Literature update week 31 (2018)

[1] *Kosmeri C, Siomou E, Vlahos AP, Milionis H*. **Review shows that lipid disorders are associated with endothelial but not renal dysfunction in children**. Acta paediatrica (Oslo, Norway : 1992) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30066344
ABSTRACT
AIM: We undertook this review to assess the effects of lipid metabolism abnormalities on endothelial and renal function in children. METHODS: A search of relevant literature published in English from January 1988 to May 2018 was performed and this included randomised controlled trials, observational cohort studies, systematic reviews and case reports. RESULTS: The search process identified 2,324 relevant studies and 29 were finally included. Non-invasive ultrasound markers of endothelial dysfunction, such as flow mediated dilation and carotid intima-media thickness, were impaired in children with dyslipidaemia. Dietary interventions and statin therapy reversed the effects of dyslipidaemia on endothelial function in children. Most data from adult studies failed to prove a causative relationship between dyslipidaemia and renal disease progression or a beneficial effect of lipid lowering treatment on renal outcomes. The limited paediatric data did not indicate dyslipidaemia as an independent risk factor for renal dysfunction, which was mainly estimated by cystatin C levels or proteinuria. Therefore, further investigation is needed to clarify a potential relationship. CONCLUSION: In view of limited available paediatric evidence, dyslipidaemia may be adversely associated with endothelial function. However, the association between lipid metabolism disorders and renal function in childhood needs to be further investigated.

[2] *Ashfield-Watt P, Haralambos K, Edwards R et al.* **ANNALS EXPRESS: Estimation of the prevalence of Cholesteryl Ester Storage Disorder (CESD) in a cohort of patients with clinical features of Familial Hypercholesterolaemia**. Annals of clinical biochemistry 2018:4563218793165.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30056760
ABSTRACT
Backgroundandaim. Familial Hypercholesterolaemia (FH) is caused by variants in the LDL-C metabolic pathway involving LDLR, APOB and PCSK9 genes. A national genetic testing service in Wales, UK has observed that no FH variant is found in almost 80% patients with the FH phenotype. It has recently been suggested that some adult patients with an FH phenotype may have Cholesteryl Ester Storage Disease (CESD) which can also present as a mixed hyperlipidaemia. The commonest genetic cause of CESD is an exon 8 splice junction variant in the LIPA gene (rs116928232, c.894G>A;E8SJM) previously found to have an allele frequency of 0.0011 (1 in 450 individuals) in a large European population. This study investigated the prevalence of the E8SJM in patients with an FH phenotype in Wales, United Kingdom. METHOD: 1203 patients with a clinical suspicion of FH, but no FH variant were invited to participate. Of these, 668 patients provided informed, written consent. Stored DNA samples from 663 patients were genotyped for the E8SJM variant. RESULTS: Three heterozygotes were identified (allele frequency 0.0023). Whole gene sequencing of the LIPA gene was undertaken in these 3 individuals, but no other variants were found. Therefore there were no CESD patients (homozygote or compound heterozygote) identified in this cohort. CONCLUSION: The allele

frequency 0.0023 (1 in 221 individuals) for the E8SJM variant was more prevalent in this cohort than in a European population study, however, no CESD homozygotes were identified. We found no evidence to support routine testing for CESD in adult patients with an FH phenotype.

[3] *Dougherty JA*. **Atorvastatin-Associated Macroglossia in a Cardioembolic Stroke Patient**. The Annals of pharmacotherapy 2018:1060028018793111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30058342
ABSTRACT

[4] *Taskinen MR, Del Prato S, Bujas-Bobanovic M et al.* **Efficacy and safety of alirocumab in individuals with type 2 diabetes mellitus with or without mixed dyslipidaemia: Analysis of the ODYSSEY LONG TERM trial**. Atherosclerosis 2018; 276:124-130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30059843
ABSTRACT
BACKGROUND AND AIMS: Alirocumab, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9, significantly reduces low-density lipoprotein cholesterol (LDL-C). We evaluated the efficacy and safety of alirocumab in individuals with type 2 diabetes mellitus (T2DM) with versus without mixed dyslipidaemia (MDL, defined as baseline LDL-C >/=70mg/dL [1.8mmol/L] and triglycerides >/=150mg/dL [1.7mmol/L]). METHODS: Data from 812 individuals with T2DM, from the placebo-controlled, 78-week, Phase 3 ODYSSEY LONG TERM trial of alirocumab 150mg every 2 weeks (Q2W), on a background of maximally tolerated statins+/- other lipid-lowering therapies, were pooled according to MDL status. Efficacy endpoints included percentage change from baseline to Week 24 in calculated LDL-C and other lipids/lipoproteins. RESULTS: In individuals with T2DM who received alirocumab 150mg Q2W, mean LDL-C changes from baseline to Week 24 were -62.6% (vs. -6.0% with placebo) in those with MDL and -56.1% (vs. 5.6%) in those without MDL, with no significant between-group difference (p-interaction=0.0842). Risk-based LDL-C goals (<70 [1.8mmol/L] or <100mg/dL [2.6mmol/L]) were achieved by 69.1% and 72.4% of alirocumab-treated individuals with and without MDL, respectively. Mean reductions in non-high-density lipoprotein cholesterol (49.2% and 47.8%) and apolipoprotein B (50.2% and 49.1%) with alirocumab were also similar in those with and without MDL, respectively. Treatment-emergent adverse event rates were comparable between alirocumab-treated individuals with T2DM, with and without MDL. CONCLUSIONS: Reductions in LDL-C and other lipids with alirocumab, as well as safety and tolerability, were comparable between individuals with T2DM and with versus without MDL.

[5] *Thompson GR*. **Atherosclerosis in cholesterol-fed rabbits and in homozygous and heterozygous LDL receptor-deficient humans**. Atherosclerosis 2018; 276:148-154.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30064057
ABSTRACT
A phenocopy is an environmentally-defined phenotype that mimics another, genetically-determined phenotype. The severity of hypercholesterolaemia, extent of down regulation of LDL receptor expression and aortic root localisation of atherosclerosis in cholesterol-fed rabbits strikingly resemble the cardinal features of homozygous familial hypercholesterolaemia (FH) in humans, suggesting that the former is a phenocopy of the latter. This review compares the

metabolic and pathological consequences of induced hypercholesterolaemia in rabbits with those of homozygous FH and contrasts their ease of reversibility on resumption of a normal diet with the refractoriness to lipid-lowering therapy of homozygotes, in whom major adverse cardiovascular events and survival depend upon the prevailing level of serum cholesterol. The monofactorial nature of the atherosclerosis in both situations corroborates Anitschkow's concept that "Cholesterin ist alles." In contrast, atherosclerosis in heterozygous FH differs in several respects from that of homozygotes, notably the lack of aortic root involvement and in its multifactorial aetiology, with raised LDL cholesterol, male gender, low HDL cholesterol and raised lipoprotein (a) all contributing to its clinical expression. In angiographic trials of LDL-lowering therapy regression of coronary lesions was observed in FH heterozygotes whereas they progressed in non-FH subjects. Similarly, carotid artery plaques progressed less in FH heterozygotes than in non-FH subjects, in both instances despite FH patients having higher LDL cholesterol levels on treatment. These findings suggest that, compared with non-FH subjects, atherosclerotic lesions in FH heterozygotes may be hyper-responsive to LDL-lowering therapy, whereas treatment of homozygous FH remains a major challenge.

[6] *Yu XH, Zhang DW, Zheng XL, Tang CK*. **C1q tumor necrosis factor-related protein 9 in atherosclerosis: Mechanistic insights and therapeutic potential**. Atherosclerosis 2018; 276:109-116.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30056359
ABSTRACT
C1q tumor necrosis factor-related protein 9 (CTRP9), a newly discovered adipokine, is the closest paralog of adiponectin. After proteolytic cleavage, it can release the globular domain (gCTRP9) that serves as the major circulatory isoform. Upon binding to adiponectin receptor 1 (AdipoR1) and N-cadherin, CTRP9 can activate a variety of signaling pathways to regulate glucose and lipid metabolism, vascular relaxation and cell differentiation. Circulating CTRP9 levels are significantly decreased in patients with coronary atherosclerosis disease. Data obtained from in vitro experiments and animal models suggest that CTRP9 exerts an atheroprotective effect by altering multiple pathological processes involved in atherosclerosis, including inflammation, foam cell formation, endothelial dysfunction, insulin resistance, and vascular smooth muscle cell dedifferentiation, proliferation and migration. In this review, we summarize the latest advances regarding the roles of CTRP9 in atherosclerosis with an emphasis on its potential as a novel therapeutic target in cardiovascular disease.

[7] *von Buedingen F, Hammer MS, Meid AD et al.* **Changes in prescribed medicines in older patients with multimorbidity and polypharmacy in general practice**. BMC family practice 2018; 19:131.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30055583
ABSTRACT
BACKGROUND: Treatment complexity rises in line with the number of drugs, single doses, and administration methods, thereby threatening patient adherence. Patients with multimorbidity often need flexible, individualised treatment regimens, but alterations during the course of treatment may further increase complexity. The objective of our study was to explore medication changes in older patients with multimorbidity and polypharmacy in general

practice. METHODS: We retrospectively analysed data from the cluster-randomised PRIMUM trial (PRIoritisation of MUltimedication in Multimorbidity) conducted in 72 general practices. We developed an algorithm for active pharmaceutical ingredients (API), strength, dosage, and administration method to assess changes in physician-reported medication data during two intervals (baseline to six-months: 1; six- to nine-months: 2), analysed them descriptively at prescription and patient levels, and checked for intervention effects. RESULTS: Of 502 patients (median age 72 years, 52% female), 464 completed the study. Changes occurred in 98.6% of patients (changes were 19% more likely in the intervention group): API changes during 1 and 2 occurred in 414 (82.5%) and 338 (67.3%) of patients, dosage alterations in 372 (74.1%) and 296 (59.2%), and changes in API strength in 158 (31.5%) and 138 (27.5%) respectively. Administration method changed in 79 (16%) of patients in both 1 and 2. Simvastatin, metformin and aspirin were most frequently subject to alterations. CONCLUSION: Medication regimens in older patients with multimorbidity and polypharmacy changed frequently. These are mostly due to discontinuations and dosage alterations, followed by additions and restarts. These findings cast doubt on the effectiveness of cross-sectional assessments of medication and support longitudinal assessments where possible. TRIAL REGISTRATION: 1. Prospective registration: Trial registration number: NCT01171339 ; Name of registry: ClinicalTrials.gov; Date of registration: July 27, 2010; Date of enrolment of the first participant to the trial: August 12, 2010. 2. Peer reviewed trial registration: Trial registration number: ISRCTN99526053 ; Name of registry: Controlled Trials; Date of registration: August 31, 2010; Date of enrolment of the first participant to the trial: August 12, 2010.

[8] *Baass A, Hegele RA*. **Getting Real With PCSK9 Inhibitors in Familial Hypercholesterolemia**. The Canadian journal of cardiology 2018; 34:959-961.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30056849
ABSTRACT

[9] *Razek O, Cermakova L, Armani H et al.* **Attainment of Recommended Lipid Targets in Patients With Familial Hypercholesterolemia: Real-World Experience With PCSK9 Inhibitors**. The Canadian journal of cardiology 2018; 34:1004-1009.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30056842
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is the most common inherited dyslipidemia and is characterized by elevated low-density lipoprotein cholesterol (LDL-C) and markedly increased risk for atherosclerotic cardiovascular disease. Lipid-lowering therapy is the mainstay of treatment, but few patients with FH are able to achieve commonly recommended lipid targets. METHODS: We examined changes in LDL-C levels in patients in the British Columbia FH Registry from 2015 to 2017, corresponding to the period immediately before, and the first 2 years after, availability of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in Canada. RESULTS: Among 275 patients with a clinical diagnosis of FH in whom a lipid profile was available between January 1, 2016 and December 31, 2017, 48 had started using a PCSK9 inhibitor. LDL-C decreased in the cohort overall from 2015 to 2017. When patients were stratified according to PCSK9 inhibitor use, the reduction in LDL-C was significantly greater in patients receiving a PCSK9 inhibitor compared with those who did not receive one. Among

patients receiving a PCSK9 inhibitor, 85.4% achieved a >/= 50% reduction in LDL-C or LDL-C < 2 mmol/L, compared with 50.2% of patients not receiving a PCSK9 inhibitor (P < 0.001). CONCLUSIONS: Our results suggest that control of lipid levels in patients with FH has improved and that the achievement of guideline-directed goals has been facilitated by access to PCSK9 inhibitors. These observations provide insight into the real-world effectiveness of PCSK9 inhibitor therapy in patients with FH.

[10] *Nikolic Turnic TR, Jakovljevic VP, Djuric D et al.* **EFFICENCY OF ATORVASTATIN AND SIMVASTATIN IN IMPROVING OF CARDIAC FUNCTION DURING THE DIFFERENT DEGREE OF HYPERHOMOCYSTEINEMIA**. Canadian journal of physiology and pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30067069
ABSTRACT
The aim of this study was to assess impact of atorvastain and simvastatin on myocardial contractility during the different degree of Hhcy in rats. Study was conducted on adult male Wistar albino rats (n=96; 4 weeks old; 100+/-15g body mass) in which HHcy was achieved by dietary manipulation. Animals were exposed to pharmacology treatment with atorvastatin in dose of 3 mg/kg/day i.p or simvastatin in dose of 5 mg/kg/day i.p in same time every day, according to equivalent therapeutic doses of these statins (10mg atorvastatin=20mg simvastatin). After the dietary manipulation and pharmacological treatment and confirmation of Hhcy, all animals were sacrified, hearts were isolated and cardiac function was tested according to Langerdorff tehnique. Size of recovery of dp/dt max, dp/dt min, SLVP, DLVP, HR and CF at the 40, 60, 80, 100 and 120 cmH2O coronary perfusion pressure were measured in state of physiological condition (Hcy less than 15 mumol/L), mild Hhcy and moderate Hhcy. Atorvastatin treatment significantly attenuated Hcy-induced impairment of myocyte contractility and dominantly decreased dp/dt max and dp/dt min, HR and induced greater changes in SLVP compared with simvastatin. Treatment with atorvastatin seems able to revert systolic abnormalities and improve contractility during the diferent degree of Hhcy.

[11] *Cho L, Dent R, Stroes ESG et al.* **Persistent Safety and Efficacy of Evolocumab in Patients with Statin Intolerance: a Subset Analysis of the OSLER Open-Label Extension Studies**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30073585
ABSTRACT
PURPOSE: Evolocumab reduced low-density lipoprotein cholesterol (LDL-C) in 12-week trials in statin-intolerant patients (GAUSS-1 and GAUSS-2); however, the persistence of efficacy during longer-term treatment is unknown. This subset analysis of the open-label extension studies (OSLER-1 and OSLER-2) aimed to evaluate the safety and efficacy of evolocumab up to 2 years in statin-intolerant patients. METHODS: Patients who completed GAUSS-1 and GAUSS-2 were enrolled in the OSLER studies and rerandomized 2:1 to evolocumab (140 mg biweekly or 420 mg monthly) plus standard of care (SOC) or SOC during year 1, and thereafter, evolocumab plus SOC. RESULTS: A total of 382 statin-intolerant patients who completed the GAUSS-1 and GAUSS-2 parent studies were enrolled and rerandomized into the OSLER studies. After year 1, 246 (98%) patients randomized to evolocumab plus SOC and 124 (95%) on SOC during year 1

remained in the OSLER studies; after year 2, 364 (95%) remained on study. Mean parent study baseline LDL-C concentration was 4.97-5.02 mmol/L (192-194 mg/dL). The median percentage reduction from baseline in LDL-C was 13% for SOC and 57% for evolocumab plus SOC at year 1, and 59% for evolocumab plus SOC at year 2. The patient incidence of muscle-related adverse events during year 1 in the SOC and evolocumab plus SOC groups was 16% and 14%, respectively, and 11% for evolocumab plus SOC at year 2. No patient discontinued the study due to adverse events. CONCLUSION: Evolocumab plus SOC was persistently safe, tolerable, and efficacious for up to 2 years in statin-intolerant patients.

[12] *Colakoglu M, Tuncer S, Banerjee S*. **Emerging cellular functions of the lipid metabolizing enzyme 15-Lipoxygenase-1**. Cell proliferation 2018:e12472.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30062726
ABSTRACT
The oxygenation of polyunsaturated fatty acids such as arachidonic and linoleic acid through lipoxygenases (LOXs) and cyclooxygenases (COXs) leads to the production of bioactive lipids that are important both in the induction of acute inflammation and its resolution. Amongst the several isoforms of LOX that are expressed in mammals, 15-LOX-1 was shown to be important both in the context of inflammation, being expressed in cells of the immune system, and in epithelial cells where the enzyme has been shown to crosstalk with a number of important signalling pathways. This review looks into the latest developments in understanding the role of 15-LOX-1 in different disease states with emphasis on the emerging role of the enzyme in the tumour microenvironment as well as a newly re-discovered form of cell death called ferroptosis. We also discuss future perspectives on the feasibility of use of this protein as a target for therapeutic interventions.

[13] *Qin J, Wang LL, Liu ZY et al.* **Ezetimibe Protects Endothelial Cells against Oxidative Stress through Akt/GSK-3beta Pathway**. Current medical science 2018; 38:398-404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30074204
ABSTRACT
Ezetimibe was reported to pharmacologically defend against oxidative stress. This study was designed to investigate whether ezetimibe can protect against the oxidative stress induced by oxidized low-density lipoprotein (oxLDL) in vitro and the underlying mechanism. Human umbilical vein endothelial cells (HUVECs) were pretreated with ezetimibe and then exposed to oxLDL for 24 h. TUNEL assay and detectionfor the protein levels of cleaved caspase-3, Bcl-xl and Bcl-2 were employed to assess the oxLDL-induced endothelial apoptosis. Intracellular reactive oxygen species (ROS) generation was evaluated by measuring dichlorofluorescein (DCF) fluorescence. The activities of endothelial antioxidant enzymes [superoxide dismutase (SOD) and catalase] were tested via an enzymatic assay. The mitochondrial membrane potential (MMP) was monitored by flow cytometry using JC-1 staining. Phosphorylation levels of glycogen synthase kinase-3p (p-GSK-3P) and Akt (p-Akt), as well as total GSK-3p and Akt were determined by Western blotting. The results showed that ezetimibe treatment inhibited HUVECs apoptosis, intracellular ROS production, and enhanced antioxidant enzyme activities elicited by oxLDL. HUVECs exposed to oxLDL alone had reduced mitochondrial function, while ezetimibe pre-intervention could significantly rescue the MMP. Furthermore, the protein levels

of p-GSK-3p and p-Akt in ezetimibe-pretreated HUVECs were markedly increased as compared with those in oxLDL-induced HUVECs. However, no significant effect on total GSK- 3P and Akt was found in ezetimibe-pretreated HUVECs. Taken together, it was concluded that ezetimibe protects against oxLDL-induced oxidative stress through restoring the MMP, which may be mediated by Akt-dependent GSK-3P phosphorylation.

[14] *Ren J, Liu W, Li GC et al.* **Atorvastatin Attenuates Myocardial Hypertrophy Induced by Chronic Intermittent Hypoxia In Vitro Partly through miR-31/PKCepsilon Pathway**. Current medical science 2018; 38:405-412.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30074205
ABSTRACT
Atorvastatin is proven to ameliorate cardiac hypertrophy induced by chronic intermittent hypoxia (CIH). However, little is known about the mechanism by which atorvastatin modulates CIH-induced cardiac hypertrophy, and whether specific hypertrophyrelated microRNAs are involved in the modulation. MiR-31 plays key roles in the development of cardiac hypertrophy induced by ischemia/hypoxia. This study examined whether miR-31 was involved in the protective role of atorvastatin against CIH-induced myocardial hypertrophy. H9c2 cells were subjected to 8-h intermittent hypoxia per day in the presence or absence of atorvastatin for 5 days. The size of cardiomyocytes, and the expression of caspase 3 and miR-31 were determined by Western blotting and RT-PCR, respectively. MiR-31 mimic or Ro 31-8220, a specific inhibitor of protein kinase C epsilon (PKCepsilon), was used to determine the role of miR-31 in the anti-hypertrophic effect of atorvastatin on cardiomyocytes. PKCepsilon in the cardiomyocytes with miR-31 upregulation or downregulation was detected using RT-PCR and Western blotting. The results showed that CIH induced obvious enlargement of cardiomyocytes, which was paralleled with increased atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and slow/beta cardiac myosin heavy-chain (MYH7) mRNA levels. All these changes were reversed by the treatment with atorvastatin. Meanwhile, miR-31 was increased by CIH in vitro. Of note, the atorvastatin pretreatment significantly increased the mRNA and protein expression of PKCe and decreased that of miR-31. Moreover, overexpression of miR-31 abolished the anti-hypertrophic effect of atorvastatin on cardiomyocytes. Upregulation and downregulation of miR-31 respectively decreased and increased the mRNA and protein expression of PKCepsilon. These results suggest that atorvastatin provides the cardioprotective effects against CIH probably via up-regulating PKCepsilon and down-regulating miR-31.

[15] *Zheng Y, Ma AG, Zheng MC et al.* **B Vitamins Can Reduce Body Weight Gain by Increasing Metabolism-related Enzyme Activities in Rats Fed on a High-Fat Diet**. Current medical science 2018; 38:174-183.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30074168
ABSTRACT
B vitamins are enzyme cofactors that play an important role in energy metabolism. The aim of this study was to elucidate whether B vitamin administration can reduce body weight (BW) gain by improving energy metabolism-related enzyme activities in rats fed on a highfat diet. Fifty rats were randomly assigned to one of the following five groups: control group (C), including rats fed on standard rat chow; four treatment groups (HO, HI, H2, and H3), in which rats were

fed on a high-fat diet. Rats in the HI group were treated daily with 100 mg/kg BW thiamine (VB1), 100 mg/kg BW riboflavin (VB2), and 250 mg/kg BW niacin (VPP); rats in the H2 group were treated daily with 100 mg/kg BW pyridoxine (VB6), 100 mg/kg BW cobalamin (VB12), and 5 mg/kg BW folate (FA); and rats in the H3 group were treated daily with all of the B vitamins administered to the HI and H2 groups. After 12 weeks, the BW gains from the initial value were 154.5+/-58.4 g and 159.1+/-53.0 g in the HI and C groups, respectively, which were significantly less than the changes in the HO group (285.2+/-14.8 g, P<0.05). In the HO group, the plasma total cholesterol (CHO) and triglyceride (TG) levels were 1.59+/-0.30 mmol/L and 1,55+/-0.40 mmol/L, respectively, which were significantly greater than those in the HI group (1.19+/-0.18 mmol/L and 0.76+/-0.34 mmol/L, respectively, P<0.05). The activities of transketolase (TK), glutathione reductase, and Na(+)/K(+) adenosine triphosphatase were significantly increased in the B vitamin-treated groups and were significantly greater than those in the HO group (P<0.05). Furthermore, the glucose-6-phosphate dehydrogenase, pyruvic acid kinase, and succinate dehydrogenase activities also were increased after treatment with B vitamins. Supplementation with B vitamins could effectively reduce BW gain and plasma levels of lipids by improving energy metabolism-related enzyme activities in rats, thus possibly providing potential benefits to humans.

[16] *Mohan H, Brandt SL, Kim JH et al.* **3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) Prevents HFD Induced Insulin Resistance via the Maintenance of Hepatic Lipid Homeostasis**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30062833
ABSTRACT
AIM: Prescription omega-3 fatty acid ethyl ester supplements are commonly used for the treatment of dyslipidemia in humans. Recent studies show that 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), a metabolite formed from fish oil supplementation, was able to prevent and reverse high fat diet (HFD) induced fatty liver in mice. In the present study, we investigated the underlying molecular mechanisms responsible for CMPF's hepatic lipid lowering effects. MATERIALS AND METHODS: CD1 male mice were i.p. injected with CMPF (Dosage: 6 mg/kg) for 7 days followed by 5wks 60% HFD to induce a fatty liver phenotype. Metabolic parameters, liver morphology, lipid content, protein expression and microarray analysis were assessed. We also utilized primary hepatocytes, an in-vitro model to further investigate the direct effects of CMPF on hepatic lipid utilization and biosynthesis. RESULTS: CMPF treated mice display enhanced hepatic lipid clearance while preventing hepatic lipid storage, thereby protecting against liver lipid accumulation and development of HFD induced hepatic insulin resistance. Mechanistically, as CMPF enters into the liver, it acts as an allosteric ACC inhibitor, which directly induces both fatty acid oxidation and hepatic FGF21 production. A feed-back loop is initiated by CMPF, which exists between ACC inhibition, fatty acid oxidation, and FGF21 production. As a consequence, an adaptive decrease in Insig2/SREBP-1c/FAS protein expression results in priming of the liver to prevent a HFD induced fatty liver phenotype. CONCLUSION: CMPF is a potential driver of hepatic lipid metabolism, preventing diet induced hepatic lipid deposition and insulin resistance long-term.

[17] *Mathur M, Vemula KD*. **Investigation of different types of nano drug delivery systems of Atorvastatin for the treatment of Hyperlipidemia**. Drug development and industrial pharmacy 2018:1-36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30073852
ABSTRACT
Different nanoparticles namely solid lipid nanoparticles, nanocrystals and nanosponges loaded with atorvastatin were successfully fabricated with desirable technological properties which reckoned promising methods of their preparation. Further, suitable characterization and evaluation parameters for in-vitro and in-vivo studies were conducted which led to increase in drug's bioavailability, provided better in-vivo efficacy and reduced toxicity in treating hyperlipidemia systemically. Particle sizes were found to be less than 300nm, with minimal polydispersity indices and maximized entrapment efficiency which are pre requisites for their absorption in intestines. Drug release studies showed sustained release for a prolonged period which was justified by release kinetics. Augmented bioavailability and reduced lipoprotein levels were the key observations. In addition, reduced hepatotoxicty, decreased myotoxicity and diminished drug distribution were also the important highlights of these developed nanosystems as compared to the pure drug and marketed formulation. Histopathology of liver confirmed reduced hepatotoxicity. An elaborate comparison of these nanoparticles along with pure drug and marketed formulation concluded that nanosponges are potentially one of the best nanosystems for treating hyperlipidemia by systemic delivery.

[18] *Jerome RN, Pulley JM, Roden DM et al.* **Reply to Ward and Colleagues' Comment on "Using Human Experiments of Nature to Predict Drug Safety Issues: An Example with PCSK9 Inhibitors"**. Drug Saf 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30066313
ABSTRACT

[19] *Ward LD, Moffat GJ, Yuan J, Nioi P*. **Comment on "Using Human 'Experiments of Nature' to Predict Drug Safety Issues: An Example with PCSK9 Inhibitors"**. Drug Saf 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30066314
ABSTRACT

[20] *Winter MP, Wiesbauer F, Blessberger H et al.* **Lipid Profile and Long-term Outcome in Premature Myocardial Infarction**. European journal of clinical investigation 2018:e13008.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30062727
ABSTRACT
BACKGROUND: Premature myocardial infarction (</=40 years) represents a rare disease with a distinct risk factor-profile and a lipid phenotype that is characterized by a predominance of elevated triglyceride-rich lipoproteins. So far high-density and low-density lipoproteins remain the primary targets for risk stratification and treatment evaluation in coronary artery disease, but this strategy might be insensitive in patients with premature myocardial infarction. AIM: Aim of the present study was to investigate the predictive value of different lipid fractions on long term cardiovascular outcome in patients with premature myocardial infarction. METHODS: We prospectively enrolled 102 consecutive AMI survivors (</= 40 years) in this prospective

multicentre study and investigated the influence of the familial combined hypercholesterolemia phenotype and a corresponding multimarker panel of different lipid fractions on cardiovascular outcome. RESULTS: Total cholesterol, non- HDL cholesterol, remnant cholesterol and Apo B lipoprotein were significantly higher in patients experiencing MACE as compared to those who did not. The familial combined hypercholesterolemia phenotype was associated with an unfavourable cardiovascular outcome even after adjustment for potential cofounders (adjusted HR 3.04,95% CI, 1.26-7.34, p= 0.013). Remnant cholesterol revealed the strongest association with MACE (adj.HR 1.94, 95%CI. 1.30-2.99, p= 0.001). Interestingly LDL and HDL revealed no significant impact on cardiovascular outcome in the present study cohort. CONCLUSION: Non-HDL and remnant cholesterol are strongly associated with an unfavourable outcome in patients with premature myocardial infarction and might be the preferred treatment target for lipid-lowering therapy.

[21] *Wang HM, Gao JH, Lu JL*. **Pravastatin improves atherosclerosis in mice with hyperlipidemia by inhibiting TREM-1/DAP12**. European review for medical and pharmacological sciences 2018; 22:4995-5003.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30070336
ABSTRACT
OBJECTIVE: To study the protective effect of pravastatin on blood vessels in mice with hyperlipemia. MATERIALS AND METHODS: Apolipoprotein E (ApoE)-/- and triggering receptor expressed on myeloid (TREM)-/ApoE-/- mice were selected and fed with high-fat food, which were then subdivided into the control group and the pravastatin intervention group. C57BL/6J mice were used as controls. Oil Red O staining was used to stain aortas and sections so as to observe the level and basic composition of plaques. Immunohistochemistry was applied to detect inflammatory cells expression in aortic plaques. Real-time polymerase chain reaction (PCR) was employed to detect the expressions of TREM-1, tumor necrosis factor-alpha (TNF-alpha), and interleukin-1 (IL-1) messenger ribonucleic acids (mRNAs) in vascular tissues of mice in different groups, and the expressions of TREM-1, DNAX-activating protein of molecular mass 12 (DAP12), TNF-alpha, and IL-1 were detected via Western blotting technique. RESULTS: Pravastatin reduced the area of atherosclerotic plaques and improved the plaque formation by reducing lipid deposits and alleviating plaque inflammatory responses. In the pravastatin group, the expression of TREM-1 in the aorta atherosclerotic plaque of mice was decreased, the expressions of TREM-1 and DAP12 genes and proteins in vascular tissue cells declined, and the expressions of the downstream inflammatory factors, TNF-alpha, IL-1 were reduced. CONCLUSIONS: Pravastatin improves atherosclerosis (AS) in mice by inhibiting TREM-1/DAP12.

[22] *Singh A, Davidson M*. **Update on PCSK9 therapies for the treatment of dyslipidemia**. Expert review of endocrinology & metabolism 2016; 11:87-95.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30063452
ABSTRACT
The mechanistic role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in cholesterol metabolism has been well elucidated, and serves as an example of how genetics has informed modern drug development with the advent of PCSK9 inhibitors. PCSK9 is intimately involved in the hepatic regulation of the Low-density lipoprotein (LDL) receptor, which in turn plays a key

role in the circulation of serum LDL. Monoclonal antibodies targeting PCSK9, which act by inhibiting PCSK9 thereby allowing for constitutively active LDL receptors, are now well established as an effective method for significant LDL lowering. Ongoing cardiovascular outcomes trials will hopefully highlight a concomitant and clinically meaningful reduction in adverse outcomes with their use. In the meantime, the PCSK9 journey, from initial discovery and description in 2003, to FDA approval in 2015, illustrates the interest and need for novel lipid therapies, as there are large populations for whom statin therapy alone is not adequate in optimizing their cardiovascular risk profile.

[23] *Bagchi S, Genardi S, Wang CR*. **Linking CD1-Restricted T Cells With Autoimmunity and Dyslipidemia: Lipid Levels Matter**. Frontiers in immunology 2018; 9:1616.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30061888
ABSTRACT
Dyslipidemia, or altered blood lipid content, is a risk factor for developing cardiovascular disease. Furthermore, several autoimmune diseases, including systemic lupus erythematosus, psoriasis, diabetes, and rheumatoid arthritis, are correlated highly with dyslipidemia. One common thread between both autoimmune diseases and altered lipid levels is the presence of inflammation, suggesting that the immune system might act as the link between these related pathologies. Deciphering the role of innate and adaptive immune responses in autoimmune diseases and, more recently, obesity-related inflammation, have been active areas of research. The broad picture suggests that antigen-presenting molecules, which present self-peptides to autoreactive T cells, can result in either aggravation or amelioration of inflammation. However, very little is known about the role of self-lipid reactive T cells in dyslipidemia-associated autoimmune events. Given that a range of autoimmune diseases are linked to aberrant lipid profiles and a majority of lipid-specific T cells are reactive to self-antigens, it is important to examine the role of these T cells in dyslipidemia-related autoimmune ailments and determine if dysregulation of these T cells can be drivers of autoimmune conditions. CD1 molecules present lipids to T cells and are divided into two groups based on sequence homology. To date, most of the information available on lipid-reactive T cells comes from the study of group 2 CD1d-restricted natural killer T (NKT) cells while T cells reactive to group 1 CD1 molecules remain understudied, despite their higher abundance in humans compared to NKT cells. This review evaluates the mechanisms by which CD1-reactive, self-lipid specific T cells contribute to dyslipidemia-associated autoimmune disease progression or amelioration by examining available literature on NKT cells and highlighting recent progress made on the study of group 1 CD1-restricted T cells.

[24] *Moriarty F, Bennett K, Fahey T*. **Fixed-dose combination antihypertensives and risk of medication errors**. Heart 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30072364
ABSTRACT
OBJECTIVE: While fixed-dose combinations (FDC) can improve adherence, they may add complexity to the prescribing/dispensing process, potentially increasing risk of medication errors. This study aimed to determine if prescriptions for antihypertensive FDCs increase the risk of therapeutic duplication and drug-drug interactions (DDI). METHODS: This retrospective

observational study used administrative pharmacy claims data from the Irish Primary Care Reimbursement Service. Prescriptions dispensed to adults in 2015 were included if they contained an antihypertensive FDC, or the same drugs prescribed separately. The outcomes were therapeutic duplication and potentially serious DDI involving FDC drugs. Relative risk (RR) of these outcomes, adjusted for prescription and patient factors, was determined using generalised linear models with Poisson distributions and propensity score matching. RESULTS: This study included 307 833 FDC prescriptions (67.0%) and 151 632 separate component prescriptions. Half of patients prescribed FDCs were female with a mean age of 67.1 (SD 12.5) years and, compared with separate component prescriptions, FDCs were less often coprescribed with other cardiovascular medications. Therapeutic duplication occurred in 0.8% of prescriptions, most often involving calcium channel blockers, and 10.6% contained a DDI (most often amlodipine and simvastatin). The RR of therapeutic duplication on FDC prescriptions compared with separate component prescriptions was 1.46 (95% CI 1.17 to 1.83) and the adjusted RR was 2.06 (95% CI 1.64 to 2.60). For DDIs, there was no significant difference between FDC and separate component prescriptions after confounder adjustment. CONCLUSIONS: This study found FDCs were associated with increased risk of duplication. When considering prescribing FDCs, this safety consideration should be weighed against potential benefits.

[25] *Nose D, Shiga Y, Ueda Y et al.* **Correction to: Association between plasma levels of PCSK9 and the presence of coronary artery disease in Japanese**. Heart Vessels 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30076455
ABSTRACT
In the original publication of the article, Tables 1, 2 and 3 was published incorrectly. Unnecessary inequality symbols were added to all the numbers in the 'p value' of Tables 1, 2 and 3. The correct tables should be as follows.

[26] *Liberale L, Bertolotto M, Carbone F et al.* **Resistin exerts a beneficial role in atherosclerotic plaque inflammation by inhibiting neutrophil migration**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30075966
ABSTRACT
BACKGROUND: Neutrophil functions have been shown to be modulated by adipocytokines during atherogenesis. The immuno-regulatory role of resistin on neutrophil-mediated activities in atherosclerotic patients remains elusive. Here, we aimed at exploring the association between serum levels of resistin and neutrophil products either in the systemic circulation or within plaques in a cohort of patients with severe carotid plaque stenosis undergoing endarterectomy. In addition, we assessed the effects of resistin on neutrophil pro-atherosclerotic functions in vitro. METHODS: Inflammatory biomarkers, neutrophil products and resistin levels were assessed in patients' sera and carotid plaques by ELISA and immunohistochemistry analysis. In vitro, human primary neutrophils isolated from healthy donors were assessed on different substrate cultures for: degranulation (by ELISA), migration (by microchemotaxis Boyden chamber), F-actin polymerization (by fluorescent assay), integrin and chemokine receptor expression (by flow cytometry) and apoptosis (by both morphologic

analysis and flow cytometry). RESULTS: Serum resistin was positively correlated with serum levels of neutrophil granule products, but inversely with intraplaque neutrophil and MMP-9 contents. In vitro, resistin was detected in supernatants of degranulating neutrophils and positively correlated with other granule products. Although resistin did not affect neutrophil degranulation, apoptosis and integrin or chemokine receptor expression, pre-incubation with human recombinant resistin abrogated CXCL8-induced neutrophil migration and F-actin polymerization by inhibiting ERK2 phosphorylation. CONCLUSION: Resistin can be released by degranulating neutrophils and blunts neutrophil plaque infiltration by modulating their migration towards known atherosclerotic mediators. These results suggest a potential immunoregulatory role of resistin in inhibiting neutrophil-mediated atherosclerotic activities.

[27] *Wang L, Wang Z, Shi J et al.* **Inhibition of proprotein convertase subtilisin/kexin type 9 attenuates neuronal apoptosis following focal cerebral ischemia via apolipoprotein E receptor 2 downregulation in hyperlipidemic mice**. International journal of molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30066942
ABSTRACT
The inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) protects a variety of cell types against neuronal apoptosis by binding to apolipoprotein E receptor 2 (ApoER2). The present study aimed to determine the association between PCSK9/ApoER2 signaling and neuronal apoptosis following middle cerebral artery occlusion (MCAO) injury in hyperlipidemic mice. For this purpose, C57BL/6 mice fed with a highfat diet (HFD) for 6 weeks were exposed to MCAO. Subsequently, PCSK9 was inhibited by a lentiviral vector harboring shorthairpin RNA (shRNA) targeting PCSK9, which was stereotaxically injected into the cerebral cortex of mice. At 48 h postischemia, hematoxylineosin staining and a terminal deoxynucleotidyl transferase dUTP nick end labeling assay were performed to determine cerebral tissue injury and apoptosis. PCSK9 and ApoER2 expression levels were assessed by reverse transcriptionquantitative polymerase chain reaction, immunohistochemistry and western blotting. The results indicated that hyperlipidemia and increased PCSK9 expression were evident in HFD mice. Cerebral histological injury and neuronal apoptosis, as well as PCSK9 and ApoER2 levels, which were increased upon ischemia in hyperlipidemic mice, were attenuated by PCSK9 shRNA treatment. These protective effects of PCSK9 shRNA interference were associated with decreased neuronal apoptosis and a reduced level of ApoER2 expression in the hippocampus and cortex. The data of the present study demonstrated that the PCSK9 shRNAmediated antiapoptotic effect induced by MCAO in hyperlipidemic mice is associated with ApoER2 downregulation, which may be a potential new therapy for stroke treatment in patients with hyperlipidemia.

[28] *Pohlen M, Pirker L, Lustrik M, Dreu R*. **A redispersible dry emulsion system with simvastatin prepared via fluid bed layering as a means of dissolution enhancement of a lipophilic drug**. Int J Pharm 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30075251
ABSTRACT
The purpose of the study was to develop a redispersible dry emulsion, containing a lipophilic, poorly water soluble model drug simvastatin, by employing fluid bed coating technology. The presented dry emulsion manufacturing approach produces pellets in a way, where a layer of

the dry emulsion is applied to a neutral core. In the preliminary formulation development phase 1-oleoyl-rac-glycerol was chosen as the oily lipid phase, based on the high drug solubility and potential bioavailability enhancement capability. Mannitol, HPMC and Tween 20 were selected as the solid carriers and surfactant, respectively. The design of experiments, specifically the mixture design approach, was used to obtain the optimal formulation composition. The emulsion reconstitution ability and stability were the main responses, used as the decisive parameters for formulation optimisation. Optimised formulations showed narrow droplet size distribution upon reconstitution, high stability, suitable drug loading and enhanced dissolution profile, compared to a non-lipid based tablet and the pure drug. The scanning electron microscopy, Raman spectroscopy and image analysis disclosed a uniform morphology of the applied layer with separated droplets with simvastatin and uniform size distribution and a circular shape of coated pellets. The study represents the proof of concept of designing redispersible dry emulsions using a fluid bed layering approach.

[29] *Zhao Y, Chen ZY*. **Roles of Spicy Foods and Their Bioactive Compounds in Management of Hypercholesterolemia**. Journal of agricultural and food chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30056715
ABSTRACT
Hypercholesterolemia, as one of the major risk factors in development of cardiovascular diseases, is of mounting prevalence worldwide in recent years. Many nutraceuticals and phytochemical supplements serve as a promising complementary therapy in the management of hypercholesterolemia. Among them, spicy foods have attracted a special attention. Plasma lipid-lowering activity of garlic, ginger, and turmeric have been well studied in both humans and animals. Consumption of either 3 g/day of ginger or 2 g/day curcumin for over 4 weeks effectively reduced blood cholesterol in hypercholesterolemia subjects. However, effects of chili and black peppers on blood cholesterol are little studied clinically. The present review is to summarize the findings of recent studies on the efficacy and mechanism of spicy foods and their primary bioactive components in management of hypercholesterolemia from preclinical studies to clinical trials.

[30] *Sturm AC, Knowles JW, Gidding SS et al.* **Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel**. Journal of the American College of Cardiology 2018; 72:662-680.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30071997
ABSTRACT
Although awareness of familial hypercholesterolemia (FH) is increasing, this common, potentially fatal, treatable condition remains underdiagnosed. Despite FH being a genetic disorder, genetic testing is rarely used. The Familial Hypercholesterolemia Foundation convened an international expert panel to assess the utility of FH genetic testing. The rationale includes the following: 1) facilitation of definitive diagnosis; 2) pathogenic variants indicate higher cardiovascular risk, which indicates the potential need for more aggressive lipid lowering; 3) increase in initiation of and adherence to therapy; and 4) cascade testing of at-risk relatives. The Expert Consensus Panel recommends that FH genetic testing become the standard of care for patients with definite or probable FH, as well as for their at-risk relatives.

Testing should include the genes encoding the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin 9 (PCSK9); other genes may also need to be considered for analysis based on patient phenotype. Expected outcomes include greater diagnoses, more effective cascade testing, initiation of therapies at earlier ages, and more accurate risk stratification.

[31] *Teramoto T, Usami M, Takagi Y, Baccara-Dinet MT*. **Efficacy and Safety of Alirocumab in Japanese Patients with Diabetes Mellitus: Post-hoc Subanalysis of ODYSSEY Japan**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30068817
ABSTRACT
AIM: To examine the efficacy and safety of alirocumab in Japanese patients with dyslipidemia with or without diabetes mellitus (DM). METHODS: Patients (n=216) with heterozygous familial hypercholesterolemia (heFH), non-FH at high cardiovascular risk with coronary artery disease (CAD), or category III (primary prevention) were enrolled; 148 (68.5%) patients had a diagnosis of DM at baseline. Patients were randomized (2:1), with stratification factor (heFH, non-FH), to alirocumab (75 mg every 2 weeks [Q2W] with increase to 150 mg if week 8 LDL-C was above predefined limits) or placebo subcutaneously for 52 weeks on top of stable statin therapy. RESULTS: At Week 24, least square (LS) mean+/-standard error changes in low-density lipoprotein cholesterol (LDL-C) concentration from baseline in alirocumab-treated patients were 63.1+/-1.6% and 60.8+/-2.7% in those with and without DM. These LDL-C reductions were maintained to Week 52: 63.0+/-1.6% (LS mean difference vs placebo 62.4+/-3.0%; P0.0001) with DM and 61.3+/-2.8% (LS mean difference vs placebo 53.4+/-4.0%; P0.0001) without DM. The most common adverse events in the alirocumab group were nasopharyngitis, back pain, injection site reaction, and fall. No particular safety signals or concerns were noted between DM and non-DM groups at 52 weeks. A dose-increase in alirocumab from 75 to 150 mg Q2W was necessary in two heFH patients, neither of whom had DM. CONCLUSIONS: In high-cardiovascular-risk Japanese patients with hypercholesterolemia on stable statin therapy, alirocumab produced substantial and sustained LDL-C reductions throughout the 52-week study regardless of DM status at baseline, with a similar safety profile to placebo.

[32] *Bittner VA, Giugliano RP, Brinton EA, Guyton JR*. **PCSK9 inhibitors for prevention of atherosclerotic cardiovascular disease**. Journal of clinical lipidology 2018; 12:835-843.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30055750
ABSTRACT
The discovery of proprotein convertase subtilisin kexin-type 9 (PCSK9) and the development of inhibitors of PCSK9 function appear to mark an epochal advance in clinical lipidology. PCSK9 is a circulating protein that binds to low-density lipoprotein (LDL) receptors and facilitates their lysosomal degradation following internalization in cells. Blocking PCSK9 thus increases the recycling of LDL receptors and results in more receptors on the cell surface, particularly in the liver, thereby lowering LDL levels. In this Roundtable, we discuss the recent large cardiovascular outcomes trials in which evolocumab and alirocumab, monoclonal antibodies directed against PCSK9, successfully reduced major cardiovascular events. We discuss the safety of these drugs

as well as the safety of maintaining very low LDL cholesterol levels. Finally, we address pragmatic considerations affecting the use of PCSK9 inhibitors in clinical practice.

[33] *Salvador C, Entenmann A, Salvador R et al.* **Combination therapy of omega-3 fatty acids and acipimox for children with hypertriglyceridemia and acute lymphoblastic leukemia**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30055974
ABSTRACT
BACKGROUND: Lipemic alterations are commonly seen in pediatric patients with acute lymphoblastic leukemia (ALL) treated with corticosteroids and L-asparaginase. OBJECTIVE: In these children, hypertriglyceridemia rarely causes symptoms and mostly responds well to a low-fat diet. Only few patients demand further therapy, which is not clearly approved in the literature to date. Therefore, it may be important to compile generally accepted standard procedures for lipid-lowering therapy in the pediatric ALL population. METHODS: We performed a study on 119 newly diagnosed pediatric patients with ALL, all treated according to the ALL-BFM 2000 protocol at our institution between the years 2000 and 2009, to evaluate the incidence of hypertriglyceridemia and the efficacy of a combination therapy with omega-3 fatty acids and acipimox in hypertriglyceridemic patients who did not respond to diet. RESULTS: We observed hypertriglyceridemia in 34.5% of patients in this collective. In the majority, normalization of triglycerides was successfully managed by administration of a low-fat diet. However, 7.6% of patients (related to total study population) with hypertriglyceridemia did not show diminished lipid levels during diet and/or presented with symptoms such as abdominal pain, dyspnea, or anginal chest pain. In these cases, we performed a lipid-lowering combination therapy with omega-3 fatty acids and acipimox. We observed a prompt decline of serum triglycerides to normal values and an improvement of symptoms within days after onset of this therapy without occurrence of any side effects. CONCLUSION: In summary, the combination treatment with omega-3 fatty acids and acipimox could represent an alternative to other reported lipid-lowering therapies without severe adverse reactions.

[34] *Sampietro T, Bigazzi F, Sbrana F et al.* **Personalized regimen for PCSK9 inhibitors: A therapeutic option that maintains efficacy and reduces costs**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30057259
ABSTRACT

[35] *Roelfsema F, Yang RJ, Veldhuis JD*. **Estradiol Does Not Influence Lipid Measures and Inflammatory Markers in Testosterone-Clamped Healthy Men**. Journal of the Endocrine Society 2018; 2:882-892.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30057969
ABSTRACT
Context: Experimentally controlled studies of estrogenic regulation of lipid measures and inflammatory cytokines in men are rare. Objective: To delineate the effect of estradiol (E2) on lipids and inflammatory markers. Design: This was a placebo-controlled, single-masked, prospectively randomized study comprising experimentally degarelix-downregulated healthy

men [n = 74; age 65 years (range, 57 to 77)] assigned to four treatment groups: (1) IM saline and oral placebo; (2) IM testosterone and oral placebo; (3) IM testosterone and oral anastrozole (aromatase inhibitor); and (4) IM testosterone, oral anastrozole, and transdermal E2 for 22 (+/-1) days. Results: Mean mass spectrometry-quantified serum E2 concentrations ranged from 1.2 to 82 pg/mL in the four treatment groups. E2 extremes did not alter total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol (HDL-C) , non-HDL-C, apolipoprotein B, lipoprotein (a), IL-6, or high-sensitivity C-reactive protein (hsCRP) concentrations. Higher E2 concentrations elevated both sex hormone-binding globulin and prolactin as positive controls. LDL cholesterol, adiponectin, and leptin were higher in hypogonadal subjects without testosterone or E2 addback (P = 0.018, 0.039, and 0.023, respectively). Abdominal visceral fat area by CT (independent variable) correlated negatively with HDL-C (P = 0.017), and positively with triglycerides (P = 0.004), hsCRP (P = 0.005), and leptin (P < 0.0001). Conclusion: In this placebo-controlled prospectively randomized study, wide variations in circulating E2 did not influence lipid measures and inflammatory markers when testosterone concentrations were controlled experimentally. However, medically induced central hypogonadism in older men was accompanied by increased LDL cholesterol and metabolic cytokines, adiponectin and leptin. Abdominal visceral fat correlated strongly and positively with triglycerides, hsCRP, and leptin, but negatively with HDL.

[36] *Pose E, Trebicka J, Mookerjee RP et al.* **Statins: old drugs as new therapy for liver diseases?** Journal of hepatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30075229
ABSTRACT
In addition to their effects in lowering cholesterol levels, statins have pleiotropic effects, particularly anti-inflammatory, antiangiogenic, and antifibrotic, that may be beneficial in some chronic inflammatory conditions. The effects of statins as potential treatment in chronic liver diseases have not been investigated until very recently due to concerns related to their safety in patients with liver impairment. A number of experimental studies in animal models of liver diseases have shown that statins decrease hepatic inflammation, fibrogenesis and portal pressure. In addition, retrospective cohort studies in large populations of patients with cirrhosis and pre-cirrhotic conditions have shown that treatment with statins with the purpose of decreasing high cholesterol levels was associated with reduced risk of disease progression, hepatic decompensation, hepatocellular carcinoma development, and death. These beneficial effects persisted after adjustment for disease severity and other potential confounders. Finally, few randomized controlled trials have shown that treatment with simvastatin decreases portal pressure (two studies) and mortality (one study). Statin treatment was generally well tolerated but a few patients developed severe side effects, particularly rhabdomyolysis. Despite these promising beneficial effects, further randomized controlled trials in large series of patients with hard clinical endpoints should be performed before statins can be recommended for use in clinical practice.

[37] *Kander T, Lindblom E, Schott U*. **Dose-response effects of omega-3 on platelet aggregation: an observational study**. J Int Med Res 2018:300060518789817.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30060687

ABSTRACT
Objective This study aimed to evaluate the dose-response effects of supplemental omega-3 fatty acids on platelet function in healthy volunteers. Methods Twelve healthy volunteers ingested a normal supplemental dose of 1260 mg omega-3 fatty acids daily for 5 days, followed by a high dose of 2520 mg daily for another 5 days. Multiple electrode aggregometry (MEA) with four different agonists was used to measure platelet aggregation before and after the normal- and high-dose regimes. In vitro spiking using physiological doses of omega-3 fatty acids was also performed to determine whether MEA is capable of detecting a platelet-inhibiting effect due to omega-3 fatty acids. Results There were no differences in platelet aggregation measured by the MEA assay in healthy volunteers after intake of either the normal or high dose of omega-3 fatty acids. In the in vitro experiment, a platelet-inhibiting effect of omega-3 fatty acids was shown by an arachidonic acid agonist in MEA . Conclusions Supplemental omega-3 fatty acids do not evoke their positive health effects through inhibition of platelet aggregation measurable with MEA.

[38] *Zhang X, Xiao S, Li Q*. **Pravastatin polarizes the phenotype of macrophages toward M2 and elevates serum cholesterol levels in apolipoprotein E knockout mice**. J Int Med Res 2018:300060518787671.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30058421
ABSTRACT
Objective Statins are clinically used for protection against cardiovascular disease with lipid-lowering and anti-inflammatory properties. These properties tip the balance of macrophage polarization, which is an essential process in the development and progression of atherosclerosis. This study aimed to investigate the effect of pravastatin on atherosclerosis of the aorta in apolipoprotein E knockout (apoE-KO) mice without high lipid feeding. Methods Six 8-week-old apoE-KO male mice were randomly divided into two groups: a control group and a pravastatin (40 mg.kg(-1).day(-1))-treated group. At 35 weeks, the mice were sacrificed and the size of plaques on the aorta was assessed by Oil Red O staining. M1 and M2 macrophages were identified by inducible nitric oxide synthase and arginase-I, respectively, using immunohistochemistry. Results Pravastatin increased the size of atherosclerotic plaques in apoE-KO mice without high lipid feeding. The ratio of M1/M2 macrophages increased in atherosclerotic plaques, which might slow the process of atherosclerosis, while blood cholesterol levels were elevated. Conclusion Our study suggests that pravastatin polarizes the phenotype of macrophages toward M2 in atherosclerotic lesions, despite an increase in serum cholesterol levels in ApoE-KO mice.

[39] *Rampanelli E, Ochodnicky P, Vissers JPC et al.* **Excessive dietary lipid intake provokes an acquired form of lysosomal lipid storage disease in the kidney**. The Journal of pathology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30073645
ABSTRACT
Obesity and dyslipidaemia are features of the metabolic syndrome and risk factors for chronic kidney disease. The cellular mechanisms connecting metabolic syndrome with chronic kidney disease onset and progression remain largely unclear. We show that proximal tubular epithelium is a target site for lipid deposition upon overnutrition with a cholesterol-rich

Western-type diet. Affected proximal tubule epithelial cells displayed giant vacuoles of lysosomal or autophagosomal origin, harbouring oxidized lipoproteins and concentric membrane layer structures (multilamellar bodies), reminiscent of lysosomal storage diseases; lipidomic analysis revealed renal deposition of cholesterol and phospholipids, including lysosomal phospholipids. Proteomic profiles of renal multilamellar bodies were distinct from those of epidermis or lung multilamellar bodies and of cytoplasmic lipid droplets. Tubular multilamellar bodies were observed in kidney biopsies of obese hypercholesterolaemic patients, and the concentration of the phospholipidosis marker di-docosahexaenoyl (22:6) bis(monoacylglycerol) phosphate was doubled in urine from individuals with metabolic syndrome and chronic kidney disease. The enrichment of proximal tubule epithelial cells with phospholipids and multilamellar bodies was accompanied by enhanced inflammation, fibrosis, tubular damage markers and higher urinary electrolyte content. Concomitantly to the intralysosomal lipid storage, a renal transcriptional response was initiated to enhance lysosomal degradation and lipid synthesis. In cultured proximal tubule epithelial cells, inhibition of cholesterol efflux transport or oxysterol treatment induced effects very similar to the in vivo situation, such as multilamellar body and phospholipid amassing, and induction of damage, inflammatory, fibrotic and lipogenic molecules. Onset of phospholipidosis onset in proximal tubule epithelial cells is a novel pathological trait in metabolic syndrome-related chronic kidney disease, and emphasizes the importance of healthy lysosomes and nutrition for kidney wellbeing.

[40] *Jiang R, Zhao S, Wang R et al.* **Safety and Efficacy of Atorvastatin for Chronic Subdural Hematoma in Chinese Patients: A Randomized ClinicalTrial**. JAMA neurology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30073290

ABSTRACT

Importance: Chronic subdural hematoma (CSDH) is a trauma-associated condition commonly found in elderly patients. Surgery is currently the treatment of choice, but it carries a significant risk of recurrence and death. Nonsurgical treatments remain limited and ineffective. Our recent studies suggest that atorvastatin reduces hematomas and improves the clinical outcomes of patients with CSDH. Objective: To investigate the safety and therapeutic efficacy of atorvastatin to nonsurgically treat patients with CSDH. Design, Setting, and Participants: The Effect of Atorvastatin on Chronic Subdural Hematoma (ATOCH) randomized, placebo-controlled, double-blind phase II clinical trial was conducted in multiple centers in China from February 2014 to November 2015. For this trial, we approached 254 patients with CSDH who received a diagnosis via a computed tomography scan; of these, 200 (78.7%) were enrolled because 23 patients (9.1%) refused to participate and 31 (12.2%) were disqualified. Interventions: Patients were randomly assigned to receive either 20 mg of atorvastatin or placebo daily for 8 weeks and were followed up for an additional 16 weeks. Main Outcomes and Measures: The primary outcome was change in hematoma volume (HV) by computed tomography after 8 weeks of treatment. The secondary outcomes included HV measured at the 4th, 12th, and 24th weeks and neurological function that was evaluated using the Markwalder grading scale/Glasgow Coma Scale and the Barthel Index at the 8th week. Results: One hundred ninety-six patients received treatment (169 men [86.2%]; median [SD] age, 63.6 [14.2] years). The baseline HV and clinical presentations were similar between patients who were taking atorvastatin (98 [50%])

and the placebo (98 [50%]). After 8 weeks, the HV reduction in patients who were taking atorvastatin was 12.55 mL more than those taking the placebo (95% CI, 0.9-23.9 mL; P = .003). Forty-five patients (45.9%) who were taking atorvastatin significantly improved their neurological function, but only 28 (28.6%) who were taking the placebo did, resulting in an adjusted odds ratio of 1.957 for clinical improvements (95% CI, 1.07-3.58; P = .03). Eleven patients (11.2%) who were taking atorvastatin and 23 (23.5%) who were taking the placebo underwent surgery during the trial for an enlarging hematoma and/or a deteriorating clinical condition (hazard ratio, 0.47; 95% CI, 0.24-0.92; P = .03). No significant adverse events were reported. Conclusions and Relevance: Atorvastatin may be a safe and efficacious nonsurgical alternative for treating patients with CSDH. Trial Registration: ClinicalTrials.gov Identifier: NCT02024373.

[41] *Atherton JJ, Sindone A, De Pasquale CG et al.* **National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of heart failure 2018**. The Medical journal of Australia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30067937
ABSTRACT
INTRODUCTION: Heart failure (HF) is a clinical syndrome that is secondary to an abnormality of cardiac structure or function. These clinical practice guidelines focus on the diagnosis and management of HF with recommendations that have been graded on the strength of evidence and the likely absolute benefit versus harm. Additional considerations are presented as practice points. Main recommendations: Blood pressure and lipid lowering decrease the risk of developing HF. Sodium-glucose cotransporter 2 inhibitors decrease the risk of HF hospitalisation in patients with type 2 diabetes and cardiovascular disease. An echocardiogram is recommended if HF is suspected or newly diagnosed. If an echocardiogram cannot be arranged in a timely fashion, measurement of plasma B-type natriuretic peptides improves diagnostic accuracy. Angiotensin-converting enzyme inhibitors, beta-blockers and mineralocorticoid receptor antagonists improve outcomes in patients with HF associated with a reduced left ventricular ejection fraction. Additional treatment options in selected patients with persistent HF associated with reduced left ventricular ejection fraction include switching the angiotensin-converting enzyme inhibitor to an angiotensin receptor neprilysin inhibitor; ivabradine; implantable cardioverter defibrillators; cardiac resynchronisation therapy; and atrial fibrillation ablation. Multidisciplinary HF disease management facilitates the implementation of evidence-based HF therapies. Clinicians should also consider models of care that optimise medication titration (eg, nurse-led titration). Changes in management as a result of the guideline: These guidelines have been designed to facilitate the systematic integration of recommendations into HF care. This should include ongoing audit and feedback systems integrated into work practices in order to improve the quality of care and outcomes of patients with HF.

[42] *Lugat A, Joubert M, Cariou B, Prieur X*. **[At the heart of diabetic cardiomyopathy: Bscl2 knockout mice to investigate glucotoxicity]**. Medecine sciences : M/S 2018; 34:563-570.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30067203
ABSTRACT

Type 2 diabetes mellitus (T2DM) is a well-recognized independent risk factor for heart failure (HF). T2DM is associated with altered cardiac energy metabolism, leading to ectopic lipid accumulation and glucose overload. However, the relative contribution of these two parameters remains unclear. In order to get new insight into the mechanism involved in diabetic cardiomyopathy, the cardiac phenotype of a unique T2DM mice model has been performed: the seipin knockout mice (SKO). Cardiac phenotyping revealed a diastolic dysfunction associated with hyperglycemia in these mice with a chronic activation of the hexosamine biosynthetic pathway (HBP), suggesting a glucose overload. An inhibitor of the renal sodium/glucose cotransporter 2 (SGLT2), dapagliflozin, successfully prevented the development of cardiomyopathy in SKO mice. This is particularly relevant, given that SGLT2i treatment reduces cardiovascular event in T2DM patients. Therefore, glucose lowering appears an important therapeutic target to prevent cardiac dysfunction associated with T2DM.

[43] *Ye H, Wang S, Hu Y et al.* **Therapeutic effects of different Atorvastatin doses on vulnerable plaques in coronary arteries assessed by intracoronary optical coherence tomography**. Medicine (Baltimore) 2018; 97:e11718.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30075578
ABSTRACT
The aim of this study was to evaluate optical coherence tomography (OCT) as an assessment of the efficacy of atorvastatin treatment.Twenty-four acute coronary syndrome (ACS) patients were allocated to conventional-dose (20 mg atorvastatin, n = 12) and intensive-dose (40-80 mg atorvastatin, n = 12) groups and correlations between changes in the OCT measurements and blood routine indexes were analyzed 9 months post-percutaneous coronary intervention (PCI).Treatment with atorvastatin resulted in a significant increase in the target thin cap fibroatheroma (TCFA) fibrous cap thicknesses in both groups. The increase was bigger in the intensive-dose group than in the conventional-dose group (184.1 +/- 57.4 mum vs. 125.1 +/- 28.6, P = .005). The TCFA lipid core arc in both groups was significantly decreased compared with baseline (72.9 +/- 29.3 vs. 127.6 +/- 50.8, P < .01 and 74.6 +/- 32.9 vs. 132.6 +/- 51.3, P < .01, respectively). Correlation analyses showed an inverse relationship between low-density lipoprotein cholesterol (LDL-c) levels and the TCFA cap thickness, and a direct relationship between C-reactive protein (CRP) level and lipid core arc.Statins significantly increased the TCFA fibrous cap thickness and reduced the lipid core arc, and OCT measurements accurately reflected the levels of blood LDL-c and CRP. TRIAL REGISTRATION: (Chinese Clinical Trial Registry) ChiCTR-IPR-17010874.

[44] *da Silva Junior WS, das Gracas Coelho de Souza M, Neto JFN et al.* **Constitutive DPP4 activity, inflammation, and microvascular reactivity in subjects with excess body weight and without diabetes**. Microvascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30071203
ABSTRACT
OBJECTIVE: In patients with diabetes, dipeptidyl peptidase 4 (DPP4) inhibition is associated with attenuation of inflammation and endothelial dysfunction. Here, we investigated the associations between constitutive DPP4 activity, inflammatory biomarkers, and microvascular reactivity in subjects with excess body weight without diabetes. METHODS: Forty subjects of

BMI>/=25.0kg/m(2) and without diabetes were cross-sectionally evaluated. We assessed microvascular blood flow and vasomotion by laser Doppler flowmetry, and measured at baseline, 30, and 60min after a standardized meal: DPP4 activity, glucose, insulin, hs-CRP, TNF-alpha, IL-6, PAI-1, ICAM-1, and VCAM-1. HOMA-IR and HOMA-AD were used to assess insulin resistance. Linear correlations of DPP4 activity with the biomarkers of inflammation and components of microvascular function were conducted. In step further, multiple regression analyses were performed to test whether some of these variables could influence, or be influenced by, the plasma DPP4 activity. RESULTS: DPP4 activity was inversely associated with VCAM-1 at baseline (P<0.05), and DPP4 activityAUC was inversely correlated with the myogenic componentAUC of vasomotion (P<0.05). In multiple regression analysis, HOMA-AD, IL-6, VCAM-1, PAI-1, blood flow, and vasomotion influenced DPP4 activity and explained almost 40% of the variance on it. When HOMA-AD, VCAM-1, and blood flow were placed respectively as dependent variables, DPP4 activity exerted a significant effect in all of them. CONCLUSIONS: Constitutive DPP4 activity was associated with early markers of endothelial proinflammatory activation and microvascular function, and may have an influence and even be influenced by inflammation and microvascular blood flow in subjects with excess body weight without diabetes.

[45] *Ashour H, Rashed LA, El-Sebaie MM et al.* **Combined gemfibrozil (peroxisome proliferator-activated receptor alpha agonist) with reduced steroid dose gives a similar management picture as the full steroid dose in a rat adjuvant-induced arthritis model**. Modern rheumatology 2018:1-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30074417
ABSTRACT
OBJECTIVES: The study aimed to evaluate the efficacy of combined gemfibrozil with prednisolone in the management of adjuvant-induced arthritis (AIA) rat model. METHODS: Seventy two adult male Wistar albino rats were divided equally into 1-control group, three diseased groups: 2- Adjuvant induced arthritis (AIA), 3- high fat diet (HF), and 4- combined AIA-HF, and treated groups: 5- gemfibrozil 30 mg/kg treated AIA group (AIA-G) and the combined AIA-HF treated groups: 6- prednisolone equivalent to human 10 mg (AIA-HF-P10), 7-prednisolone equivalent to human 5 mg (AIA-HF-P5) 8- gemfibrozil (HF-AIA-G) and 9- combined treatment (HF-AIA-G-P5). RESULTS: HF diet represents a precipitating factor for knee arthritis. Gemfibrozil improved the inflammatory findings in both AIA and AIA-HF groups. Combined administration of gemfibrozil with reduced steroid dose, gave a similar therapeutic effect to the full steroid dose. Fortunately, we reported more reduction in the nuclear factor kappa-B (NF-kappaB) and high mobility group box 1 (HMGB1) in the HF-AIA-G-P5 compared to the HF-AIA-P10 group. The improvement was proved by the histological findings. CONCLUSION: Combined reduced prednisolone dose with gemfibrozil potentiates its anti-inflammatory activity. This could be a target in the management of rheumatoid arthritis.

[46] *Chen Z, Xiang Y, Bao B et al.* **Simvastatin improves cerebrovascular injury caused by ischemiareperfusion through NFkappaBmediated apoptosis via MyD88/TRIF signaling**. Molecular medicine reports 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30066928

ABSTRACT
Cerebrovascular injury is the most prevalent human cerebrovascular disease and frequently results in ischemic stroke. Simvastatin may be a potential therapeutic agent for the treatment of patients with cerebrovascular injury. The present study aimed to investigate the efficacy of and the potential mechanisms regulated by simvastatin in a rat model of ischemiareperfusion (I/R)induced cerebrovascular injury. Cerebrovascular injury model rats were established and were subsequently treated with simvastatin or a vehicle control following I/R injury. Cell damage, neurological functions and neuronal apoptosis were examined, as well as the nuclear factor (NF)kappaBmediated myeloid differentiation primary response protein 88 (MyD88)/tollinterleukin1 receptor domaincontaining adapter molecule 1 (TRIF) signaling pathway following simvastatin treatment. The results of the present study demonstrated that simvastatin treatment led to a reduction in cell damage, improvement of neurological functions and decreased neuronal apoptosis compared with vehicletreated I/R model rats, 14 days posttreatment. In addition, simvastatin treatment reduced cerebral water content and bloodbrain barrier disruption in cerebrovascular injury induced by I/R. The results also revealed that simvastatin treatment inhibited neuronal apoptosis via the NFkappaBmediated MyD88/TRIF signaling pathway. In conclusion, simvastatin treatment may reduce I/Rinduced neuronal apoptosis via inhibition of the NFkappaBmediated MyD88/TRIF signaling pathway.

[47] *Choi NY, Kim JY, Hwang M et al.* **Atorvastatin Rejuvenates Neural Stem Cells Injured by Oxygen-Glucose Deprivation and Induces Neuronal Differentiation Through Activating the PI3K/Akt and ERK Pathways**. Mol Neurobiol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30073508

ABSTRACT
Oxygen and glucose (OGD) deprivation is one of the most important pathogenic mechanisms in cerebral infarction and is widely used as an in vitro model for ischemic stroke. OGD also damages neural stem cells (NSCs), which are important in brain recovery after cerebral infarction. To enhance recovery, there have been many studies aimed at determining methods to protect NSCs after stroke. Because atorvastatin has diverse protective effects on neural cells, we studied whether it could rejuvenate NSCs injured by OGD. Primary cultured NSCs were exposed to OGD for 8 h, and the main characteristics of stem cells, such as survival, proliferation, migration, and differentiation, were evaluated to confirm the effect of OGD on NSCs. Next, cells were treated with various concentrations of atorvastatin with exposure to OGD for 8 h to confirm whether it could rejuvenate NSCs. OGD significantly affected the survival, proliferation, migration, and differentiation of NSCs. However, treatment with atorvastatin meaningfully restored survival, proliferation, migration, and differentiation of NSCs. These beneficial effects of atorvastatin were blocked by treatment with either a PI3K inhibitor or an ERK inhibitor. In conclusion, OGD damages NSCs and causes them to lose the main characteristics of stem cells so that they cannot contribute to brain recovery after cerebral infarction. However, treatment with atorvastatin after cerebral infarction can effectively rejuvenate NSCs through activating the PI3K and ERK pathways to aid in brain regeneration.

[48] *Irwig MS*. **Cardiovascular health in transgender people**. Reviews in endocrine & metabolic disorders 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30073551
ABSTRACT
This review examines the relationship between exogenous sex steroids and cardiovascular events and surrogate markers in trans (transgender) people. Data from trans populations is compared to data from postmenopausal women and hypogonadal men when appropriate. In an age-adjusted comparison with cisgender people, trans people appear to have an increased risk for myocardial infarction and death due to cardiovascular disease. It is uncertain whether hormone therapy in trans people affects their risk of stroke. In studies that followed trans people on hormone therapy, the rates of myocardial infarction and stroke were consistently higher in trans women than trans men. There is strong evidence that estrogen therapy for trans women increases their risk for venous thromboembolism over 5 fold. Extrapolating from studies of hormone therapy in postmenopausal women, transdermal estrogen likely carries a lower risk for venous thromboembolism than oral estrogen. Regarding red blood cells, testosterone therapy increases hemoglobin in trans men, and lowering testosterone in trans women has the opposite effect. Regarding blood pressure, the effects of hormone therapy on systolic blood pressure in trans women are inconsistent, with most studies showing an increase. In trans men, testosterone therapy consistently increases systolic blood pressure and may increase diastolic blood pressure. For lipids, hormone therapy may increase triglycerides in both trans women and men. In trans men, testosterone therapy also may increase LDL-cholesterol and decrease HDL-cholesterol.

[49] *Fadaei R, Poustchi H, Meshkani R et al.* **Impaired HDL cholesterol efflux capacity in patients with non-alcoholic fatty liver disease is associated with subclinical atherosclerosis**. Scientific reports 2018; 8:11691.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30076407
ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is associated with a substantial increased risk of atherosclerotic cardiovascular disease (ASCVD), which is partly related to dyslipidemia and low HDL-C level. The cardioprotective activity of HDL in the body is closely connected to its role in promoting cholesterol efflux, which is determined by cholesterol efflux capacity (CEC). Hitherto, the role of HDL, as defined by CEC has not been assessed in NAFLD patients. In this research study, we present the results of a study of cAMP-treated J774 CEC and THP-1 macrophage CEC in ApoB-depleted plasma of 55 newly diagnosed NAFLD patients and 30 controls. Circulating levels of ApoA-I, ApoB, prebeta-HDL, plasma activity of CETP, PLTP, LCAT and carotid intima-media thickness (cIMT) were estimated. cAMP-treated J774 and THP-1 macrophage CEC were found to be significantly lower in NAFLD patients compared to controls ($P < 0.001$ and $P = 0.003$, respectively). In addition, it was discovered that both ApoA-I and prebeta1-HDL were significantly lower in NAFLD patients ($P < 0.001$). Furthermore, cAMP-treated J774 CEC showed independent negative correlation with cIMT, as well as the presence of atherosclerotic plaque in NAFLD patients. In conclusion, our findings showed that HDL CEC was suppressed in NAFLD patients, and impaired cAMP-treated J774 CEC was an independent risk factor for subclinical

atherosclerosis in NAFLD patients, suggesting that impaired HDL functions as an independent risk factor for atherosclerosis in NAFLD.