 1 (TTF-1 also known as NKX2-1) and cholesterol metabolism. Our published work implicates that TTF-1 positively regulates miR-33a which is known to repress ATP-binding cassette transporter 1 (ABCA1) and thus its cholesterol efflux activity. We set out to demonstrate that a higher TTF-1 expression would presumably inhibit cholesterol efflux and consequently raise intracellular cholesterol level. Surprisingly, raising TTF-

1 expression actually lowers intracellular cholesterol level, which, we believe, is attributed to a direct transactivation of ABCA1 by TTF-1. Subsequently, we show that lung cancer cells primed with a TTF-1-driven decrease of cholesterol were more vulnerable to simvastatin, a frequently prescribed cholesterol biosynthesis inhibitor. In view of the fact that pathologists routinely interrogate human lung cancers for TTF-1 immunopositivity to guide diagnosis and the prevalent use of statins, TTF-1 should be further investigated as a putative biomarker of lung cancer vulnerability to statins.

[52] *Mark L, Nagy M, Dani G et al.* **[Lipid-lowering therapy of patients suffering from acute coronary syndrome in a Hungarian county hospital in 2015]**. Orvosi hetilap 2018; 159:478-484.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29552926
ABSTRACT
INTRODUCTION: The actual guidelines of cardiovascular prevention lay special emphasis on the lipid-lowering therapy of patients suffering from acute coronary syndrome (ACS). AIM: To evaluate the occurrence of high-intensity statin therapy, recommended by guidelines, at discharge in a Hungarian county hospital with hemodynamic laboratory in patients who underwent percutaneous intervention, furthermore the LDL-cholesterol (LDL-C) levels and goal attainment rate in the first year. METHOD: Retrospective data collection from the hospital database regarding the therapy at discharge and the lipid levels in the year following the intervention due to ACS in 2015. RESULTS: Due to ACS event, 454 patients had coronary intervention in 2015, at discharge more than 90% of them received high-intensity statin (more than 80% rosuvastatin, 40 mg) or corresponding combination therapy. In 154 cases we found half-year lipid results; the median of LDL-C was 1.9 mmol/L, the 1.8 mmol/L target value attainment rate was 48.7%. Results after one year were found in 292 cases (73% without the deceased and foreign patients); the LDL-C median proved to be 2.0 mmol/L, the target level attainment rate was 37.3%. There was no significant difference between the results of patients from the three different ACS forms and between those of men and women. CONCLUSIONS: The lipid lowering therapy of the revascularized patients who come back for medical visits is acceptable, but greater emphasis has to be laid on increasing the rate of controlled patients compared to the present two-thirds. Orv Hetil. 2018; 159(12): 478-484.

[53] *Bosworth HB, Ngouyombo B, Liska J et al.* **The importance of cholesterol medication adherence: the need for behavioral change intervention programs**. Patient preference and adherence 2018; 12:341-348.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29563777
ABSTRACT
Lipid-lowering medications have been shown to be efficacious, but adherence is suboptimal. This is a narrative, perspective review of recently published literature in the field of medication adherence research for lipid-lowering medications. We provide an overview of the impact of suboptimal adherence and use a World Health Organization framework (patient, condition, therapy, socioeconomic, and health system-related systems) to discuss factors that influence hyperlipidemia treatment adherence. Further, the review involves an evaluation of intervention strategies to increase hyperlipidemia treatment adherence with a special focus on mHealth interventions, patient reminders on packaging labels, nurse- and pharmacist-led interventions,

and health teams. It also highlights opportunities for pharmaceutical companies to support and scale such behavioral interventions. Medication adherence remains a challenge for the long-term management of chronic conditions, especially those involving asymptomatic disease such as hyperlipidemia. To engage patients and enhance motivation over time, hyperlipidemia interventions must be targeted to individual patients' needs, with sequencing and frequency of contact tailored to the various stages of behavioral change.

[54] *Audo R, Deckert V, Daien CI et al.* **PhosphoLipid transfer protein (PLTP) exerts a direct pro-inflammatory effect on rheumatoid arthritis (RA) fibroblasts-like-synoviocytes (FLS) independently of its lipid transfer activity**. PloS one 2018; 13:e0193815.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29565987
ABSTRACT
Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with modification of lipids profile and an increased risk of cardiovascular events related to inflammation. Plasma phospholipid transfer protein (PLTP) exerts a lipid transfer activity through its active form. PLTP can also bind to receptors such as ATP-binding cassette transporter A1 (ABCA1). In addition to its role in lipoprotein metabolism and atherosclerosis, the latest advances came in support of a complex role of PLTP in the regulation of the inflammatory response, both with pro-inflammatory or anti-inflammatory properties. The aim of the present study was to decipher the role of PLTP in joint inflammation and to assess its relevance in the context of RA. PLTP expression was examined by western-blot and by immunochemistry. ABCA1 expression was analyzed by flow cytometry. Lipid transfer activity of PLTP and pro-inflammatory cytokines were measured in sera and synovial fluid (SF) from RA patients and controls (healthy subjects or osteoarthritis patients [OA]). FLS were treated with both lipid-transfer active form and inactive form of recombinant human PLTP. IL-8, IL-6, VEGF and MMP3 produced by FLS were assessed by ELISA, and proliferation by measuring 3H-Thymidine incorporation. RA synovial tissues showed higher PLTP staining than OA and PLTP protein levels were also significantly higher in RA-FLS. In addition, RA, unlike OA patients, displayed elevated levels of PLTP activity in SF, which correlated with pro-inflammatory cytokines. Both lipid-transfer active and inactive forms of PLTP significantly increased the production of cytokines and proliferation of FLS. ABCA1 was expressed on RAFLS and PLTP activated STAT3 pathway. To conclude, PLTP is highly expressed in the joints of RA patients and may directly trigger inflammation and FLS proliferation, independently of its lipid transfer activity. These results suggest a pro-inflammatory role for PLTP in RA.

[55] *Mbundu Ilunga R, Helbling C, Favre L, Collet TH*. **[Management of obesity-associated dyslipidemia : an approach based on food choices]**. Revue medicale suisse 2018; 14:627-632.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29561571
ABSTRACT
Obesity is associated with elevated levels of triglycerides, sometimes LDL-cholesterol, and lower levels of HDL-cholesterol. Management should first focus on dietary advices and increased physical activity, while lipid-lowering drugs are indicated only in patients at intermediate or high cardiovascular risk. We summarize nutritional recommendations from scientific societies: although they do not always overlap, they agree on lowering consumption

of dietary fat (20-35 % of total energy intake) and favoring non-saturated fatty acids. Physicians must review the intake of carbohydrates as well, by limiting added sugars and increasing dietary fibers (vegetables, wholegrain cereals, legumes and nuts). Multidisciplinary management shared between physicians and trained dieticians improves long-term healthy lifestyle.

[56] *He SJ, Liu Q, Li HQ et al.* **Role of statins in preventing cardiac surgery-associated acute kidney injury: an updated meta-analysis of randomized controlled trials**. Therapeutics and clinical risk management 2018; 14:475-482.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29551897
ABSTRACT
Background: The prevention of cardiac surgery-associated acute kidney injury (CSA-AKI) by statins remains controversial. Therefore, the present meta-analysis including randomized controlled trials (RCTs) was performed to assess the effect of perioperative statin on CSA-AKI. Methods: Two reviewers independently searched for RCTs about perioperative statin for prevention of CSA-AKI. The primary endpoint was CSA-AKI. Relative risk was calculated between statin and placebo for preventing CSA-AKI using the random-effect model or fixed-effect model according to different heterogeneity. Results: Eight RCTs met inclusion criteria, including five studies with atorvastatin, two with rosuvastatin, and one with simvastatin. There were 1,603 patients receiving statin treatment and 1,601 with placebo. Perioperative statin therapy did not reduce the incidence of CSA-AKI (relative risk =1.17, 95% CI: 0.98-1.39, p=0.076). Furthermore, perioperative statin increased the risk of CSA-AKI in the subgroup analysis with clear definition of CSA-AKI and those with JADAD score >3. Perioperative rosuvastatin produced slightly significantly higher risk of AKI than atorvastatin therapy (p=0.070). Statin intervention both pre and post surgery slightly increased the risk of CSA-AKI versus preoperative statin therapy alone (p=0.040). Conclusions: Perioperative statin therapy might increase the risk of CSA-AKI after cardiac surgery.

[57] *Yan F, Sun Y, Mao Y et al.* **Ultrasound Molecular Imaging of Atherosclerosis for Early Diagnosis and Therapeutic Evaluation through Leucocyte-like Multiple Targeted Microbubbles**. Theranostics 2018; 8:1879-1891.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29556362
ABSTRACT
Cardiovascular diseases resulting from atherosclerosis have become a serious threat to human health. It is well-known that an ongoing inflammatory response is involved during atherosclerosis progression that ultimately results in the accumulation of lipids and formation of plaques. Monitoring the pathological changes during the inflammatory response will be of great significance for early diagnosis and therapeutic evaluation of atherosclerosis. Targeted contrast-enhanced ultrasonography has been shown to be a promising noninvasive imaging technique for evaluating the degree of atherosclerosis and may potentially be translated to clinical imaging in the future. However, inadequate cell adhesion of targeted microbubbles (MBs) in large arterial vessels still remains a great challenge. Methods: By mimicking the leucocytes that are recruited to the vessel wall during the initiation of atherosclerosis through selectin-dependent arrest and cell adhesion molecule-mediated firm cell adhesion, we

developed VCAM-1/ICAM-1/P-selectin-targeted MBVIS by integrating VCAM-1 and ICAM-1 antibodies and synthetic polymeric sialyl Lewis X (sLe(x)) onto the MB surface. Results: The resulting MBVIS had a high affinity to inflammatory bEnd.3 cells in both static and dynamic flow conditions. Significantly enhanced ultrasound imaging signals were achieved by MBVIS in detecting the atherosclerosis progress when compared with the single- or dual-targeted MBs. Taking advantage of the artificial MBVIS, less ultrasound imaging signals were found in the atorvastatin-treated, but not placebo-treated, ApoE-deficient mice with atherosclerosis, revealing a potential therapeutic efficacy of atorvastatin for early stage atherosclerosis. This was further confirmed by histologic staining examination. Conclusions: Our study provides a promising ultrasound molecular imaging probe for early-stage diagnosis and therapeutic evaluation of atherosclerosis.