Literature update week 42 (2018)

[1] *Pradhan AD, Paynter NP, Everett BM et al.* **Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study**. American heart journal 2018; 206:80-93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30342298
ABSTRACT
Observational, genetic, and experimental data indicate that triglyceride rich lipoproteins (TRLs) likely participate causally in atherothrombosis. Yet, robust clinical trial evidence that triglyceride (TG) lowering therapy reduces cardiovascular events remains elusive. The selective peroxisome proliferator-activated receptor alpha modulator (SPPARM-alpha), pemafibrate, will be used to target residual cardiovascular risk remaining after treatment to reduce low-density lipoprotein cholesterol (LDL-C) in individuals with the dyslipidemia of type 2 diabetes mellitus (T2). The PROMINENT study will randomly allocate approximately 10,000 participants with T2D, mild-to-moderate hypertriglyceridemia (TG: 200-499 mg/dl; 2.26-5.64 mmol/l) and low high-density lipoprotein cholesterol levels (HDL-C: </=40 mg/dl; 1.03 mmol/l) to either pemafibrate (0.2 mg twice daily) or matching placebo with an average expected follow-up period of 3.75 years (total treatment phase 5 years; 24 countries). At study entry, participants must be receiving either moderate-to-high intensity statin therapy or meet specified LDL-C criteria. The study population will be one-third primary and two-thirds secondary prevention (established cardiovascular disease). The primary endpoint is a composite of nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina requiring urgent coronary revascularization, and cardiovascular death. This event-driven study will complete when 1092 adjudicated primary endpoints have accrued with at least 200 occurring in women. Statistical power is at least 90% to detect an 18% reduction in the primary endpoint. Pre-specified secondary and tertiary endpoints include all-cause mortality, hospitalization for heart failure, new or worsening peripheral artery disease, new or worsening diabetic retinopathy and nephropathy, and change in biomarkers including select lipid and non-lipid biomarkers, inflammatory and glycemic parameters.

[2] *Trinder M, Genga KR, Kong HJ et al.* **Cholesteryl Ester Transfer Protein Influences High-Density Lipoprotein Levels and Survival in Sepsis**. American journal of respiratory and critical care medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30321485
ABSTRACT
RATIONALE: High-density lipoprotein cholesterol (HDL-C) levels decline during sepsis, and lower levels are associated with worse survival. However, the genetic mechanisms underlying changes in HDL-C during sepsis, and whether the relationship with survival is causative, is largely unknown. OBJECTIVES: We hypothesized that variation in genes involved in HDL metabolism would contribute to changes in HDL-C levels and clinical outcomes during sepsis. METHODS: We performed targeted re-sequencing of HDL-related genes in 200 patients admitted to an emergency department with sepsis (Early Infection cohort). We examined the association of genetic variants with HDL-C levels, 28-d survival, 90-d survival, organ dysfunction, and need for vasopressor or ventilatory support. Candidate variants were further assessed in the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock trial (VASST) cohort (n=632) and St. Paul's Hospital ICU 2 (SPHICU2) cohort (n=203). MAIN RESULTS: We identified a rare

missense variant in cholesteryl ester transfer protein gene (CETP; rs1800777-A) that was associated with significant reductions in HDL-C levels during sepsis. Carriers of the A allele (n=10) had decreased survival, more organ failure, and greater need for organ support compared to non-carriers. We replicated this finding in the VASST and SPHICU2 cohorts, in which carriers of rs1800777-A (n=35 and n=12, respectively) had significantly reduced 28-day survival. Mendelian randomization was consistent with genetically-reduced HDL levels being a causal factor for decreased sepsis survival. CONCLUSIONS: Our results identify CETP as a critical regulator of HDL levels and clinical outcomes during sepsis. These data point towards a critical role for HDL in sepsis.

[3] *Kalinin RE, Suchkov IA, Mzhavanadze ND et al.* **[Promising methods of studying perfusion in patients with atherosclerosis of peripheral arteries]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2018; 24:32-37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30321144
ABSTRACT
Prevalence of atherosclerotic peripheral artery disease (PAD) has steadily been increasing all over the world, affecting approximately 10% of the population. PAD dramatically decreases the patients' quality of life and is accompanied by high risks of limb amputation and death. Reconstructive and restorative interventions make it possible to achieve the highest success in treatment of PAD. Their results largely depend on the state of the patient's peripheral bed. Currently, the periphery is objectively assessed by means of ultrasonographic duplex examination, digital subtraction angiography, roentgen computed tomographic angiography (CTA), and in a series of cases magnetic resonance tomographic angiography (MRA). Widely known are the scale of assessing peripheral vascular resistance, suggested by R. Rutherford and the Bollinger scoring system. All these methods study predominantly the major blood flow, only slightly touching the microcirculatory bed. Promising methods in this area are radionuclide methods - single-photon emission computed tomography (SPECT) and positron-emission tomography (PET). Used singly, they possess high sensitivity but low spatial resolution, therefore they are supplemented by CTA or MRA. It is supposed that the use of radionuclide methods would make it possible to accurately assess the state of an atherosclerotic plaque and angiogenesis in conditions of ischaemia. Yet another method of diagnosis of microperfusion is contrast-enhanced ultrasonography (CEUS). CEUS reveals deficit of perfusion of the gastrocnemius muscles of patients with PAD in accordance with severity of the disease and degree of the development of collaterals. It is also used for determining the results of therapy with agents improving microcirculation. The degree of blood supply to tissues may be evaluated with the help of perfusion computed tomography (PCT). The main area of its application is diagnosis of impairments of cerebral circulation. Under study is a possibility of using PCT in atherosclerosis of lower-limb arteries, as well as assessing the efficacy of the reconstructive and restorative procedures performed.

[4] *Korula J*. **In primary biliary cholangitis, adding bezafibrate to ursodeoxycholic acid increased complete biochemical response**. Annals of internal medicine 2018; 169:Jc45.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30326089
ABSTRACT

[5] *Tiainen S, Kiviniemi A, Hautala A et al.* **Effects of a Two-Year Home-Based Exercise Training Program on Oxidized LDL and HDL Lipids in Coronary Artery Disease Patients with and without Type-2 Diabetes**. Antioxidants (Basel, Switzerland) 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30332828

ABSTRACT

We investigated the effect of two-year home-based exercise training program on oxidized low-density lipoprotein LDL (ox-LDL) and high-density lipoprotein HDL (ox-HDL) lipids in patients with coronary artery disease (CAD), both with and without type-2 diabetes (T2D). Analysis of lipoprotein-oxidized lipids was based on the determination of baseline conjugated dienes in lipoprotein lipids. In order to study the effect of an exercise load on ox-LDL and ox-HDL lipids patients in both CAD and CAD + T2D intervention, groups were divided in three based on exercise load (high, medium, and low). During the two-year home-based exercise training program, the study showed that only higher training volume resulted in a decreased concentration of ox-LDL, while the two groups with lower training volumes showed no change. This result indicates that the training load needs to be sufficiently high in order to decrease the concentration of atherogenic ox-LDL lipids in patients with CAD and CAD + T2D. Interestingly, the concentration of ox-HDL did not change in any of the subgroups. This could indicate that the lipid peroxide-transporting capacity of HDL, suggested by results from exercise training studies in healthy adults, may not function similarly in CAD patients with or without T2D. Moreover, the lipid-lowering medication used may have had an influence on these results.

[6] *van der Sluis RJ, Verwilligen RAF, Lendvai Z et al.* **HDL is essential for atherosclerotic lesion regression in Apoe knockout mice by bone marrow Apoe reconstitution**. Atherosclerosis 2018; 278:240-249.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30340108

ABSTRACT

BACKGROUND AND AIMS: Although studies in mice have suggested that lesion regression is feasible, the underlying mechanisms remain largely unknown. Here we determined the impact of high-density lipoprotein (HDL) on atherosclerosis regression outcome. METHODS: Atherosclerotic lesion dynamics were studied upon bone marrow transplantation-mediated re-introduction of apolipoprotein E (Apoe) in Apoe knockout mice. Probucol was used to pharmacologically deplete HDL. RESULTS: Restoration of Apoe function was associated with an initial growth of atherosclerotic lesions and parallel decrease in lesional macrophage foam cell content (47+/-4%at 4 weeks versus 72+/-2% at baseline: p<0.001), despite the fact that cholesterol levels were markedly reduced. Notably, significant lesion regression was detected from 4 weeks onwards, when plasma cholesterol levels had returned to the normolipidemic range. As a result, lesions were 41% smaller (p<0.05) at 8 weeks than at 4 weeks after bone marrow transplantation. Regressed lesions contained an even lower level of macrophage foam cells (33+/-5%: p<0.001) and were rich in collagen. Probucol co-treatment was associated with a 3.2-fold lower (p<0.05) plasma HDL-cholesterol level and a more pro-inflammatory (CCR2+) monocyte phenotype. Importantly, probucol-treated mice exhibited atherosclerotic lesions that were larger than those of regular chow diet-fed bone marrow transplanted mice at 8 weeks (186 +/- 15*10(3)mum(2) for probucol-treated versus 120 +/- 19*10(3)mum(2) for controls:

p<0.05). CONCLUSIONS: We have shown that probucol-induced HDL deficiency impairs the ability of established lesions to regress in response to reversal of the genetic hypercholesterolemia in Apoe knockout mice. Our studies thus highlight a crucial role for HDL in the process of atherosclerosis regression.

[7] *Yu XH, He LH, Gao JH et al.* **Pregnancy-associated plasma protein-A in atherosclerosis: Molecular marker, mechanistic insight, and therapeutic target**. Atherosclerosis 2018; 278:250-258.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30340109
ABSTRACT
Pregnancy-associated plasma protein-A (PAPP-A), a member of the metzincin metalloproteinase superfamily, can enhance local insulin-like growth factor (IGF) bioavailability through proteolytic cleavage of three IGF binding proteins. In patients with coronary atherosclerosis disease (CAD), elevated PAPP-A levels are significantly associated with a higher risk of cardiovascular events. Accumulating evidence indicates that this protease exerts a proatherogenic effect by altering a variety of pathological processes involved in atherosclerosis, including lipid accumulation, vascular inflammation, endothelial dysfunction, vascular smooth muscle cell proliferation and migration, plaque stability, and thrombus formation. Moreover, blockade of its proteolytic activity by stanniocalcin or microRNAs is protective against atherosclerosis development. In this review, we summarized the latest advances regarding the roles of PAPP-A in the pathogenesis of atherosclerosis with an emphasis on its diagnostic and prognostic values in CAD.

[8] *Chimini JS, Possomato-Vieira JS, Silva M, Dias-Junior CA*. **Placental nitric oxide formation and endothelium-dependent vasodilation underlie pravastatin effects against angiogenic imbalance, hypertension in pregnancy and intrauterine growth restriction**. Basic & clinical pharmacology & toxicology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318719
ABSTRACT
preeclampsia and hypertensive disorders of pregnancy are frequently associated with feto-placental growth restriction and that may be triggered by angiogenic imbalance and endothelial dysfunction. Impaired nitric oxide (NO) bioavailability seems to be involved in these pathophysiological changes observed in hypertensive pregnancy. Pravastatin has shown efficacy and to be safe during hypertension in pregnancy. However, NO involvement in pravastatin effects during maternal hypertension and feto-placental development is unclear. Therefore, we aimed to examine pravastatin effects on placental NO formation, endothelium-dependent vasodilation, systolic blood pressure and feto-placental development in hypertensive pregnant rats. Biochemical determinants of angiogenesis and oxidative stress were also assessed. Pregnant rats were distributed into four groups: normal pregnancy (Norm-Preg), pregnancy+Pravastatin (Preg-Prava), hypertensive pregnancy (HTN-Preg) and hypertensive pregnancy+Pravastatin (HTN-Preg+Prava). Our results showed that pravastatin treatment blunts hypertension and feto-placental growth restriction. Also, increases in placental NO levels were found in the HTN-Preg+Prava group. Pravastatin prevents impaired endothelium-dependent acetylcholine-induced vasodilation, exacerbated contractile response

to phenylephrine and increases in oxidative stress in the HTN-Preg+Prava group. Increased soluble fms-like tyrosine kinase-1 and placental growth factor (sFlt-1/PlGF) ratio is reversed by pravastatin treatment in the HTN-Preg+Prava group. We conclude that NO formation and endothelium-dependent vasodilation underlie pleiotropic effects associated with pravastatin treatment against hypertension in pregnancy, intrauterine growth restriction, vascular dysfunction and angiogenic imbalance.

[9] *Masuyama A, Mita T, Azuma K et al.* **Defective autophagy in vascular smooth muscle cells enhances atherosclerotic plaque instability**. Biochem Biophys Res Commun 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318118
ABSTRACT
Autophagy is considered as an evolutionarily conserved cellular catabolic process. Defective autophagy has been implicated in various human diseases, including cardiovascular diseases. Recently, we and others demonstrated that defective autophagy in vascular smooth muscle cells (SMCs) promotes the progression of atherosclerosis. In this study, we investigated the role of autophagy in SMCs on plaque instability in vivo. We generated mice with a defect atg7in which is an essential gene for autophagy, in SMCs by crossing Atg7(f/f) mice with transgelin (Tagln) Cre(+/0) mice (Atg7cKO). Then, Atg7cKO and apolipoprotein E (apoe)-deficient (apoeKO) mice were crossed to generate Atg7cKO:apoeKO mice. To generate a mouse model of plaque instability, we conducted to form a tandem stenosis in the carotid artery of Atg7cKO:apoeKO mice and their controls (apoeKO mice) at the age of 10 weeks. At 5 weeks after surgery, the percentage of cross-sectional stenosis area in the operated common carotid artery of Atg7cKO:apoeKO mice was significantly higher than that in apoeKO mice. In addition, thrombus, which was not observed in apoeKO mice, was frequently found in Atg7cKO:apoeKO mice. Furthermore, the number of Berlin blue staining-positive areas, which indicated intraplaque hemorrhage, was significantly higher in Atg7cKO:apoeKO mice than in control apoeKO mice. Taken together, our data suggest that defective autophagy in SMCs enhances plaque instability and the risk of plaque rupture.

[10] *Chen ZZ, Xie YD, Shao LH et al.* **5-(4-Hydroxyphenyl)-3H-1,2-dithiole-3-thione-based fibrates as potential hypolipidemic and hepatoprotective agents**. Bioorganic & medicinal chemistry letters 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30337230
ABSTRACT
Hypolipidemic effects of the newly synthesized 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione-based fibrates were evaluated in Triton WR-1339 and high-fat diet (HFD)-induced hyperlipidemic mice. Preliminary screening of all the synthesized compounds was done by using an acute model (Triton WR-1339 model), in which compound 6 shown more significant antidyslipidemic activity than fenofibrate (FF). The compound 6 was also found to reduce serum triglyceride (TG), total cholesterol (TC) and low density lipoprotein cholesterin (LDL) in HFD-induced hyperlipidemic mice. Moreover, compound 6 displayed hepatoprotective effect, a significant amelioration in hepatic indices (AST and ALT) toxicity was observed and the histological examination showed that compound 6 inhibited the development of hepatic lipid accumulation and ameliorated the damage in hepatic tissue compared to model mice.

Additional effects such as the potent antioxidant and anti-inflammatory action confirmed and reinforced the efficacy of compound 6 as a new agent of dual-effect hypolipidemic and hepatoprotective activities.

[11] *Chen Y, Zhu R, Ma F et al.* **Assessment of OATP Transporter-Mediated Drug-Drug Interaction using Physiologically-Based Pharmacokinetic (PBPK) Modeling - A Case Example**. Biopharmaceutics & drug disposition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30335192
ABSTRACT
GDC-0810 was under development as an oral anti-cancer drug for the treatment of estrogen receptor-positive breast cancer as a single agent or in combination. In vitro data indicated that GDC-0810 is a potent inhibitor of OATP1B1/1B3. To assess clinical risk, PBPK model was developed to predict the transporter drug-drug interaction (tDDI) between GDC-0810 and pravastatin in human. The PBPK model was constructed in Simcyp(R) by integrating in vitro and in vivo data for GDC-0810. The prediction of human pharmacokinetics (PK) was verified using GDC-0810 phase I clinical PK data. The Simcyp transporter DDI model was verified using known OATP1B1/1B3 inhibitors (rifampicin, cyclosporine and gemfibrozil) and substrate (pravastatin), prior to using the model to predict GDC-0810 tDDI. The effect of GDC-0810 on pravastatin PK was then predicted based on the proposed clinical scenarios. Sensitivity analysis was conducted on the parameters with uncertainty. The developed PBPK model described the PK profile of GDC-0810 reasonably well. In the tDDI verification, the model reasonably predicted pravastatin tDDI caused by rifampicin and gemfibrozil OATP1B1/3 inhibition but under-predicted tDDI caused by cyclosporine. The effect of GDC-0810 on pravastatin PK was predicted to be low to moderate (pravastatin Cmax ratios 1.01 ~2.05 and AUC ratio 1.04 ~2.23). The observed tDDI (Cmax ratio 1.20 and AUC ratio 1.41) was within the range of the predicted values. This work demonstrates an approach using PBPK model to prospectively assess tDDI caused by new chemical entity as an OATP 1B1/3 uptake transporter inhibitor to assess clinical risk and support development strategy.

[12] *Thereaux J, Lesuffleur T, Czernichow S et al.* **Multicentre cohort study of antihypertensive and lipid-lowering therapy cessation after bariatric surgery**. The British journal of surgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30325504
ABSTRACT
BACKGROUND: Few studies have assessed changes in antihypertensive and lipid-lowering therapy after bariatric surgery. The aim of this study was to assess the 6-year rates of continuation, discontinuation or initiation of antihypertensive and lipid-lowering therapy after bariatric surgery compared with those in a matched control group of obese patients. METHODS: This nationwide observational population-based cohort study used data extracted from the French national health insurance database. All patients undergoing gastric bypass or sleeve gastrectomy in France in 2009 were matched with control patients. Mixed-effect logistic regression models were used to analyse factors that influenced discontinuation or initiation of treatment over a 6-year interval. RESULTS: In 2009, 8199 patients underwent primary gastric bypass (55.2 per cent) or sleeve gastrectomy (44.8 per cent). After 6 years, the proportion of

patients receiving antihypertensive and lipid-lowering therapy had decreased more in the bariatric group than in the control group (antihypertensives: -40.7 versus -11.7 per cent respectively; lipid-lowering therapy: -53.6 versus -20.2 per cent; both P < 0.001). Gastric bypass was the main predictive factor for discontinuation of therapy for hypertension (odds ratio (OR) 9.07, 95 per cent c.i. 7.72 to 10.65) and hyperlipidaemia (OR 11.91, 9.65 to 14.71). The proportion of patients not receiving treatment at baseline who were subsequently started on medication was lower after bariatric surgery than in controls for hypertension (5.6 versus 15.8 per cent respectively; P < 0.001) and hyperlipidaemia (2.2 versus 9.1 per cent; P < 0.001). Gastric bypass was the main protective factor for antihypertensives (OR 0.22, 0.18 to 0.26) and lipid-lowering medication (OR 0.12, 0.09 to 0.15). CONCLUSION: Bariatric surgery is associated with a good discontinuation of antihypertensive and lipid-lowering therapy, with gastric bypass being more effective than sleeve gastrectomy.

[13] *Mondul AM, Joshu CE, Barber JR et al.* **Longer-term lipid-lowering drug use and risk of incident and fatal prostate cancer in black and white men in the ARIC Study**. Cancer prevention research (Philadelphia, Pa.) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30327368
ABSTRACT
Lipid-lowering medications, particularly statins, may protect against aggressive prostate cancer. Fatal prostate cancer, the most clinically relevant outcome, remains understudied for this association. We prospectively studied lipid-lowering medication use and both incident and fatal prostate cancer in black and white men in the Atherosclerosis Risk in Communities (ARIC) Study. 6,518 men without cancer at visit 2 (1990-1992), the start of the statin era, were followed for prostate cancer incidence and death through 2012. Medication use was collected during study visits and telephone calls at up to 9 time points during follow-up. Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of total (white N=541, black N=259) and fatal (white N=56, black N=34) prostate cancer overall and by race. Lipid-lowering medication use was modeled as time-dependent current use or duration (never, <10, >/=10 years). By visit 4 (1996-1998), 21% of white and 11% of black men had used a lipid-lowering medication, mostly statins. There was a suggestion that current users were less likely to die from prostate cancer than non-users (HR=0.67, 95% CI=0.42-1.07) after multivariable adjustment. We observed no statistically significant differences between black and white men. Current use was not associated with incident prostate cancer, although long-term use was statistically significantly inversely associated with incidence (HR=0.68, 95% CI=0.50-0.92). Long-term lipid-lowering medication use was associated with lower risk of prostate cancer. Current use was possibly associated with fatal prostate cancer.

[14] *Wu X, Gong C, Weinstock J et al.* **Associations of the SLCO1B1 Polymorphisms With Hepatic Function, Baseline Lipid Levels, and Lipid-lowering Response to Simvastatin in Patients With Hyperlipidemia**. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2018:1076029618805863.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336686
ABSTRACT

Our goal was to examine the associations of the 388A>G and 521T>C polymorphisms in the solute carrier organic anion transporter 1B1 (SLCO1B1) gene with hepatic function, baseline lipid levels, and the lipid-lowering efficiency of simvastatin. We recruited 542 patients with hyperlipidemia. The 388A>G and 521T>C polymorphisms were genotyped. Serum alanine aminotransferase (ALT) and aspartate transaminase (AST), Serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were measured before and after an oral 20-mg dose of simvastatin. Individuals with the 388AA genotype had higher ALT and AST levels than those with the 388AG or 388GG genotypes (P = .037 and P = .002, respectively). Individuals with both the 388AA and the 521TT genotypes had the highest levels of ALT and AST (P = .001 and P = .001, respectively). Moreover, we divided all patients into normal and abnormal subgroups based on elevated ALT and AST values (>/= 40 U/L), participants in the abnormal subgroup had a higher frequency of the 388A/521T haplotype and a lower frequency of the 388G/521T haplotype compared to those in the normal subgroup. In addition, compared to 388G allele and 521C allele carriers, individuals with the 388G allele and 521TT genotype carriers had greater TC and LDL-C reduction in response to simvastatin after 4 weeks of treatment. Our conclusion suggests that the interaction between the SLCO1B1 388A>G and 521T>C polymorphisms could be an important genetic determinant of hepatic function and the therapeutic efficiency of simvastatin in Chinese patients with hyperlipidemia.

[15] *Bjornstad P, Eckel RH*. **Pathogenesis of Lipid Disorders in Insulin Resistance: a Brief Review**. Current diabetes reports 2018; 18:127.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30328521
ABSTRACT
PURPOSE OF REVIEW: Insulin resistance (IR) is recognized to play an important role in the pathogenesis of dyslipidemia. This review summarizes the complex interplay between IR and dyslipidemia in people with and without diabetes. RECENT FINDINGS: IR impacts the metabolism of triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) by several mechanisms. Trials with insulin sensitizing therapies, including biguanides and thiazolidinediones, have provided inconsistent results on lipid lowering in people with and without diabetes. In this review, we focus on the pathophysiological interplay between IR and dyslipidemia and recapitulate lipid and lipoprotein data from insulin-sensitizing trials. Further research elucidating the reciprocal relationship between IR and dyslipidemia is needed to better target these important risk factors for cardiovascular disease.

[16] *Ganda O*. **Beyond Statins: Who and When to Prescribe?** Current diabetes reports 2018; 18:126.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30324282
ABSTRACT
PURPOSE OF REVIEW: Statins are the most evidence-based therapy to target LDL-C to reduce atherosclerotic events. Yet, many people are unable to achieve adequate reduction in this key atherogenic factor. Moreover, residual risk of cardiovascular events may persist even after "optimal" LDL-C due to elevations in triglyceride-rich lipoproteins. Therefore, additional

therapies beyond statins are needed, particularly in patients with diabetes. RECENT FINDINGS: Clinical trials with ezetimibe and PCSK9 inhibitors have reported further reductions in cardiovascular events, beyond statins. The latter are particularly effective in lowering LDL-cholesterol and in reducing event rates. However, they are not effective in lowering triglycerides. Currently available fibrates and niacin have not proven effective in combination with statins in clinical trials, while the top line results of the REDUCE-IT trial with EPA, a pure omega-3 fatty acid, reporting 25% relative risk reduction in primary endpoints are of great interest. Recently approved agents have the promise to improve cardiovascular outcomes beyond statins. Many novel drugs in development have the potential to further improve prognosis.

[17] *Anagnostis P, Siolos P, Krikidis D et al.* **Should we consider lipoprotein (a) in cardiovascular disease risk assessment in patients with familial hypercholesterolaemia?** Current pharmaceutical design 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30317988
ABSTRACT
BACKGROUND: Familial hypercholesterolaemia (FH) is a genetically determined lipid disorder, affecting 1 per 200-500 individuals in the general population. It is significantly and independently associated with increased risk of cardiovascular disease (CVD), although it remains still an underrecognized and undertreated disease. Lipoprotein (a) [Lp(a)] is a low-density-lipoprotein (LDL)-like molecule, containing an additional protein, apolipoprotein (a). OBJECTIVE: This review aims to present and discuss available data on the role of Lp(a) in patients with FH, in terms of its potential augmentation of CVD risk. METHODS: A comprehensive search of the literature was performed to identify studies evaluating the CV effects of Lp(a) in patients with FH. RESULTS: Lp(a) has been recognised as an independent risk factor for CVD, mainly coronary artery disease (CAD). Most, but not all, studies show increased Lp(a) concentrations in adults and children with FH. There is also evidence of an independent association between Lp(a) and CVD (mainly CAD) risk in these patients. CONCLUSION: Some therapeutic modalities, such as niacin, oestrogens, tibolone and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may effectively reduce Lp(a) concentrations by 25-30%, although their clinical benefit of this effect remains to be established.

[18] *Maliachova O, Stabouli S*. **Familial Hypercholesterolemia in Children and Adolescents: Diagnosis and Treatment**. Current pharmaceutical design 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30317987
ABSTRACT
Familial hypercholesterolemia is a hereditary genetic disorder predisposing in premature atherosclerosis and cardiovascular complications. Early diagnosis as well as effective treatment strategies in affected children are challenges among experts. Universal screening and cascade screening among families with familial hypercholesterolemia are being controversially discussed. Diagnosis of familial hypercholesterolemia in children and adolescents is usually based on clinical phenotype upon LDL-C levels and family history of premature cardiovascular and/or elevated LDL-C. Treatment approaches for familial hypercholesterolemia in the pediatric population are multidisciplinary and aim to reduce total cardiovascular risk. The most widely

recommended and effective pharmacotherapy in the pediatric age group is currently statins. Ezetimibe and bile acid sequestrants are usually used as second line agents. New therapeutic approaches, such as mipomersen and PCSK9 inhibitors seem promising. The main gap of evidence remains the lack of longitudinal follow up studies investigating cardiovascular outcomes, side effects, and effectiveness of treatment starting from childhood. Evidence would be expected in the near future by cohort and registry studies.

[19] *Papademetriou V, Stavropoulos K, Papadopoulos C et al.* **Role of PCSK9 inhibitors in high risk patients with dyslipidemia: Focus on familial hypercholesterolemia**. Current pharmaceutical design 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30317985
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder that is characterized by substantially increased low-density lipoprotein cholesterol (LDL-C) levels. Patients with FH have a significantly higher risk for cardiovascular (CV) events, and the timely reduction of LDL-C is of paramount importance to ameliorate the risk for CV disease. Among the available lipid-lowering therapies, the novel proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as a very promising class of drugs for the management of such patients. OBJECTIVE: The purpose of this review is to present available data on the efficacy and safety of the two available PCSK9 inhibitors in patients with FH, and importantly to discuss potential differences between the two drugs. METHODS: A comprehensive literature search was performed to identify available data from clinical studies evaluating the impact of evolocumab or alirocumab on lipid and CV parameters in patients with FH. RESULTS: Several studies have assessed the lipid-lowering profile of PCSK9 inhibitors in patients with FH. Both evolocumab and alirocumab were found to significantly reduce LDL-C by more than 50-60% in FH patients. Furthermore, data also support a lower rate of lipid apheresis in FH patients receiving a PCSK9 inhibitor. In terms of CV outcomes, both drugs were found to possess CV-ameliorating effects of the same extent in patients with CV disease. However, alirocumab reduced all-cause mortality, as well, a finding not observed with evolocumab. Several differences in the study population characteristics might explain this and other mild differences observed in the CV trials of these drugs. CONCLUSION: Available evidence suggests similar potency of alirocumab and evolocumab in reducing lipids and CV events.

[20] *Theocharidou E, Papademetriou M, Reklou A et al.* **The role of PCSK9 in the pathogenesis of non-alcoholic fatty liver disease and the effect of PCSK9 inhibitors**. Current pharmaceutical design 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30317984
ABSTRACT
BACKGROUND: Statin treatment exhibits a beneficial effect on non-alcoholic fatty liver disease (NAFLD) and on cardiovascular disease (CVD) in patients with NAFLD. OBJECTIVE: The aim of this review is to summarize the role of proprotein convertase subtilisin kexin type-9(PCSK9) in the pathogenesis of NAFLD and discuss the effects of the new hypolipidaemic drugs PCSK9 inhibitors on NAFLD. RESULTS: Data indicates that high intrahepatic or circulating PCSK9 levels increase muscle and liver lipid storage, adipose energy storage and hepatic fatty acids, as well

as triglycerides storage and secretion, thus contributing to the pathogenesis of NAFLD. The findings of animal and human studies, aiming to reduce PCSK9 with inhibitors (human IGG antibodies, antisense particles against PCSK9 mRNA, and small anti PCSK9 antibodies) point towards liver protection from NAFLD through inhibition of PCSK9 expression in the induction of degradation of hepatic HNF1a protein, insulin resistance (IR), and other mechanisms. CONCLUSIONS: The use of PCSK9 inhibitors ameliorates NAFLD, aside from beneficial effects on CVD and independently of low density lipoprotein cholesterol level reduction.

[21] *Tsouka AN, Tellis CC, Tselepis AD*. **Pharmacology of PCSK9 inhibitors: Current status and future perspectives**. Current pharmaceutical design 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30317986
ABSTRACT
Protein Convertase Subtilisin/Kexin type 9 (PCSK9) is a serine protease primarily expressed in the liver, which represents the main source of the plasma enzyme. The best characterized function of PCSK9 relates to the binding to low-density lipoprotein receptor (LDL-R) in hepatocytes, increasing its endosomal and lysosomal degradation. This results in the inhibition of LDL-R recycling to the cell surface and therefore the reduction of the hepatic uptake of LDL, leading to the increase in plasma levels of LDL-cholesterol, a major risk factor of cardiovascular diseases (CVD). Therefore, PCSK9 is an important therapeutic target to reduce LDL-cholesterol levels. PCSK9 inhibition can occur at the level of its interaction with LDL-R as well as at several sites across the pathway of its intracellular synthesis and secretion. Two fully human mAbs, Alirocumab and Evolocumab, that selectively bind to PCSK9 and prevent its interaction with the LDL-R, are currently used in the clinical practice. These mAbs are the most potent cholesterol-lowering agents available today and can decrease LDL-cholesterol levels up to 73% while they also reduce the risk of atherosclerotic CVD. Ongoing research has led to the development of new PCSK9 inhibitors through genome editing technology (CRISPR-Cas9), siRNA or antisense oligonucleotide silencing agents, vaccines, mimetic peptides, adnectins, and inhibitors of PCSK9 secretion. The above inhibitors have been studied in vitro, in animal models in vivo, as well as in phase I and II trials and have demonstrated an important efficacy profile. Future studies with these agents will demonstrate their possible clinical value and will further enlighten the various targets and activities of PCSK9 intracellularly and extracellularly, the underlying mechanisms, as well as the clinical significance of these actions beyond the inhibition of LDL-R recycling.

[22] *Grigoropoulou P, Tentolouris A, Eleftheriadou I et al.* **Effect of 12-month intervention with low-dose atorvastatin on pulse wave velocity in subjects with type 2 diabetes and dyslipidaemia**. Diabetes & vascular disease research 2018:1479164118805320.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30328360
ABSTRACT
Cardiovascular disease is the leading cause of morbidity and mortality in subjects with type 2 diabetes mellitus. Increased aortic stiffness, assessed with the carotid-femoral pulse wave velocity, is an independent risk factor for cardiovascular disease. Statins reduce effectively cardiovascular disease and mortality in high-risk patients. The aim of this prospective non-randomized, observational study was to examine the impact of treatment with either 10 mg atorvastatin plus diet or diet alone on carotid-femoral pulse wave velocity in subjects with type

2 diabetes mellitus and dyslipidaemia. A total of 79 subjects with type 2 diabetes mellitus and dyslipidaemia were included; 46 subjects were treated with atorvastatin 10 mg daily plus diet and 33 were managed by diet alone for 12 months. Carotid-femoral pulse wave velocity and carotid-radial pulse wave velocity were measured using applanation tonometry. In the atorvastatin-treated group, carotid-femoral pulse wave velocity reduced significantly during the study and there was a trend for reduction in the carotid-radial pulse wave velocity. Total cholesterol, low-density lipoprotein cholesterol, triglycerides and C-reactive protein were reduced only in the atorvastatin-treated participants. No significant changes were found in body mass index, blood pressure, heart rate, diabetes control and high-density lipoprotein cholesterol in either study group. Treatment with low-dose atorvastatin for 12 months improves carotid-femoral pulse wave velocity in subjects with type 2 diabetes mellitus and dyslipidaemia.

[23] *Murata M*. **Inflammation and cancer**. Environmental health and preventive medicine 2018; 23:50.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30340457
ABSTRACT
Infection and inflammation account for approximately 25% of cancer-causing factors. Inflammation-related cancers are characterized by mutagenic DNA lesions, such as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-nitroguanine. Our previous studies demonstrated the formation of 8-oxodG and 8-nitroguanine in the tissues of cancer and precancerous lesions due to infection (e.g., Opisthorchis viverrini-related cholangiocarcinoma, Schistosoma haematobium-associated bladder cancer, Helicobacter pylori-infected gastric cancer, human papillomavirus-related cervical cancer, Epstein-Barr virus-infected nasopharyngeal carcinoma) and pro-inflammatory factors (e.g., asbestos, nanomaterials, and inflammatory diseases such as Barrett's esophagus and oral leukoplakia). Interestingly, several of our studies suggested that inflammation-associated DNA damage in cancer stem-like cells leads to cancer development with aggressive clinical features. Reactive oxygen/nitrogen species from inflammation damage not only DNA but also other biomacromolecules, such as proteins and lipids, resulting in their dysfunction. We identified oxidatively damaged proteins in cancer tissues by 2D Oxyblot followed by MALDI-TOF/TOF. As an example, oxidatively damaged transferrin released iron ion, which may mediate Fenton reactions and generate additional reactive oxygen species. Dysfunction of anti-oxidative proteins due to this damage might increase oxidative stress. Such damage in biomacromolecules may form a vicious cycle of oxidative stress, leading to cancer development. Epigenetic alterations such as DNA methylation and microRNA dysregulation play vital roles in carcinogenesis, especially in inflammation-related cancers. We examined epigenetic alterations, DNA methylation and microRNA dysregulation, in Epstein-Barr virus-related nasopharyngeal carcinoma in the endemic area of Southern China and found several differentially methylated tumor suppressor gene candidates by using a next-generation sequencer. Among these candidates, we revealed higher methylation rates of RAS-like estrogen-regulated growth inhibitor (RERG) in biopsy specimens of nasopharyngeal carcinoma more conveniently by using restriction enzyme-based real-time PCR. This result may help to improve cancer screening strategies. We profiled microRNAs of nasopharyngeal carcinoma tissues using microarrays. Quantitative RT-PCR analysis confirmed the concordant

downregulation of miR-497 in cancer tissues and plasma, suggesting that plasma miR-497 could be used as a diagnostic biomarker for nasopharyngeal carcinoma. Chronic inflammation promotes genetic and epigenetic aberrations, with various pathogeneses. These changes may be useful biomarkers in liquid biopsy for early detection and prevention of cancer.

[24] *de Knegt MC, Linde JJ, Fuchs A et al.* **Relationship between patient presentation and morphology of coronary atherosclerosis by quantitative multidetector computed tomography**. European heart journal cardiovascular Imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30325406
ABSTRACT
Aims: Quantitative computed tomography (QCT) allows assessment of morphological features of coronary atherosclerosis. We aimed to test the hypothesis that clinical patient presentation is associated with distinct morphological features of coronary atherosclerosis. Methods and results: A total of 1652 participants, representing a spectrum of clinical risk profiles [787 asymptomatic individuals from the general population, 468 patients with acute chest pain without acute coronary syndrome (ACS), and 397 patients with acute chest pain and ACS], underwent multidetector computed tomography. Of these, 274 asymptomatic individuals, 254 patients with acute chest pain without ACS, and 327 patients with acute chest pain and ACS underwent QCT to assess coronary plaque volumes and proportions of dense calcium (DC), fibrous, fibro fatty (FF), and necrotic core (NC) tissue. Furthermore, the presence of vulnerable plaques, defined by plaque volume and tissue composition, was examined. Coronary plaque volume increased significantly with worsening clinical risk profile [geometric mean (95% confidence interval): 148 (129-166) mm3, 257 (224-295) mm3, and 407 (363-457) mm3, respectively, $P < 0.001$]. Plaque composition differed significantly across cohorts, $P < 0.0001$. The proportion of DC decreased, whereas FF and NC increased with worsening clinical risk profile (mean proportions DC: 33%, 23%, 23%; FF: 50%, 61%, 57%; and NC: 17%, 17%, 20%, respectively). Significant differences in plaque composition persisted after multivariable adjustment for age, gender, body surface area, hypertension, statin use at baseline, diabetes, smoking, family history of ischaemic heart disease, total plaque volume, and tube voltage, $P < 0.01$. Conclusion: Coronary atherosclerotic plaque volume and composition are strongly associated to clinical presentation.

[25] *Ferrieres J, De Ferrari GM, Hermans MP et al.* **Predictors of LDL-cholesterol target value attainment differ in acute and chronic coronary heart disease patients: Results from DYSIS II Europe**. European journal of preventive cardiology 2018:2047487318806359.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30335504
ABSTRACT
Background Patients with coronary heart disease (CHD) and survivors of acute coronary syndrome (ACS) are at very high risk for adverse cardiovascular events. Lowering low-density lipoprotein cholesterol (LDL-C) can reduce the risk, with effective lipid-lowering therapy (LLT) readily available; however, dyslipidemia remains prevalent throughout Europe. Design The observational Dyslipidemia International Study II (DYSIS II) aimed to identify unmet treatment needs in adult ACS and CHD patients. Data for the seven participating European countries are presented herein. Methods The study was carried out from December 2012 to November 2014.

Use of LLT and attainment of European-guideline-recommended LDL-C targets were assessed. For ACS patients, changes in lipid levels and LLT were evaluated 4 months post-hospitalization. Results Of the 4344 patients enrolled, 2946 were attending a physician visit for the assessment of stable CHD, while 1398 had been hospitalized for an ACS event. In both patient sets, mean LDL-C levels were high (89.5 and 112.5 mg/dl, respectively) and <70 mg/dl target attainment extremely poor. The mean daily statin dosage (normalized to atorvastatin potency) was 27 +/- 20 mg for CHD and 22 +/- 17 mg for ACS patients. Treatment was intensified slightly for ACS subjects after hospitalization, with the dosage reaching 35 +/- 24 mg/day. LDL-C target attainment was higher by the end of the 4-month follow up (30.9% and 41.5% for patients on LLT and without LLT at baseline, respectively; $p < 0.05$). Conclusion Elevated blood cholesterol levels are highly prevalent across Europe, with low numbers of coronary patients reaching their recommended LDL-C target. While use of LLT is widespread, there is significant scope for intensifying treatment.

[26] *Nerild HH, Christensen MB, Knop FK, Bronden A*. **Preclinical discovery and development of colesevelam for the treatment of type 2 diabetes**. Expert opinion on drug discovery 2018:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336707
ABSTRACT
INTRODUCTION: Type 2 diabetes (T2D) is a major global health challenge associated with increased cardiovascular morbidity and mortality. Intervention strategies managing multiple risk factors (hyperglycemia, hypertension and dyslipidemia) in patients with T2D can reduce the risk of cardiovascular disease by ~50%. Areas covered: Herein, the authors provide an update on the development and clinical potential of colesevelam as a glucose-lowering drug in T2D. Furthermore, they outline the pharmacokinetics, pharmacodynamics, and the clinical efficacy and safety data from the studies carried out to obtain market authorization for colesevelam. Expert opinion: Four phase III clinical trials provide evidence that colesevelam, as a monotherapy and add-on to various background glucose-lowering treatments, confers placebo-corrected reductions in HbA1c of ~5 mmol/mol. In addition, colesevelam reduces low-density lipoprotein (LDL) cholesterol and total cholesterol. Some antidiabetic agents seem superior to colesevelam in terms of clinical efficiency (HbA1c lowering), tolerability/convenience, and price. Nonetheless, colesevelam offers a clinically relevant combination of HbA1c- and LDL-lowering that in selected patients could be relevant as add-on treatment to other glucose-lowering drugs and a statin. Potential patients include those with renal impairment, and patients that are close to reaching their lipid and glycemic treatment goals but need further LDL and HbA1c reductions.

[27] *Okopien B, Buldak L, Boldys A*. **Benefits and risks of the treatment with fibrates--a comprehensive summary**. Expert Rev Clin Pharmacol 2018:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30328735
ABSTRACT
INTRODUCTION: The need to reduce residual cardiovascular risk led to the development of novel therapeutic strategies to improve patients' outcomes. The residual risk in people with atherogenic dyslipidemia, despite LDL reduction obtained mainly by statins, remains high. Fibrates in those patients lead to significant clinical improvements. Those include reduction in

the progression of atherosclerosis, which translates into decrease in cardiovascular events and improvements in microvascular diabetic complications. Furthermore, there are other clinical and biochemical benefits connected with fibrate therapy (e.g. improved insulin sensitivity). Nevertheless, similar to all effective therapeutic modalities, fibrates are associated with unfavorable effects that may lead to complications or treatment discontinuation. Here, we provide up-to-date review of benefits and potential risks associated with the therapy with fibrates. Area covered: A review of available data from clinical trials, meta-analyses and case-reports on the efficacy of fibrate treatment was performed. A specific attention was given to clinical and biochemical benefits as well as adverse events that were reported. Expert commentary: Fibrates are performing well as drugs that reduce residual risk in patients with atherogenic dyslipidemia and hypertriglyceridemia. The adverse events rate is not negligible, but definitely manageable by selection of proper target population and supervision of treated patients.

[28] *Cauvi DM, Hawisher D, Dores-Silva PR et al.* **Macrophage reprogramming by negatively charged membrane phospholipids controls infection**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201801579R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30325674
ABSTRACT
Extracellular vesicles (ECVs) are heterogeneous membrane-enclosed structures containing proteins, nucleic acids, and lipids that participate in intercellular communication by transferring their contents to recipient cells. Although most of the attention has been directed at the biologic effect of proteins and microRNA, the contribution of phospholipids present in ECVs on cellular activation has not been extensively addressed. We investigated the biologic effect of phosphatidylserine (PS) and phosphatidylcholine (PC), 2 phospholipids highly abundant in ECVs. A transcriptomic analysis revealed that approximately 4700 genes were specifically modified by exposing peritoneal macrophages to PS or PC liposomes in vivo. Among them, the expression of several chemokines and cytokines was highly upregulated by PS liposome treatment, translating into a massive neutrophil infiltration of the peritoneum capable of neutralizing a septic polymicrobial insult. Both the l and d stereoisomers of PS induced the same response, suggesting that the effect was related to the negative charge of the phospholipid head. We concluded that an increase in the internal negative charge of the cell triggers a signaling cascade activating an innate immune response capable of controlling infection.-Cauvi, D. M., Hawisher, D., Dores-Silva, P. R., Lizardo, R. E., De Maio, A. Macrophage reprogramming by negatively charged membrane phospholipids controls infection.

[29] *Li J, Li K, Gao J et al.* **Maternal exposure to an n-3 polyunsaturated fatty acid diet decreases mammary cancer risk of female offspring in adulthood**. Food & function 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30327803
ABSTRACT
Maternal exposure to dietary factors during pregnancy influences the risk of many adult-onset diseases in the later life of offspring. Here, we investigated the effects of maternal n-3 polyunsaturated fatty acid (PUFA) diet on breast cancer risk of female offspring. Pregnant C57BL/6J mice were fed a normal diet (control group), or a high-fat diet rich in safflower oil

(SO), fish oil (FO) or flaxseed oil (FSO) (n = 10) throughout gestation and lactation. Their female offspring were fed an AIN-93G diet from weaning. Tumor incidences in offspring induced by 7,12-dimethylbenz[alpha]anthracene (DMBA) were higher in high-fat groups than in the control group, and were lower in FO and FSO groups than in the SO group. The plasma concentrations of 17beta-estradiol (E2), in both pregnant dams and offspring, were significantly lower in FO and FSO groups compared with the SO group. The FO and FSO offspring showed delayed puberty onset, and their mammary glands contained decreased numbers of epithelial terminal end buds (TEBs, targets for malignant transformation) compared with SO offspring. Reduced cell proliferation and increased apoptosis in FO and FSO offspring were observed compared with SO offspring. In line with these changes, maternal exposure to FO promoted the expression of long noncoding RNA (lncRNA) in p53 and apoptosis signaling pathways and inhibited that in NF-kappaB and Jak-STAT signaling pathways, while FSO promoted the expression of lncRNA in p53 signaling pathways and inhibited that in NF-kappaB, Jak-STAT and MAPK signaling pathways. In conclusion, maternal exposure to a high-fat diet rich in n-3 PUFAs, both marine- and plant-based, has a protective effect on mammary tumor risk of female offspring in later life.

[30] *Zhang YG, Xia Y, Lu R, Sun J*. **Inflammation and intestinal leakiness in older HIV+ individuals with fish oil treatment**. Genes & diseases 2018; 5:220-225.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30320186
ABSTRACT
Fish oil is a natural product that has shown efficacy for managing inflammatory conditions with few side effects. There is emerging evidence that crosstalks between gut epithelial cells and immune cells contribute to chronic infectious diseases. HIV-infected (HIV+) older adults show age-related co-morbidities at a younger age than their uninfected counterparts. Persistent inflammation related to the chronic viral infection and its sequelae is thought to contribute to this disparity. However, little is known about whether fish oil reduces intestinal inflammation in HIV + patients. We measure inflammation and gut barrier function in HIV + older adults (median age = 52, N = 33), following 12 weeks of fish oil supplementation (a total daily dose of 1.6 g of omega-3 fatty acids). We showed a reduction in inflammation and gut permeability as measured by CD14, inflammatory cytokines, lipopolysaccharide, and lipopolysaccharide binding protein. The results indicate that older HIV + adults may benefit from a diet supplemented with the omega-3 fatty acids found in fish oil.

[31] *Nelson CP, Erridge C*. **Are toll-like receptors potential drug targets for atherosclerosis? Evidence from genetic studies to date**. Immunogenetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30327825
ABSTRACT
Low-density lipoprotein cholesterol lowering, most notably via statin therapy, has successfully reduced the burden of coronary artery disease (CAD) in recent decades. However, the residual risk remaining even after aggressive lipid lowering has renewed interest in alternative targets. Anti-inflammatory drugs are thought to have much potential in this context, but side effects associated with long-term use of conventional anti-inflammatories, such as NSAIDs and glucocorticoids, preclude their use as preventive agents for CAD. Evidence from epidemiological

studies and murine models of atherosclerosis suggests that toll-like receptors (TLRs) may have utility as targets for more focused anti-inflammatories, but it remains unclear if this pathway is causally related to CAD in man. Here, we review recent insight into this question gained from genetic studies of cardiovascular risk and innate immune function, focussing on the potential of Mendelian randomisation approaches based on intracellular-signalling pathways to identify and prioritise targets for drug development.

[32] *Wang XL, Sun W, Zhou YL, Li L*. **Rosuvastatin stabilizes atherosclerotic plaques by reducing CD40L overexpression-induced downregulation of P4Halpha1 in ApoE(-/-) mice**. The international journal of biochemistry & cell biology 2018; 105:70-77.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336263
ABSTRACT
Background Cluster of differentiation 40 ligand (CD40L) and rosuvastatin (RSV) affect atherosclerotic plaque stability, but little is known about their roles in extracellular matrix (ECM) production. We investigated the effects of CD40L and RSV on pre-existing advanced plaques. Methods and results Pre-existing advanced plaques were induced in apolipoprotein E-knockout (ApoE(-/-)) mice by the surgical placement of carotid constrictive silastic collars. Two weeks after surgery, mice were divided into the following treatment groups: control, empty adenovirus, CD40L adenovirus, CD40L adenovirus + RSV, and RSV. Mice received adenovirus via two tail-vein injections (2 x 10(9) pfu each) and/or RSV via intragastric administration (5 mg/kg; daily for 4 weeks). Mice in the CD40L adenovirus group exhibited increased plaque disruption rates, increased relative plaque macrophage and lipid content, reduced plaque collagen content, and increased local inflammation compared to the other treatment groups, but no significant differences in plaque area were observed among the groups. Notably, in the atherosclerotic plaques of the CD40L adenovirus group, both the mRNA and protein expression of prolyl-4-hydroxylase alpha 1 (P4Halpha1) was significantly decreased, leading to a consequent decrease in the protein expression of collagen types I and III. Treatment with RSV decreased the serum levels of CD40L in a lipid-independent fashion and attenuated the effects of CD40L overexpression, particularly with respect to P4Halpha1 downregulation. Conclusions CD40L destabilized advanced plaques in the carotid arteries of ApoE(-/-) mice, in part by decreasing P4Halpha1 expression, and consequently collagen expression. These destabilizing effects were attenuated by RSV.

[33] *Zhang H, Lu X, Liu Z, Du K*. **Rosuvastatin reduces the pro-inflammatory effects of adriamycin on the expression of HMGB1 and RAGE in rats**. International journal of molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30320373
ABSTRACT
Rosuvastatin has cardiac protective effects through its antiinflammatory effects. The nuclear protein highmobility group box 1 (HMGB1) can activate inflammatory pathways when released from dying cells. The present study aimed to investigate the effects of rosuvastatin in adriamycin (ADR)treated rats. Adult male rats were randomized to three groups: i) Control group, ii) ADR group, and iii) ADR+rosuvastatin group. Serum biochemical indices were measured using an enzymelinked immunosorbent assay. Cardiac function was assessed by

echocardiography. The expression of HMGB1 and receptors for advanced glycation end products (RAGE) were assessed by reverse transcriptionquantitative polymerase chain reaction analysis, western blot analysis, and immunohistochemistry. Cytokines were measured using flow cytometry. Rosuvastatin improved the biochemical indices and cardiac morphology and alleviated the pathological lesions. In the ADR+rosuvastatin group, the mRNA and protein levels of HMGB1 and RAGE in the myocardium were significantly lower compared with those in the ADR group (both P<0.05). The results showed that rosuvastatin significantly reduced the levels of HMGB1 and RAGE in the myocardium of the ADRtreated rats. These results suggest that the protective effects of rosuvastatin may be associated with attenuation of the HMGB1/RAGEmediated inflammatory response in ADRtreated rats. Despite this protective effect of rosuvastatin in the present study, it did not improve cardiac function in terms of the diastolic left ventricular internal dimension, systolic left ventricular internal dimension, left ventricular ejection fraction and left ventricular fractional shortening; this may be due the observation duration being insufficient.

[34] *Lohoff FW*. **Lipid-lowering drug effects beyond the cardiovascular system: relevance for neuropsychiatric disorders**. The international journal of neuropsychopharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30329063
ABSTRACT

[35] *Nicholls SJ, Puri R, Anderson T et al.* **Effect of Evolocumab on Coronary Plaque Composition**. Journal of the American College of Cardiology 2018; 72:2012-2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336824
ABSTRACT
BACKGROUND: Incremental low-density lipoprotein (LDL) cholesterol lowering with the proprotein convertase subtilisin kexin type 9 inhibitor evolocumab regresses coronary atherosclerosis in statin-treated patients. OBJECTIVES: The purpose of this study was to evaluate the effect of adding evolocumab to statin therapy on coronary plaque composition. METHODS: A total of 968 statin-treated coronary artery disease patients underwent serial coronary intravascular ultrasound imaging at baseline and following 76 weeks of treatment with placebo or evolocumab 420 mg monthly. Plaque composition changes were determined in 331 patients with evaluable radiofrequency analysis of the ultrasound backscatter signal. RESULTS: Compared with statin monotherapy, evolocumab further reduced LDL cholesterol (33.5 mg/dl vs. 89.9 mg/dl; p < 0.0001) and induced regression of percent atheroma volume (-1.2% vs. +0.17%; p < 0.0001) and total atheroma volume (-3.6 mm(3) vs. -0.8 mm(3); p = 0.04). No difference was observed between the evolocumab and placebo groups in changes in calcium (1.0 +/- 0.3 mm(3) vs. 0.6 +/- 0.3 mm(3); p = 0.49), fibrous (-3.0 +/- 0.6 mm(3) vs. -2.4 +/- 0.6 mm(3); p = 0.49), fibrofatty (-5.0 +/- 1.0 mm(3) vs. -3.0 +/- 1.0 mm(3); p = 0.49), and necrotic (-0.6 +/- 0.5 mm(3) vs. -0.1 +/- 0.5 mm(3); p = 0.49) volumes. An inverse correlation was observed between changes in LDL cholesterol and plaque calcification (r = -0.15; p < 0.001). CONCLUSIONS: The addition of evolocumab to a statin did not produce differential changes in plaque composition compared with statin monotherapy. This suggests that evaluation of plaque morphology using virtual histology imaging may provide no incremental information about the plaque effects of evolocumab beyond measurement of plaque burden. (GLobal

Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound [GLAGOV]; NCT01813422).

[36] *Stone GW, Mintz GS, Virmani R*. **Vulnerable Plaques, Vulnerable Patients, and Intravascular Imaging**. Journal of the American College of Cardiology 2018; 72:2022-2026.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336825
ABSTRACT

[37] *Wander GS, Hukkeri MYK, Yalagudri S et al.* **Rosuvastatin: Role in Secondary Prevention of Cardiovascular Disease**. The Journal of the Association of Physicians of India 2018; 66:65-69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30341873
ABSTRACT
Cardiovascular (CV) diseases are a major cause of premature death and disability. Non-communicable diseases (NCD) are responsible for 52% of mortality amongst Indians, of these CV diseases are responsible for 66% of NCD mortality in India. We not only need widespread primary preventive strategy but also need effective secondary prevention protocols to reduce this. Secondary prevention in patients who already had myocardial infarction (MI) or revascularization is of utmost importance to reduce mortality, cardiac events and improve quality of life. Lifestyle changes and medical therapy have a very important role in secondary prevention of CVD. Optimal control of hypertension, diabetes mellitus and dyslipidemia plays a critical role in secondary prevention. Statins are one of the most commonly used drugs in secondary prevention as a part of medical therapy. Effective LDL reduction, more patients achieving LDL goals, reduction in intima thickness, improvement in endothelial dysfunction, reduction in inflammatory markers are considered to be surrogate markers of reduced risk with statins. Rosuvastatin is one of the two most commonly used statins. It is a potent, effective and safe HMG-COA reductase inhibitor. Data related to secondary prevention is limited with rosuvastatin. Most of the clinical evidences with rosuvastatin have shown more effective LDL reduction than other statins. More number of patients achieve LDL goals and reduction in intima thickness. This article attempts to explore data on role of rosuvastatin for secondary prevention.

[38] *Kitagawa K, Hosomi N, Nagai Y et al.* **Cumulative Effects of LDL Cholesterol and CRP Levels on Recurrent Stroke and TIA**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318492
ABSTRACT
AIMS: To investigate the relative contribution of on-treatment low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) to the risk of recurrent stroke and transient ischemic attack (TIA) in patients with history of ischemic stroke. METHODS: A total of 1095 patients with non-cardioembolic ischemic stroke were randomized into two groups: control and patients receiving 10 mg of pravastatin per day. After excluding 18 patients who did not have baseline CRP data, the effects of LDL cholesterol and CRP on recurrent stroke and TIA were prospectively assessed in 1077 patients. RESULTS: During the follow-up of 4.9+/-1.4 years, there were 131 recurrent stroke or TIA cases. Patients with ontreatment LDL cholesterol 120 mg/dL showed 29% reduction in recurrent stroke and TIA than those with LDL cholesterol >/= 120 mg/dL

(event rate 2.20 vs. 3.11 per 100 person-years, hazard ratio [HR] 0.71, 95% confidence interval (CI) 0.50-0.99, p0.048). Patients with CRP 1 mg/L had 32% reduction compared with that of patients with CRP >/= 1 mg/L (event rate 2.26 vs. 3.40 per 100 person-years; HR 0.68, 95% CI 0.48-0.96, p0.031). Although LDL cholesterol and CRP levels were not correlated in individual patients, those who achieved both LDL cholesterol 120 mg/dL and CRP 1 mg/L showed 51% reduction compared with that of patients with LDL cholesterol >/= 120 mg/dL and CRP >/= 1 mg/L (event rate 2.02 vs. 4.19 per 100 person-years; HR 0.49, 95% CI 0.31-0.79). CONCLUSIONS: The control of both LDL cholesterol and CRP levels appears to be effective for preventing recurrent stroke and TIA in patients with non-cardiogenic ischemic stroke.

[39] *Cao S, Xu P, Yan J et al.* **Berberrubine and its analog, hydroxypropyl-berberrubine, regulate LDLR and PCSK9 expression via the ERK signal pathway to exert cholesterol-lowering effects in human hepatoma HepG2 cells**. Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30335889
ABSTRACT
Berberine (BBR), the major isoquinoline alkaloid in Chinese herb Rhizoma coptidis, has significant lipid-lowering effect by upregulating hepatic low-density lipoprotein receptor (LDLR) expression. In a previous study, we have indicated that berberrubine (M3), a major metabolite of BBR in vivo, displays the most potential hypolipidemic effects via upregulating LDLR expression in human hepatoma (HepG2) cells compared with BBR and 3 other metabolites. Accordingly, 9 M3 analogs (A1-A9) were modified at the C9 position. We aimed to find a new promising agent by evaluating the cholesterol-lowering effect and clarifying the related molecular mechanism. In the current study, the cellular cholesterol content was assayed with a commercial cholesterol assay kit. Real-time polymerase chain reaction and Western blot assay were used to explore the molecular mechanism of M3 and its analogs on the hypolipidemic effect. Among M3 and its analogs, hydroxypropyl-berberrubine (A8) exhibited the highest potential effects on the upregulation of LDLR expression, which was accompanied by a steady decline of proprotein convertase subtilisin/kexin type 9 (PCSK9) messenger RNA and protein levels. Furthermore, inhibition of extracellular signal-regulated kinase (ERK) activity with PD98059 prevented the upregulation of LDLR and downregulation of PCSK9 induced by A8. The current study revealed that M3 and its structurally modified analog, A8, could regulate hepatic LDLR and PCSK9 expression to exert lipid-lowering effects via the ERK signal pathway, while A8 showed a stronger effect and might be a promising drug candidate against hyperlipidemia.

[40] *Elia E, Montecucco F, Portincasa P et al.* **Update on pathological platelet activation in coronary thrombosis**. Journal of cellular physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30317596
ABSTRACT
Although coronary thrombosis (CT) is integral to cardiovascular outcomes, the underlying pathophysiological mechanisms remain unclear. CT may occur in case of atherosclerotic plaque erosion/rupture, or even after stenting implantation. Platelets (PLT) activation is the keystone of atherothrombosis and depends on many dysregulated elements, including endothelial dysfunction, oxidized lipoproteins, and immune response. Besides the classical view of PLT as an effector of hemostatic response, a new repertoire of PLT activities is emerging. PLT lipidome

oxidation is a self-maintaining process which promotes PLT reactivity, coagulation cascade, and inflammatory cell activation. PLT-innate immune cell interaction is also sustained by neutrophil extracellular traps and NLRP3 inflammasome pathways. Other noteworthy emerging mechanisms are implicated in the crosstalk between PLT and surrounding cells. Especially, microvesicles (MVs) released from PLT may extend their signaling network far beyond the classical cell-cell interactions. Moreover, the recognition of noncoding RNA in PLT MVs introduce another layer of complexity in terms of intercellular signaling by a direct regulation of messenger RNA profile and gene expression in the recipient cells. The aim of this narrative review is to update the recent advance in CT and intracoronary stent thrombosis, including causal factors and potential translation of experimental evidence into the clinical setting.

[41] *Blom DJ, O'Dea L, Digenio A et al.* **Characterizing familial chylomicronemia syndrome: Baseline data of the APPROACH study**. Journal of clinical lipidology 2018; 12:1234-1243.e1235.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318066

ABSTRACT

BACKGROUND: Familial chylomicronemia syndrome (FCS) is a rare metabolic disorder caused by mutations in lipoprotein lipase (LPL) or genes required for LPL functionality and is characterized by hyperchylomicronemia that results in recurrent episodes of acute pancreatitis. Owing to the rarity of FCS, there are few case series describing the phenotypic variability in FCS patients in detail. OBJECTIVE: To provide baseline characteristics in the largest study population to date of patients with FCS. METHODS: We analyzed baseline demographic and clinical characteristics of adult FCS patients in the phase 3 APPROACH study of volanesorsen sodium (antisense inhibitor of apolipoprotein C-III). RESULTS: Sixty-six patients were included in the analysis. Mean (SD) age was 46 (13) years; and mean body mass index was 24.9 (5.7) kg/m(2). We identified causal mutations in 79% (52) of patients, with LPL mutations accounting for 62% (41) of cases. Median age at diagnosis was 24 years, 54% were females, and 81% were Caucasian. All patients followed a low-fat diet, 43% received fibrates, 27% fish oils, and 21% statins. Median fasting triglyceride levels (P25, P75) were 1985 (1179, 3047 mg/dL). Overall, 76% of patients reported >/=1 lifetime episode of acute pancreatitis; 23 patients reported a total of 53 pancreatitis events in the 5 years before enrollment. CONCLUSIONS: Our data emphasize the severe hypertriglyceridemia characteristic of FCS patients despite restrictive low-fat diets and frequent use of existing hypolipemic therapies. Acute pancreatitis and recurrent acute pancreatitis are frequent complications of FCS. Diagnosis at an older age suggests likely underdiagnosis and underappreciation of this rare disorder.

[42] *Boffa MB, Stranges S, Klar N et al.* **Lipoprotein(a) and secondary prevention of atherothrombotic events: A critical appraisal**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30316749

ABSTRACT

Elevated plasma concentrations of lipoprotein(a) [Lp(a)] are an independent, and possibly causal, risk factor for atherothrombotic diseases including coronary heart disease. The principal evidence base for this comes from large population studies focusing on first atherothrombotic events. However, inconsistent findings have been reported from studies investigating the impact of elevated Lp(a) on atherothrombotic events in subjects with preexisting cardiovascular

disease. This question is very important because the secondary prevention population is recommended for Lp(a) screening by some guidelines and could be an important target group for Lp(a)-lowering therapies that are currently on the horizon. In this review, we survey the secondary prevention literature as it relates to Lp(a) and identify some possible confounding factors that may underlie the inconsistent findings, such as index event bias.

[43] *Gaudet D, Langslet G, Gidding SS et al.* **Efficacy, safety, and tolerability of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia: Rationale and design of the HAUSER-RCT study**. Journal of clinical lipidology 2018; 12:1199-1207.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318065

ABSTRACT

BACKGROUND: Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, is safe and effective in reducing low-density lipoprotein cholesterol in adults with familial hypercholesterolemia. A dedicated study, HAUSER-RCT, is being conducted to examine the efficacy and safety of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia (HeFH). OBJECTIVE: To present the rationale and design of the HAUSER-RCT study. METHODS: The HAUSER-RCT study is a double-blind, randomized, multicenter, placebo-controlled study designed to characterize the efficacy, safety, and tolerability of evolocumab treatment as an add-on to diet and lipid-lowering therapy, including a stable, optimized dose of statin, in pediatric patients aged 10 to 17 years with HeFH. Approximately, 150 patients will be randomized in a 2:1 ratio to receive 24 weeks of monthly evolocumab or placebo. The study will include approximately 51 sites located in North America, South America, Europe, South Africa, Australia, and New Zealand. The primary efficacy endpoint is the percent change in low-density lipoprotein cholesterol from baseline to week 24. A key secondary efficacy endpoint is the percent change in other lipid parameters from baseline to week 24. Other assessments include Tanner staging, carotid intima-media thickness, and cognitive tests. At the end of the study, consenting patients can participate in an 18-month open-label extension study (HAUSER-OLE). RESULTS: The study is ongoing and the results will be communicated at the end of the study. CONCLUSIONS: The HAUSER-RCT study, the largest randomized, placebo-controlled study with proprotein convertase subtilisin/kexin type 9 inhibitors being conducted in the pediatric HeFH population, aims to provide efficacy, safety, and tolerability data of evolocumab as an add-on therapy in these patients.

[44] *Mannarino MR, Sahebkar A, Bianconi V et al.* **PCSK9 and neurocognitive function: Should it be still an issue after FOURIER and EBBINGHAUS results?** Journal of clinical lipidology 2018; 12:1123-1132.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318062

ABSTRACT

The serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) modulates the levels of low-density lipoprotein cholesterol and cardiovascular risk. Potential risks of adverse neurological effects of intensive lipid-lowering treatment have been hypothesized, as cholesterol is a component of the central nervous system. Moreover, several observations suggest that PCSK9 might play a role in neurogenesis, neuronal migration and apoptosis. In rodents, increased expression of PCSK9 has been detected in specific areas of the central

nervous system during embryonic development; also, PCSK9 modulates low-density lipoprotein receptor levels in the ischemic brain areas. Despite a putative participation of PCSK9 in nervous system physiology, the absence of PCSK9 in knockout mice or in humans with loss-of-function mutations of PCSK9 gene has not been linked to neurological alterations. In recent years, some concerns have been raised about the potential neurological side effects of cholesterol-lowering treatments and, more specifically of PCSK9 inhibitors. In this review, the evidence regarding the function of PCSK9 in neuron differentiation, apoptosis, and migration and in nervous system development and latest clinical trials evaluating the effects of PCSK9 inhibitors on neurocognitive function will be described.

[45] *Mirzaee S, Thein PM, Nogic J et al.* **The effect of combined ezetimibe and statin therapy versus statin therapy alone on coronary plaque volume assessed by intravascular ultrasound: A systematic review and meta-analysis**. Journal of clinical lipidology 2018; 12:1133-1140.e1115.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318063
ABSTRACT
BACKGROUND: Current guidelines recommend an intensive lipid-lowering therapy to achieve the low-density lipoprotein cholesterol (LDL-C) target in patients with high risk of cardiovascular disease. Former studies suggested adding ezetimibe to statin therapy in the above setting may promote plaque changes; however, this effect has not been consistently reported. METHODS: Electronic searches were performed in MEDLINE, EMBASE, and Cochrane library on November 30, 2017 to identify prospective trials assessing the effects of combined ezetimibe and statin therapy versus statin therapy alone on atheroma volume using intravascular ultrasound. The effect size between treatment groups within individual studies was assessed by weighted mean difference (MD) using a random-effects model. RESULTS: Eight studies were obtained for systematic review and 6 of them compromising total of 583 subjects that meet the criteria were meta-analyzed. There was a significant reduction from baseline to follow-up in total atheroma volume with an MD of -3.71 mm(3) (95% confidence interval: -5.98 to -1.44, P < .001), whereas analysis for percent atheroma volume demonstrated weighted MD of - 0.77% (-1.68 to 0.14, P = .10). A substantial decrease in LDL-C was observed with MD -16.75 mg/dL (-20.89 to -12.60, P < .00001). CONCLUSION: The addition of ezetimibe to statin therapy is effective in reducing total atheroma volume assessed by intravascular ultrasound and also resulted in effective reduction of plasma LDL-C levels.

[46] *Saeed A, Virani SS, Jones PH et al.* **Case reports of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition nonresponse**. Journal of clinical lipidology 2018; 12:1141-1145.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318064
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a novel class of monoclonal antibodies, reduces low-density lipoprotein cholesterol levels and improves cardiovascular outcomes. Given the short time frame, these agents have been available for use; reports of nonresponse to the PCSK9 inhibitor therapy are scarce in literature. We describe 2 cases with substantially lesser than expected low-density lipoprotein cholesterol lowering on PCSK9 therapy. Nonresponse to PCSK9 inhibition was attributed to autosomal recessive

hypercholesterolemia (secondary to low-density lipoprotein receptor adaptor protein 1 mutation) and plasmapheresis after PCSK9 inhibitor drug injections. Additional PCSK9 inhibitor nonresponders are likely to emerge as the use of these agents increases overtime.

[47] *Aarestrup J, Jess T, Kobylecki CJ et al.* **Cardiovascular risk profile among patients with inflammatory bowel disease: a population-based study of >100,000 individuals**. Journal of Crohn's & colitis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30321330
ABSTRACT
Background and Aims: Patients with inflammatory bowel disease have increased risks of cardiovascular diseases but the role of traditional and non-traditional cardiovascular risk factors remains unclear. We investigated if the cardiovascular risk profile differs between patients with inflammatory bowel disease and individuals in the general population. Methods: We included a population of 108,789 participants from The Copenhagen General Population Study of individuals of Danish descent aged 20-100 years. The population included 1,203 individuals with prevalent inflammatory bowel disease (347 with Crohn's disease and 856 with ulcerative colitis). The cardiovascular risk profile was assessed by traditional risk factors (plasma lipids and glucose, body composition measures, and blood pressure) and non-traditional risk factors (inflammatory markers and biomarkers of liver and pancreas function). Results: Even though patients with inflammatory bowel disease more frequently are diagnosed with cardiovascular diseases, traditional cardiovascular risk factors were not increased. Conversely, patients with inflammatory bowel disease had slightly lower plasma levels of total cholesterol and low-density lipoprotein cholesterol. Levels of inflammatory markers, particularly high-sensitivity C-reactive protein, were higher in individuals with versus without a diagnosis of inflammatory bowel disease, when assessed at a random point in time during the disease course. Conclusions: The increased risk of cardiovascular diseases in patients with inflammatory bowel disease may be linked to chronic systemic inflammation rather than to traditional cardiovascular risk factors. Further studies need to examine whether cardiovascular-preventive strategies should focus on optimizing management of inflammation in patients with inflammatory bowel disease rather than focusing on traditional cardiovascular risk factors.

[48] *Gentile S, Strollo F, Viazzi F et al.* **Five-Year Predictors of Insulin Initiation in People with Type 2 Diabetes under Real-Life Conditions**. Journal of diabetes research 2018; 2018:7153087.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30327785
ABSTRACT
We performed a real-life analysis of clinical and laboratory parameters, in orally treated T2DM patients aiming at identifying predictors of insulin treatment initiation. Overall, 366955 patients (55.8% males, age 65 +/- 11 years, diabetes duration 7 +/- 8 years) were followed up between 2004 and 2011. Each patient was analyzed step-by-step until either eventually starting insulin treatment or getting to the end of the follow-up period. Patients switching to insulin showed a worse global risk profile, longer disease duration (10 +/- 9 years vs. 6 +/- 7 years, respectively; $p < 0.001$), higher HbA1c (8.0 +/- 1.6% vs. 7.2 +/- 1.5%, respectively; $p < 0.001$), higher triglycerides, a greater prevalence of arterial hypertension, antihypertensive, lipid-lowering and aspirin treatment, a higher rate of nonproliferative/proliferative retinopathy, and a nearly 4

times lower prevalence of the "diet alone." They also showed a higher prevalence of subjects with eGFR < 60 ml/min/1.73 m(2) (24.0% vs. 16.2%, respectively; p < 0.001). Multivariate analysis identified diabetes duration, HbA1c, triglyceride and low HDL-C values, presence of retinopathy or renal dysfunction, and sulphonylurea utilization (the risk being approximately 3 times greater in the latter case) as independent predictors of insulin treatment initiation. LDL-C, lipid-lowering treatment, and overweight/obese seem to be protective. Results of tree analysis showed that patients on sulphonylurea, with high HbA1c, eGFR below 50 ml/min/1.73 m(2), and at least 5-year disease duration, are at very high risk to start insulin treatment. We have to stick to this real-life picture, of course, until enough data are collected on patients treated with innovative medications which are expected to improve beta cell survival and further delay treatment-related insulin requirement.

[49] *Li H, Li J, Jiang X et al.* **Melatonin enhances atherosclerotic plaque stability by inducing prolyl-4-hydroxylase alpha1 expression**. Journal of hypertension 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30335670
ABSTRACT
OBJECTIVE: Melatonin, an endogenous neurohormone secreted predominately by the pineal gland, has a variety of physiological functions. However, its protective role in atherosclerosis is not clear. In this study, we sought to investigate the potential effects of melatonin in modulating atherosclerotic plaque stability in apolipoprotein E knockout (ApoE) mice. METHOD AND RESULTS: Smooth muscle cells were treated with melatonin, which significantly increased mRNA and protein levels of a key intracellular enzyme essential for collagen maturation and secretion, prolyl-4-hydroxylase alpha1 (P4Halpha1). Mechanistically, melatonin increased Akt phosphorylation and transcriptional activation of specificity protein 1 (Sp1), which bound with the P4Halpha1 promoter and then induced P4Halpha1 expression. Pretreatment with either Akt inhibitor LY294002 or Sp1 inhibitor mithramycin A (MTM) could inhibit melatonin-induced P4Halpha1 expression. Finally, atherosclerotic lesions were induced by placing a perivascular collar on the right common carotid artery of ApoE mice, which were received with or without different doses of melatonin or MTM. High-dose melatonin enhanced atherosclerotic plaque stability in ApoE mice in vivo by inducing the expression of P4Halpha1, which was reversed by MTM. CONCLUSION: We propose that melatonin supplementation may provide a novel and promising approach to atherosclerosis treatment.

[50] *Silbernagel G, Steiner LK, Hollstein T et al.* **The Interrelations between PCSK9-Metabolism and Cholesterol Synthesis and Absorption**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30323110
ABSTRACT
Very few studies have investigated the interrelations between PCSK9 metabolism, cholesterol synthesis, and cholesterol absorption. We aimed to address this issue in a large clinical trial of 245 patients with hypercholesterolemia. Serum lipids, PCSK9, lathosterol (cholesterol synthesis marker), campesterol, and sitosterol (cholesterol absorption markers) were measured before and 4-8 weeks after the start of treatment with PCSK9-antibodies (alirocumab or evolocumab). The patients had mean (standard error) LDL-cholesterol and PCSK9 concentrations of 3.87 (0.10) mmol/l and 356 (17) ng/ml, respectively. 84 patients received no lipid-lowering

pretreatment, 26 ezetimibe, 38 statins, and 97 ezetimibe + statins. Circulating PCSK9 increased in parallel with the potency of lipid-lowering pretreatment with circulating PCSK9 being highest in the ezetimibe + statin group (p<0.001). Treatment with PCSK9-antibodies strongly decreased LDL-cholesterol, lathosterol, campesterol, and sitosterol (all p<0.001) but did hardly affect non-cholesterol sterol to cholesterol ratios. Lipid-lowering pretreatment was not associated with the effects of PCSK9-antibodies on non-cholesterol sterols (all p>0.05). Summing up, circulating PCSK9 is increased by cholesterol synthesis and absorption inhibitors. Increased PCSK9 expression may partly explain the strong reductions of LDL-cholesterol achieved with PCSK9-antibodies after such pretreatments. On the other hand, treatment with PCSK9-antibodies does not significantly change the balance between cholesterol synthesis and absorption.

[51] *Bos MM, Noordam R, van den Berg R et al.* **Associations of sleep duration and quality with serum and hepatic lipids: The Netherlands Epidemiology of Obesity Study**. Journal of sleep research 2018:e12776.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30324729
ABSTRACT
Short and long sleep duration and poor sleep quality may affect serum and hepatic lipid content, but available evidence is inconsistent. Therefore, we aimed to investigate the associations of sleep duration and quality with serum and hepatic lipid content in a large population-based cohort of middle-aged individuals. The present cross-sectional study was embedded in the Netherlands Epidemiology of Obesity (NEO) study and consisted of 4260 participants (mean age, 55 years; proportion men, 46%) not using lipid-lowering agents. Self-reported sleep duration and quality were assessed using the Pittsburgh Sleep Quality Index questionnaire (PSQI). Outcomes of this study were fasting lipid profile (total cholesterol, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol and triglycerides), postprandial triglyceride (response) levels, and hepatic triglyceride content (HTGC) as measured with magnetic resonance spectroscopy. We performed multivariable linear regression analyses, adjusted for confounders and additionally for measures that link to adiposity (e.g. body mass index [BMI] and sleep apnea). We observed that relative to the group with median sleep duration (approximately 7.0 hr of sleep), the group with shortest sleep (approximately 5.0 hr of sleep) had 1.5-fold higher HTGC (95% confidence interval [CI]: 1.0-2.2). The group with PSQI score >/= 10 had a 1.1-fold (95% CI: 1.0-1.2) higher serum triglyceride level compared with the group with PSQI </= 5. However, these associations disappeared after adjustment for BMI and sleep apnea. Therefore, we concluded that previously observed associations of shorter sleep duration and poorer sleep quality with an adverse lipid profile, may be explained by BMI and sleep apnea, rather than by a direct effect of sleep on the lipid profile.

[52] *Slomka T, Drelich-Zbroja A, Jarzabek M, Szczerbo-Trojanowska M*. **Intima-media complex thickness and carotid atherosclerotic plaque formation in Lublin's population in the context of selected comorbidities**. Journal of ultrasonography 2018; 18:133-139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30335922
ABSTRACT

INTRODUCTION: Atherosclerosis (arteriosclerosis) is a chronic arterial disease of the arteries with chronic inflammatory. The pathology of atherosclerosis is complex, and the atherosclerotic process is multi-factorial, not fully understood. Risk factors of atherosclerotic lesions may include: lipid disorders, hypertension or diabetes. One of the diagnostic methods of discovering atherosclerosis covers the assessment of the intima-media complex thickness by Doppler ultrasonography. AIM: The aim of this report was an evaluation of the relationships between intima-media complex thickness in the right and left carotid arteries and the occurrence of atheromatous plaque in the Lublin population with respect to three possible concomitant medical conditions, mentioned above. MATERIAL AND METHODS: A group of 121 subjects was included into the study, all of the participants being residential inhabitants of the Lublin Voivodship. All the participating patients were requested to fill in a questionnaire. After that, the patients were submitted to Doppler sonography concentrated on intima-media complex thickness evaluation. The occurrence of atheromatous plaque was also assessed in obtained sonographic images. RESULTS: There were statistically significant differences for the intima-media complex thickness and for the atheromatous plaque according to all of the reported diseases: hypocholesterolaemia, hypertension and diabetes. Conclusions: The present study confirms that there is a relationship between the thickness of the intima-media complex in the right and left carotid arteries as well as the occurrence of the atherosclerotic plaque regarding the coexistence of specific disease entities in the subjects of the Lublin population.

[53] *Jackevicius CA, Ghaznavi Z, Lu L, Warner AL*. **Safety of Alpha Adrenergic Receptor Antagonists in Heart Failure**. JACC. Heart failure 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30316936
ABSTRACT
OBJECTIVES: This study evaluated whether alpha-blocker (AB) use following an admission for heart failure (HF) was associated with an increased risk of HF readmission or death. BACKGROUND: ABs, found to increase the risk of HF in the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) trial, are commonly used for prostatic hypertrophy, including in those with or at risk for HF. METHODS: This propensity score-matched cohort study included patients discharged from a Veterans Affairs hospital between January 2002 and September 2015 with a primary diagnosis of HF and ascertained AB use at discharge. Cox proportional hazards models were constructed to compare time to first HF readmission and death at 2 years between groups. Secondary analyses assessed effects by AB dose and type and by beta-blocker (BB) use. RESULTS: Of 169,911 HF patients, 47,638 (28%) were prescribed an AB. Propensity score matching resulted in 35,713 matched pairs. In the propensity score-matched cohort, AB use was associated with fewer HF readmissions (39.8% vs. 41.7% at 2 years; hazard ratio: 0.95; 95% confidence interval [CI]: 0.92 to 0.97; $p < 0.0001$) and death (42.8% vs. 46.5%, hazard ratio: 0.93; 95% CI: 0.91 to 0.94; $p < 0.0001$). Nonselective ABs had fewer deaths and HF readmissions ($p < 0.0001$), while higher AB doses reduced mortality ($p < 0.0001$). AB treatment was associated with reduced deaths in both BB-treated and untreated patients, with no increase in HF. CONCLUSIONS: Treatment of HF patients with an AB was not associated with a higher but instead with a lower rate of HF readmission and death. Higher doses and nonselective ABs were also associated with lower mortality, regardless of BB use.

ABs may be used safely in HF patients where clinically indicated. The finding of improved outcomes with ABs may warrant further study.

[54] *Lotta LA, Stewart ID, Sharp SJ et al.* **Association of Genetically Enhanced Lipoprotein Lipase-Mediated Lipolysis and Low-Density Lipoprotein Cholesterol-Lowering Alleles With Risk of Coronary Disease and Type 2 Diabetes**. JAMA cardiology 2018; 3:957-966.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30326043

ABSTRACT
Importance: Pharmacological enhancers of lipoprotein lipase (LPL) are in preclinical or early clinical development for cardiovascular prevention. Studying whether these agents will reduce cardiovascular events or diabetes risk when added to existing lipid-lowering drugs would require large outcome trials. Human genetics studies can help prioritize or deprioritize these resource-demanding endeavors. Objective: To investigate the independent and combined associations of genetically determined differences in LPL-mediated lipolysis and low-density lipoprotein cholesterol (LDL-C) metabolism with risk of coronary disease and diabetes. Design, Setting, and Participants: In this genetic association study, individual-level genetic data from 392220 participants from 2 population-based cohort studies and 1 case-cohort study conducted in Europe were included. Data were collected from January 1991 to July 2018, and data were analyzed from July 2014 to July 2018. Exposures: Six conditionally independent triglyceride-lowering alleles in LPL, the p.Glu40Lys variant in ANGPTL4, rare loss-of-function variants in ANGPTL3, and LDL-C-lowering polymorphisms at 58 independent genomic regions, including HMGCR, NPC1L1, and PCSK9. Main Outcomes and Measures: Odds ratio for coronary artery disease and type 2 diabetes. Results: Of the 392220 participants included, 211915 (54.0%) were female, and the mean (SD) age was 57 (8) years. Triglyceride-lowering alleles in LPL were associated with protection from coronary disease (approximately 40% lower odds per SD of genetically lower triglycerides) and type 2 diabetes (approximately 30% lower odds) in people above or below the median of the population distribution of LDL-C-lowering alleles at 58 independent genomic regions, HMGCR, NPC1L1, or PCSK9. Associations with lower risk were consistent in quintiles of the distribution of LDL-C-lowering alleles and 2 x 2 factorial genetic analyses. The 40Lys variant in ANGPTL4 was associated with protection from coronary disease and type 2 diabetes in groups with genetically higher or lower LDL-C. For a genetic difference of 0.23 SDs in LDL-C, ANGPTL3 loss-of-function variants, which also have beneficial associations with LPL lipolysis, were associated with greater protection against coronary disease than other LDL-C-lowering genetic mechanisms (ANGPTL3 loss-of-function variants: odds ratio, 0.66; 95% CI, 0.52-0.83; 58 LDL-C-lowering variants: odds ratio, 0.90; 95% CI, 0.89-0.91; P for heterogeneity = .009). Conclusions and Relevance: Triglyceride-lowering alleles in the LPL pathway are associated with lower risk of coronary disease and type 2 diabetes independently of LDL-C-lowering genetic mechanisms. These findings provide human genetics evidence to support the development of agents that enhance LPL-mediated lipolysis for further clinical benefit in addition to LDL-C-lowering therapy.

[55] *Hasenfuss G*. **Secondary prevention of cardiovascular diseases: current state of the art**. Kardiol Pol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30338502

ABSTRACT

Prevention strategies for cardiac events depend of the risk for such an event. A very high risk is defined by a risk >10% over 10 years. For example, a patient with known coronary artery disease has such a very high risk to die. However a patient with diabetes and severe hypertension without known coronary artery disease carries the same risk. Here, secondary prevention and primary prevention overlap. Prevention guidelines include a number of general recommendations such as changes in behavior, smoking intervention strategies, nutrition, body weight, and physical activity. Drug treatment-based prevention strategies address diabetes mellitus, hypercholesterinemia, platelet aggregation, and arterial hypertension. Following hospitalization for heart failure or ACS participation in a center-based or home-based rehabilitation program is recommended. There are a number of new treatment options with a promising potential to reduce events in patients with cardiovascular diseases and in patients with cardiovascular risk factors. Very recent treatment strategies include the PCSK9 inhibitors for hypercholesterinemia, the SGLT2 inhibitors for reduction of cardiovascular events in patients with Diabetes mellitus and increased CV risk.

[56] *Du J, Zhu Y, Meng X et al.* **Atorvastatin attenuates paraquat poisoning-induced epithelial-mesenchymal transition via downregulating hypoxia-inducible factor-1 alpha**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336147

ABSTRACT

AIM: This study investigated the effects of atorvastatin (ATS) on the paraquat (PQ)-induced epithelial-mesenchymal transition (EMT) and the potential mechanism through hypoxia-inducible factor-1 alpha (HIF-1alpha). MAIN METHODS: Sprague-Dawley (SD) rats were randomly divided into a control group (n=5), PQ group (n=20), PQ+ATS L group (n=20, ATS 20mg/kg daily) and PQ+ATS H group (n=20, ATS 40mg/kg daily). All treated rats were given a 20% PQ solution (50mg/kg) once by gavage and then sacrificed 12, 24, 72 and 168h after PQ exposure. The A549 and RLE-6TN cell lines were treated with ATS, PQ or both for 24h. Mesenchymal (alpha-SMA and vimentin) and epithelial (E-cadherin and ZO-1) cell marker expression was tested both in vivo and in vitro. The effects of ATS on HIF-1alpha and betacatenin expression were also evaluated. KEY FINDINGS: ATS alleviated PQ poisoning-induced lung injury and pulmonary fibrosis in vivo. This effect was dose-dependent. ATS treatment attenuated the EMT by increasing the levels of the epithelial markers E-cadherin and ZO-1 and by decreasing the expression of the mesenchymal markers alpha-SMA and vimentin in both lung tissues and in vitro cell culture. In addition, ATS treatment may decrease the HIF-1alpha and betacatenin levels both in vivo and in vitro. SIGNIFICANCE: In conclusion, ATS can attenuate PQ-induced pulmonary fibrosis. The mechanism may involve the downregulation of the HIF-1alpha/betacatenin pathway and the inhibition of the PQ-induced EMT by ATS. ATS may be considered as a therapeutic agent for PQ poisoning-induced pulmonary fibrosis.

[57] *Ai C, Zhang S, He Q, Shi J*. **Comparing the combination therapy of ezetimibe and atorvastatin with atorvastatin monotherapy for regulating blood lipids: a systematic review and meta-analyse**. Lipids in health and disease 2018; 17:239.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30326894

ABSTRACT
BACKGROUND: Although there were many studies reporting the combination therapy of Ezetimibe and Atorvastatin's efficacy and Atorvastatin monotherapy's, the conclusions were controversial. Therefore, a systematic review and meta analysis of combination therapy and monotherapy were conducted. METHODS: PubMed, Cochrane Library and Embase were searched for studies of the combination therapy of Ezetimibe and Atorvastatin and Atorvastatin monotherapy published up to October 20, 2017. Two investigators assessed the articles for eligibility and evaluated quality.The changed values and the efficacy of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), Total Cholesterol (TC) and Triglyceride (TG) indicators were the outcomes. Four doses of the comparisons were included: the combination therapy of Ezetimibe (10 mg) and Atorvastatin (10 mg) (E10 + A10) versus Atorvastatin (20 mg) monotherapy (A20); E10 + A10 vs. A10; E10 + A20 vs. A40; E10 + A40 vs. A80. Review manager software 5.1 was used for quality assessment and Stata version 12.0 software was used for statistical analysis. RESULTS: eventeen studies (11 publications) were included in the meta analysis. Compared with Atorvastatin monotherapy, the overall efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C (MD = - 15.38, 95% CI: - 16.17 to - 14.60; I(2) = 26.2%, n = 17), TC (MD = - 9.51, 95% CI: -10.28 to - 8.74; I(2) = 33.7%, n = 17) and TG (MD = - 6.42, 95% CI: -7.78 to - 5.06; I(2) = 0%, n = 15) and raising HDL-C (MD = 0.95, 95% CI: 0.34 to 1.57; I(2) = 0%, n = 17) was significant. The efficacy of the comparison on HDL-C was largely significant for the different doses. CONCLUSIONS: The overall efficacy and subgroup's efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C, TC and TG was significantly better than Atorvastatin monotherapy's. The overall and the E10 + A10/A20 group's effectiveness of combination therapy on rasing HDL-C were significantly.

[58] *Ma S, Wang S, Li M et al.* **The effects of pigment epithelium-derived factor on atherosclerosis: putative mechanisms of the process**. Lipids in health and disease 2018; 17:240.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30326915

ABSTRACT
Cardiovascular disease (CVD) is a leading cause of death worldwide. Atherosclerosis is believed to be the major cause of CVD, characterized by atherosclerotic lesion formation and plaque disruption. Although remarkable advances in understanding the mechanisms of atherosclerosis have been made, the application of these theories is still limited in the prevention and treatment of atherosclerosis. Therefore, novel and effective strategies to treat high-risk patients with atherosclerosis require further development. Pigment epithelium-derived factor (PEDF), a glycoprotein with anti-inflammatory, anti-oxidant, anti-angiogenic, anti-thrombotic and anti-tumorigenic properties, is of considerable interest in the prevention of atherosclerosis. Accumulating research has suggested that PEDF exerts beneficial effects on atherosclerotic lesions and CVD patients. Our group, along with colleagues, has demonstrated that PEDF may be associated with acute coronary syndrome (ACS), and that the polymorphisms of rs8075977 of PEDF are correlated with coronary artery disease (CAD). Moreover, we have explored the anti-atherosclerosis mechanisms of PEDF, showing that oxidized-low density lipoprotein (ox-LDL) reduced PEDF concentrations through the upregulation of reactive oxygen species (ROS), and that D-4F can protect endothelial cells against ox-LDL-induced injury by preventing the

downregulation of PEDF. Additionally, PEDF might alleviate endothelial injury by inhibiting the Wnt/beta-catenin pathway. These data suggest that PEDF may be a novel therapeutic target for the treatment of atherosclerosis. In this review, we will summarize the role of PEDF in the development of atherosclerosis, focusing on endothelial dysfunction, inflammation, oxidative stress, angiogenesis and cell proliferation. We will also discuss its promising therapeutic implications for atherosclerosis.

[59] *Kuang H, Zhou X, Li L et al.* **Early severe coronary heart disease and ischemic heart failure in homozygous familial hypercholesterolemia: A case report**. Medicine (Baltimore) 2018; 97:e12869.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30335000
ABSTRACT
RATIONALE: Familial hypercholesterolemia (FH) is a common inherited cause of coronary heart disease (CHD) and premature death in an early age. Nevertheless, an ischemic heart failure (IHF) associated with FH seems to be rare, and an early diagnosis and therapy could influence the prognosis. PATIENT CONCERNS: In this 13-year-old girl, multiple xanthomas began to develop from the first day of birth. Until June, 2017, she was admitted to our center due to edema, oliguria, and dyspnea during exertion, which was attributed to a recent respiratory infection. DIAGNOSIS: Homozygous FH (HoFH), CHD, and IHF. INTERVENTIONS: The patient has been treated with statin, ezetimibe, aspirin, and traditional heart failure (HF) medications. In addition, the beta-blocker was simultaneously administered. OUTCOMES: Genotypes of this proband indicated homozygous mutations of low-density lipoprotein receptor (LDLR) and some co-segregated mutations, such as von Willebrand factor (VWF) and fibroblast growth factor receptors. At 6-month follow-up, we found a decreased level of plasma lipid profile, in addition to a significant improvement in 6-minute walk distance and functional class. Echocardiography indicated nonsignificant improvements in the structure and function of the heart. LESSONS: This case report indicates that HoFH can lead to dramatically progressive endothelial damages and ventricular remodeling, severe atherosclerosis, even IHF. Genetic outcomes indicate IHF with HoFH could possibly result from LDLR mutations and some co-segregated mutations influencing endothelial function and cardiovascular remodeling. In a short-term follow-up, a combination of statins, ezetimibe, aspirin, and traditional HF agents is safe and effective for IHF with HoFH, and there is a need for further identification of drugs to ameliorate endothelial function and cardiovascular remodeling which may play an important role in long-term treatment.

[60] *Liu H, Dong A, Wang H*. **Long-term benefits of high-intensity atorvastatin therapy in Chinese acute coronary syndrome patients undergoing percutaneous coronary intervention: A retrospective study**. Medicine (Baltimore) 2018; 97:e12687.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30334951
ABSTRACT
There is lack of long-term data on high-intensity statin therapy of Chinese acute coronary syndrome (ACS) patients scheduled to undergo percutaneous coronary intervention (PCI). In this retrospective study, we compared the long-term efficacy and safety of high-intensity and conventional atorvastatin therapy in reducing low-density lipoprotein cholesterol (LDL-C) and

plaque size, and improving cardiac function of ACS patients who underwent PCI.We retrospectively analyzed the clinical records of 120 consecutive ACS patients who underwent PCI at our hospital. Group I received a loading dose of atorvastatin (80 mg/day) prior to PCI, followed by a maintenance dose of 40 mg/day for 3 months post-PCI. Group II received a regular dose of atorvastatin (20 mg/day) from the date of admission until 1 year post-PCI. The composite primary efficacy end point was the mean percent change in calculated LDL-C from baseline to week 48 in both groups and percentage of patients achieving the LDL-C target of </=1.81 mmol/L.Group I had significantly higher mean baseline LDL-C than group II. Moreover, 8.3% of group I patients had an LDL-C </=1.81 mmol/L versus 43.3% for group II. At week 24, 75.0% and 90.0% of group I and II patients, respectively, achieved the LDL-C target. At week 48, 85.0% and 96.7% of group I and II patients, respectively, achieved the LDL-C target. Additionally, the mean percent changes at week 4 from baseline in LDL-C were -33.6% +/- 20.0% for group I versus -12.8% +/- 19.6% for group II, and -47.0% +/- 25.5% at week 48 for group I versus -36.4% +/- 20.2% for group II. Meanwhile, significant reduction in plaque size and marked improvement in cardiac function were seen in patients receiving high-intensity atorvastatin therapy.Compared to conventional therapy, high-intensity statin therapy is more effective in reducing LDL-C and improving cardiac function of ACS patients, with a general benign safety profile over a period of 48 weeks. Our findings support the use of high-intensity statin therapy for Chinese ACS patients to improve the proportion of patients attaining the LDL-C target and reduction in plaque size and improvement cardiac function.

[61] *Sharma A, Mohan N*. **Role of niacin in current clinical practice: a review**. Minerva medica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30334440
ABSTRACT
Despite significant risk reduction with statin therapy, there remains a residual cardiovascular risk. It has been seen that aggressive statin therapy in high risk patients may not lower the low-density lipoprotein cholesterol (LDL-C) to goal in up to 40% of patients. Niacin is a potent high-density lipoprotein cholesterol-raising drug, and has been proposed as an attractive approach to reduce cardiac events in patients with or at risk of atherosclerotic cardiovascular disease. However, previous evidence for niacin has been challenged by negative outcomes in 2 large, randomized, controlled trials comparing niacin to placebo with background statin therapy. In this review, summarize the currently available evidence for the role of niacin treatment for reducing the risk of cardiovascular events in current practice.

[62] *Taysi S, Tascan AS, Uuro MG, Demir M*. **Radicals, oxidative/nitrosative stress and preeclampsia**. Mini reviews in medicinal chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30324879
ABSTRACT
Oxygen is used by eukaryotic cells for metabolic transformations and energy production in mitochondria. Under physiological conditions, there is a constant endogenous production of free radicals that interact as signaling molecules in physiological mechanisms. Free radicals are neutral molecules, which are produced by separation of ions and molecules. In regular conditions production and disposal of free radicals are at equilibrium. However this equilibrium

may not always be experienced, where these species are not eliminated by antioxidants or are excessively produced. Unequalibrium of free radicals causes a condition called oxidative stress. Oxidative stress has destroying effects on lipids, proteins, DNA, organelles and finally cells. This process is also linked to inflammation. Over last two decades scientists explore the reasons and possible outcomes of oxidative stress, since it has an obvious connection between the condiition and number of diseases such as chronic inflammation and many emerging disorders like cancer, kidney diseases, oral diseases, fibromyalgia, gastrointestinal chronic diseases or rheumatics diseases, hypertension and preeclampsia. Preeclampsia is a condition that is experienced during pregnancy and holds its place as number one cause of prenatal death. Our goal in this rewiev is to describe the oxidative/nitrosative stress and its effects on preeclampsia.

[63] *Yang Q, Yin RX, Cao XL et al.* **ANGPTL4 variants and their haplotypes are associated with serum lipid levels, the risk of coronary artery disease and ischemic stroke and atorvastatin cholesterol-lowering responses**. Nutrition & metabolism 2018; 15:70.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30323852

ABSTRACT

Background: This study aimed to assess the association between the angiopoietin-like protein 4 gene (ANGPTL4) single nucleotide polymorphisms (SNPs) and serum lipid levels, the risk of coronary artery disease (CAD) and ischemic stroke (IS), and response to atorvastatin therapy in a Southern Chinese Han population. Methods: Genotypes of the ANGPTL4 rs4076317, rs7255436, rs1044250 and rs2967605 SNPs in 1,654 unrelated subjects (CAD, 568; IS, 537; and controls, 549) were determined by the Snapshot technology. Another group of 724 hyperlipidemic patients was selected and treated with atorvastatin calcium tablet 20 mg/day for 8 weeks. Results: The rs2967605 CT/TT genotypes were associated with a decreased risk of CAD (adjusted OR = 0.68, 95% CI = 0.47-0.99, P = 0.043 for CT/TT vs. CC) and IS (adjusted OR = 0.55, 95% CI = 0.38-0.80, P = 0.020 for CT/TT vs. CC). There was no significant association between the four SNPs and angiographic severity of CAD. The subjects with the rs4076317 CG/CC genotypes in controls had higher total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels than the subjects with the GG genotype ($P < 0.001$; a $P < 0.0018$ was regarded statistically significant by the Bonferroni correction). The subjects with rs4076317CG/GG genotypes had lower TC and LDL-C levels than the subjects with CC genotype after atorvastatin treatment ($P < 0.001$). Conclusions: The observed associations suggest that the ANGPTL4 variants have a potential role on serum lipid levels and atherosclerosis-related diseases in the Chinese Han population, especially the ANGPTL4 rs4076317 and rs2967605 SNPs.

[64] *Griffin BA, Walker CG, Jebb SA et al.* **APOE4 Genotype Exerts Greater Benefit in Lowering Plasma Cholesterol and Apolipoprotein B than Wild Type (E3/E3), after Replacement of Dietary Saturated Fats with Low Glycaemic Index Carbohydrates**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30336580

ABSTRACT

We examined the impact of APOE genotype on plasma lipids and glucose in a secondary analysis of data from a five-arm, randomised controlled, parallel dietary intervention trial ('RISCK' study), to investigate the impact of replacing saturated fatty acids (SFA) with either

monounsaturated fat (MUFA) or carbohydrate of high or low glycaemic index (GI) on CVD risk factors and insulin sensitivity. We tested the impact of APOE genotype (carriage of E2 and E4 alleles versus E3/E3), determined retrospectively, on plasma lipids, lipoproteins and glucose homeostasis at baseline (n = 469), and on the change in these variables after 24 weeks of dietary intervention (n = 389). At baseline, carriers of E2 (n = 70), E4 (n = 125) and E3/E3 (n = 274) expressed marked differences in total plasma cholesterol (TC, p = 0.001), low density lipoprotein cholesterol (LDL-C, p < 0.0001), apolipoprotein B (apo B, p < 0.0001) and total to high density lipoprotein cholesterol ratio (TC:HDL-C, p = 0.002), with plasma concentrations decreasing in the order E4 > E3/E3 > E2. Following intervention, there was evidence of a significant diet x genotype interaction with significantly greater decreases in TC (p = 0.02) and apo B (p = 0.006) among carriers of E4 when SFA was replaced with low GI carbohydrate on a lower fat diet (TC -0.28 mmol/L p = 0.03; apo B -0.1 g/L p = 0.02), and a relative increase in TC (in comparison to E3/E3) when SFA was replaced with MUFA and high GI carbohydrates (TC 0.3 mmol/L, p = 0.03). Among carriers of E2 (compared with E3/E3) there was an increase in triacylglycerol (TAG) when SFA was replaced with MUFA and low GI carbohydrates 0.46 mmol/L p = 0.001). There were no significant interactions between APOE genotype and diet for changes in indices of glucose homeostasis. In conclusion, variations in APOE genotype led to differential effects on the lipid response to the replacement of SFA with MUFA and low GI carbohydrates.

[65] *Liu A, Wu Q, Guo J et al.* **Statins: adverse reactions, oxidative stress and metabolic interactions**. Pharmacology & therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30321555
ABSTRACT
Statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, are currently the most effective lipid-lowering drugs, effectively reducing the plasma total cholesterol and low-density lipoprotein, while also decreasing three triacylglycerols and increasing plasma high-density lipoprotein to a certain extent. However, the excessive or long-term use of statins can cause in vitro cytotoxicity, in vivo liver injury, liver necrosis, kidney damage, and myopathy in both human beings and animals. Many studies indicate that oxidative stress is involved in the various toxicities associated with statins, and various antioxidants have been evaluated to investigate their protective roles against statin-induced liver, kidney, and muscle toxicities. Widespread attention has been given to statin-induced oxidative stress, with and without the use of other drugs. Much of the information about the mechanism for this reduction comes from cell culture and in experimental animal studies. The primary focus of this article is to summarize the research progress associated with oxidative stress as a plausible mechanism for statin-induced toxicity, as well as its metabolic interactions. This review summarizes the research conducted over the past five years into the production of reactive oxygen species, oxidative stress as a result of statin treatments, and their correlation with statin-induced toxicity and metabolism. Statin-induced metabolism involves various CYP450 enzymes, which provide potential sites for statin-induced oxidative stress, and these metabolic factors are also reviewed. The therapeutics of a variety of compounds against statin-induced organ damage based on their anti-oxidative effects is also discussed to further understand the role of oxidative stress in statin-induced toxicity. This review sheds new light on the critical roles of oxidative stress in statin-induced toxicity and prevention of this oxidative damage, as well as on the contradictions and

unknowns that still exist regarding statin toxicity and the cellular effects in terms of organ injury and cell signaling pathways.

[66] *Sridharan K, Sivaramakrishnan G, Sequeira RP, Elamin A*. **Pharmacological interventions for non-alcoholic fatty liver disease: a systematic review and network meta-analysis**. Postgraduate medical journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30341231
ABSTRACT
AIM: Several drugs have been used for treating non-alcoholic fatty liver disease (NAFLD). The present study is a network meta-analysis of such drugs. DESIGN, SETTING AND PATIENTS: Randomised clinical trials comparing drug interventions in patients with NAFLD were analysed. OR and weighted mean difference (95 % CI) were the effect estimates for categorical and numerical outcomes, respectively. Random-effects model was used to generate pooled estimates. Surface under the cumulative ranking curve was used to rank the treatments. MAIN OUTCOME MEASURES: Proportion of responders was the primary outcome measure and non-alcoholic steatohepatitis scores, liver enzymes, lipid profile, body mass index, homeostatic model assessment of insulin resistance, intrahepatic fat and adverse events were the key secondary outcomes. RESULTS: 116 studies were included in the systematic review and 106 in the meta-analysis. Elafibranor, gemfibrozil, metadoxine, obeticholic acid, pentoxifylline, pioglitazone, probiotics, telmisartan, vildagliptin and vitamin E significantly increased the response rate than standard of care. Various other drugs were observed to modify the secondary outcomes favourably. Probiotics was found with a better response in children; and elafibranor, obeticholic acid, pentoxifylline and pioglitazone in patients with type 2 diabetes mellitus. The quality of evidence observed was either low or very low. CONCLUSION: In patients with NAFLD, several drugs have been shown to have variable therapeutic benefit. However, the estimates and the inferences should be considered with extreme caution as it might change with the advent of future head-to-head clinical trials.

[67] *Martinez J, Aguilera L, Albillos A*. **Risk stratification and treatment of primary biliary cholangitis**. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva 2018; 111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30338693
ABSTRACT
Primary biliary cholangitis is a chronic liver disorder characterized by progressive cholestasis that may evolve to liver cirrhosis. While ursodeoxycholic acid is the treatment of choice, around 30% of patients do not respond to this therapy. These patients have a poorer prognosis, hence should be identified early in order to be offered therapy options. Along these lines, improved understanding of the condition's pathophysiology has allowed the development of newer drugs, including obeticholic acid and fibrates. This review offers a perspective on risk stratification and treatment for these patients, from ursodeoxycholic acid to second-line treatments.

[68] *Uchiyama H, Tsujimoto M, Kimura A et al.* **Effects of Uremic Serum Residue on OATP1B1- and OATP1B3-Mediated Pravastatin Uptake in OATP-Expressing HEK293 Cells and Human**

Hepatocytes. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30318712
ABSTRACT
Patients with end-stage renal disease have increased plasma concentrations of statins, which is a risk factor for rhabdomyolysis, as well as elevated levels of uremic toxins (UTs). We investigated the effects of uremic serum residue and UTs on organic anion-transporting peptide (OATP1B1)- and OATP1B3-mediated pravastatin uptake. We evaluated the effects of normal serum residue with four UTs (hippuric acid, 3-carboxy-4-methyl-5-propyl-2-furan propionate, indole-3-acetic acid, and 3-indoxyl sulfate) and uremic serum residue on pravastatin uptake by OATP1B1- or OATP1B3-expressing HEK293 cells. Furthermore, we assessed the contribution of each transporter using cryopreserved human hepatocytes. Uremic serum residue and UTs significantly inhibited OATP1B1-mediated pravastatin uptake. Uremic serum residue accelerated OATP1B3-mediated pravastatin uptake, while UTs had no effect. There was no difference in pravastatin uptake between uremic- and normal serum residue-treated hepatocytes. The results suggest that the effects of uremic serum on pravastatin hepatic uptake may be considered negligible in end-stage renal disease patients.

[69] *Rattanawan C, Komanasin N, Settasatian N et al.* **Association of TAFI gene polymorphisms with severity of coronary stenosis in stable coronary artery disease**. Thrombosis research 2018; 171:171-176.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30321704
ABSTRACT
INTRODUCTION: Coronary stenosis is a consequence of atherosclerotic plaque progression that is associated with impaired fibrinolysis. Thrombin-activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor 1 (PAI-1) are fibrinolysis inhibitors whose levels are influenced by acquired conditions and by polymorphisms. This study therefore aimed to investigate the association of TAFI and PAI-1 gene polymorphisms with severity of coronary stenosis in subjects with stable coronary artery disease (CAD). MATERIALS AND METHODS: A total of 327 subjects suspected with CAD who underwent a coronary angiogram were recruited. Gensini score was applied to stratify the severity of coronary stenosis. Based on the Gensini score, the subjects were categorized into low-medium (<20) or high (>/=20) groups. The study polymorphisms included TAFI Ala147Thr (505G/A), Thr325Ile (1040C/T), +1542C/G, +1583T/A and PAI-1 -675 4G/5G. Most polymorphisms were genotyped by allele-specific polymerase chain reaction, except for TAFI Thr325Ile that was genotyped by polymerase chain reaction-restriction fragment length polymorphism. RESULTS: A significant increase in the Gensini score was found in TAFI 505A and +1583A allele carriers. Binary regression analysis revealed the independent association of the TAFI 505G/A and +1583T/A polymorphisms with a high Gensini score [adjusted OR=1.67 (95% CI: 1.03, 2.73) and 1.69 (95% CI: 1.04, 2.76), respectively]. Neither the homozygous PAI-1 -675 4G/4G nor the heterozygous 4G/5G was associated with a high Gensini score. CONCLUSIONS: The results indicated the contribution of TAFI polymorphisms to atherosclerosis progression and severity of coronary stenosis in stable CAD.

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