Literature update week 39 (2018)

[1] *Zhou X, Dai J, Xu X et al.* **Comparative Efficacy of Statins for Prevention of Contrast-Induced Acute Kidney Injury in Patients With Chronic Kidney Disease: A Network Meta-Analysis**. Angiology 2018:3319718801246.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30261736

ABSTRACT
Contrast-induced acute kidney injury (CI-AKI) is a common complication of iodinated contrast medium administration during cardiac catheterization. Statin treatment has been shown to be associated with reduced risk of CI-AKI; however, the results are inconsistent, especially for patients with chronic kidney disease (CKD). Thus, we conducted a network meta-analysis to evaluate the effects of statins in the prevention of CI-AKI. We systematically searched several databases (including, Embase, PubMed, the Cochrane Library, and ClinicalTrials.gov) from inception to January 31, 2018. The primary outcome was occurrence of CI-AKI in patients with CKD undergoing cardiac catheterization. Both pairwise and network meta-analysis were performed. Finally, 21 randomized controlled trials with a total of 6385 patients were included. Results showed that statin loading before contrast administration was associated with a significantly reduced risk of CI-AKI in patients with CKD undergoing cardiac catheterization (odds ratio: 0.46; P < .05). Atorvastatin and rosuvastatin administered at high dose may be the most effective treatments to reduce incidence of CI-AKI, with no difference between these 2 agents.

[2] *Akalanka HMK, Ekanayake S, Samarasinghe K*. **Could Anthropometric and Lipid Parameters Reflect Susceptibility to Breast Cancer? Comparison of Newly Diagnosed Breast Cancer and Apparently Healthy Women**. Asian Pacific journal of cancer prevention : APJCP 2018; 19:2475-2480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255702

ABSTRACT
Objectives: To determine and compare the serum lipid profiles and anthropometric parameters of newly diagnosed BC patients and healthy women. Methods: Serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), triglyceride (TG) and TC: HDL-C were measured in consent obtained newly diagnosed BC patients (n=155) and age matched apparently healthy females (n=75). Weight (W), height (H), waist circumference (WC), hip circumference (HC) and mid upper arm circumference (MUC) of each women were recorded. Cut off values for each parameter was found by receiver operative characteristic (ROC) curves and risk associated with was calculated using SPSS version 16. Results: Majority (67%) of BC women were postmenopausal. The mean TC, HDL-C, LDL-C, VLDL-C, TC: HDL-C, TG concentrations of BC patients who were not on cholesterol lowering drugs (n= 126) were 234 mg/dL (+/-51), 43 mg/dL (+/-10), 164 mg/dL (+/-44), 27 mg/dL (+/-14), 5.7(+/-1.7) and 135 mg/dL (+/-69) respectively. TC, LDL-C and TC: HDL-C of BC patients were significantly elevated when compared with healthy females. Significant difference in serum lipid profile parameters was not observed (p> 0.05) according to the menopausal status of BC and healthy women. One third (30.3%) of BC patients were overweight and 45% were obese. Majority had elevated WC (72%), W: H ratios (89%) and MUC (89%). BMI, W: H and MUC of BC women were significantly higher (p<0.05) when compared with healthy females. Conclusions: The lipid parameters TC, LDL-C and

TC: HDL-C above 203 mg/dL, 139 mg/dL and 3.9 respectively were risk factors. Among anthropometric measures, BMI>25 kg/m2 showed the highest risk while elevated W:H and MUC were also significant risk factors among the study group.

[3] *Gallego-Colon E, Wojakowski W, Francuz T.* **Incretin drugs as modulators of atherosclerosis**. Atherosclerosis 2018; 278:29-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30248550
ABSTRACT

Atherosclerosis is a major underlying cause of ischemic heart diseases, ischemic stroke, and peripheral artery disease. Atherosclerotic plaque progression is characterized by chronic progressive inflammation of the arterial wall, endothelial cell dysfunction, and subendothelial lipoprotein retention. Incretin drugs, glucagon-like peptide-1 receptor (GLP-1R) agonists, and dipeptidyl peptidase-IV (DPP-IV) inhibitors, are promising anti-hyperglycemic agents used for the treatment of type 2 diabetes mellitus (T2DM). In addition to glucose-lowering effects, emerging data suggest that incretin drugs have anti-atherogenic effects with the potential to stabilize atherosclerotic plaques and treat arterial inflammation. Clinical and preclinical studies have reported a plethora of therapeutic benefits of incretin drugs, including modulation of inflammatory response, reduction of intima-media thickening, improvement in lipid profiles, endothelial and smooth muscle cell modulation. Despite extensive research and widespread clinical use of incretin-based therapies, the research on the incretin hormones continues to expand. This review outlines clinical studies, molecular aspects, and potential therapeutic implications of incretin drugs in attenuation of atherosclerosis.

[4] *Gylling H, Korhonen M, Mutanen A et al.* **Serum non-cholesterol sterols and cholesterol metabolism in childhood and adolescence**. Atherosclerosis 2018; 278:91-96.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30261473
ABSTRACT

BACKGROUND AND AIMS: The profile of cholesterol metabolism, i.e., high absorption vs. high synthesis, may have a role in the development of atherosclerosis, the early lesions of which can be present already in childhood. Since there is no information on cholesterol metabolism in children from birth to adolescence, we evaluated cholesterol metabolism in 0-15 year-old children and adolescents without dyslipidemia. METHODS: The study population consisted of 96 children (39 girls, 57 boys) divided into age groups <1 (n=14), 1-5 (n=37), 6-10 (n=24), and 11-15 (n=21) years. Cholesterol metabolism was assessed by analysing serum non-cholesterol sterols, biomarkers of cholesterol synthesis and absorption, with gas-liquid chromatography. RESULTS: Serum non-cholesterol sterol ratios to cholesterol did not differ between gender. Cholesterol precursors squalene, cholestenol, and desmosterol were higher in the <1 year than in the older age groups, whereas lathosterol was highest in the 11-15 year old. Plant sterols were low in the age group <1 year, after which they did not differ between the groups. Cholestanol was not age-dependent. From the age of 1 year, cholesterol homeostasis was intact. Cholesterol absorption prevailed cholesterol synthesis from 1 to 10 years of age (e.g., lathosterol/cholestanol ratio 0.35+/-0.03 and 0.45+/-0.05 in 1-5 and 6-10 vs. 0.66+/-0.08 in 11-15 year-old (mean+/-SE, p<0.001). CONCLUSIONS: Serum non-cholesterol sterols had different individual profiles by age in childhood and adolescence. From 1 to 10 years of age, cholesterol

absorption prevailed cholesterol synthesis. This novel finding emphasizes the importance of dietary aspects related to cardiovascular risk even from early childhood.

[5] *Vozenilek AE, Blackburn CMR, Schilke RM et al.* **AAV8-mediated overexpression of mPCSK9 in liver differs between male and female mice**. Atherosclerosis 2018; 278:66-72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30253291
ABSTRACT

BACKGROUND AND AIMS: The recombinant adeno-associated viral vector serotype 8 expressing the gain-of-function mutation of mouse proprotein convertase subtilisin/kexin type 9 (AAV8- PCSK9) is a new model for the induction of hypercholesterolemia. AAV8 preferentially infects hepatocytes and the incorporated liver-specific promoter should ensure expression of PCSK9 in the liver. Since tissue distribution of AAVs can differ between male and female mice, we investigated the differences in PCSK9 expression and hypercholesterolemia development between male and female mice using the AAV8-PCSK9 model. METHODS: Male and female C57BL/6 mice were injected with either a low-dose or high-dose of AAV8-PCSK9 and fed a high-fat diet. Plasma lipid levels were evaluated as a measure of the induction of hypercholesterolemia. RESULTS: Injection of mice with low dose AAV8-PCSK9 dramatically elevated both serum PCSK9 and cholesterol levels in male but not female mice. Increasing the dose of AAV8-PCSK9 threefold in female mice rescued the hypercholesterolemia phenotype but did not result in full restoration of AAV8-PCSK9 transduction of livers in female mice compared to the low-dose male mice. Our data demonstrate female mice respond differently to AAV8-PCSK9 injection compared to male mice. CONCLUSIONS: These differences do not hinder the use of female mice when AAV8-PCSK9 doses are taken into consideration. However, localization to and production of AAV8-PCSK9 in organs besides the liver in mice may introduce confounding factors into studies and should be considered during experimental design.

[6] *Wargny M, Ducluzeau PH, Petit JM et al.* **Circulating PCSK9 levels are not associated with the severity of hepatic steatosis and NASH in a high-risk population**. Atherosclerosis 2018; 278:82-90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30261472
ABSTRACT

BACKGROUND AND AIMS: Some studies suggested that proprotein convertase subtilisin kexin type 9 (PCSK9) is linked to liver steatosis severity and non-alcoholic steatohepatitis (NASH). We aimed to assess whether circulating PCSK9 levels are associated with either liver fat content (LFC) or histological markers of NASH in high-risk patients. METHODS: We present results from three cross-sectional studies from two French Hospitals: Dijon and Numevox (departments of Endocrinology) and Angers (department of Hepatology). Only patients without lipid-lowering therapy were included. All 132 patients had type 2 diabetes in Dijon, compared to 55/224 in Numevox (25%) and 39/122 in Angers (32%). LFC was assessed on MRI (Dijon and Numevox), and NASH lesion on liver biopsy (Angers). Additionally, we included mRNA results from 138 overweight patients of a Belgian Hospital (Antwerp). RESULTS: While circulating levels of PCSK9 were positively correlated with total cholesterol, LDL-C, triglycerides and non-HDL-C in all 3 cohorts, no significant association was found between PCSK9 and transaminases. Furthermore, no association was found between plasma PCSK9 levels and LFC in both Numevox

(betaadjusted=0.71+/-1.33, p=0.60) and Dijon (betaadjusted=-1.03+/-0.90, p=0.25). There was no correlation between circulating PCSK9 and histological liver lesions: steatosis severity (betaadjusted=-3.95+/-2.75, p=0.15), NASH activity score (betaadjusted=-0.31+/-0.17, p=0.082), lobular (beta=-0.067+/-0.055, p=0.22) or portal inflammation (beta=-0.088+/-0.079, p=0.27), ballooning (beta=-0.025+/-0.065, p=0.70) and fibrosis (beta=-0.17+/-0.11, p=0.12). Finally, hepatic PCSK9 mRNA levels were not correlated with NASH histological severity. CONCLUSIONS: Circulating PCSK9 concentrations are not associated with the severity of liver steatosis or histological markers of NASH. These data are reassuring regarding the clinical use of PCSK9 inhibitors in cardiovascular diseases.

[7] *Fan R, Toney AM, Jang Y et al.* **Maternal n-3 PUFA supplementation promotes fetal brown adipose tissue development through epigenetic modifications in C57BL/6 mice**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2018; 1863:1488-1497.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30266429
ABSTRACT

Brown adipose tissue (BAT) is a crucial regulator of energy expenditure. Emerging evidence suggests that n-3 PUFA potentiate brown adipogenesis in vitro. Since the pregnancy and lactation is a critical time for brown fat formation, we hypothesized that maternal supplementation of n-3 PUFA promotes BAT development in offspring. Female C57BL/6 mice were fed a diet containing n-3 PUFA (3%) derived from fish oil (FO), or an isocaloric diet devoid of n-3 PUFA (Cont) during pregnancy and lactation. Maternal n-3 PUFA intake was delivered to the BAT of neonates significantly reducing the n-6/n-3 ratio. The maternal n-3 PUFA exposure was linked with upregulated brown-specific gene and protein profiles and the functional cluster of brown-specific miRNAs. In addition, maternal n-3 PUFA induced histone modifications in the BAT evidenced by 1) increased epigenetic signature of brown adipogenesis, i.e., H3K27Ac and H3K9me2, 2) modified chromatin-remodeling enzymes, and 3) enriched the H3K27Ac in the promoter region of Ucp1. The offspring received maternal n-3 PUFA nutrition exhibited a significant increase in whole-body energy expenditure and better maintenance of core body temperature against acute cold treatment. Collectively, our results suggest that maternal n-3 PUFA supplementation potentiates fetal BAT development via the synergistic action of miRNA production and histone modifications, which may confer long-lasting metabolic benefits to offspring.

[8] *Masquelier J, Alhouayek M, Terrasi R et al.* **Lysophosphatidylinositols in inflammation and macrophage activation: Altered levels and anti-inflammatory effects**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2018; 1863:1458-1468.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30251703
ABSTRACT

Lysophosphatidylinositols (LPI) are bioactive lipids that are implicated in several pathophysiological processes such as cell proliferation, migration and tumorigenesis and were shown to play a role in obesity and metabolic disorders. Often, these effects of LPI were due to activation of the G protein-coupled receptor GPR55. However, the role of LPI and GPR55 in inflammation and macrophage activation remains unclear. Therefore, we thought to study the effect of macrophage activation and inflammation on LPI levels and metabolism. To do so, we

used J774 and BV2 cells in culture activated with lipopolysaccharides (LPS, 100ng/mL) as well as primary mouse alveolar and peritoneal macrophages. We also quantified LPI levels in the cerebellum, lung, liver, spleen and colon of mice with a systemic inflammation induced by LPS (300mug/kg) and in the colon of mice with acute colitis induced by dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS) and chronic DSS-induced colitis. Our data show that LPS-induced macrophage activation leads to altered LPI levels in both the cells and culture medium. We also show that cytosolic phospholipase A2alpha (cPLA2alpha) and alpha/betahydrolase domain 6 (ABHD6) are among the enzymes implicated in LPI metabolism in J774 macrophages. Indeed, ABHD6 and cPLA2alpha inhibition increased 20:4-LPI levels in LPS-activated macrophages. Furthermore, incubation of LPS-activated cells with LPI decreased J774 activation in a GPR55-dependent manner. In vivo, LPI levels were altered by inflammation in the liver, spleen and colon. These alterations are tissue dependent and could highlight a potential role for LPI in inflammatory processes.

[9] *Pahlavani M, Wijayatunga NN, Kalupahana NS et al.* **Transcriptomic and MicroRNA analyses of gene networks regulated by eicosapentaenoic acid in brown adipose tissue of diet-induced obese mice**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30261280
ABSTRACT

Brown adipose tissue (BAT) dissipates chemical energy as heat via thermogenesis and protects against obesity by increasing energy expenditure. However, regulation of BAT by dietary factors remains largely unexplored at the mechanistic level. We investigated the effect of eicosapentaenoic acid (EPA) on BAT metabolism. Male C57BL/6J (B6) mice fed either a high-fat diet (HF, 45% kcal fat) or HF diet supplemented with EPA (HF-EPA, 6.75% kcal EPA) were used for 11weeks. RNA sequencing (RNA-Seq) and microRNA (miRNA) profiling were performed on RNA from BAT using Illumina HiSeq and miSeq respectively. We conducted pathway analyses using ingenuity pathway analysis software (IPA(R)) and validated some genes and miRNAs using qPCR. We identified 479 genes that were differentially expressed (2-fold change, n=3, P</=0.05) in BAT from HF compared to HF-EPA. Genes negatively correlated with thermogenesis such as hypoxia Inducible factor 1 alpha subunit inhibitor (Hif1alphan), was downregulated by EPA. Pathways related to thermogenesis such as peroxisome proliferator-activated receptor (PPAR) were upregulated by EPA while pathways associated with obesity and inflammation such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) were downregulated by EPA. MiRNA profiling identified nine and six miRNAs that were upregulated and downregulated by EPA, respectively (log2 fold change>1.25, n=3, P</=0.05). Key regulatory miRNAs were involved in thermogenesis, such as miR-455-3p and miR-129-5p were validated using qPCR. In conclusion, the depth of transcriptomic and miRNA profiling revealed novel mRNA-miRNA interaction networks in BAT which are involved in thermogenesis which regulated by EPA.

[10] *Borges CC, Bringhenti I, Mandarim-de-Lacerda CA, Aguila MB*. **Vitamin D deficiency aggravates the liver metabolism and inflammation in ovariectomized mice**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 107:878-888.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30257400
ABSTRACT
AIMS: A prevalence of vitamin D deficiency has been reported in association with the postmenopause. Thus, we aimed to experimentally study the effect of the vitamin D deficiency and ovariectomy, alone or combined, in the liver damage. MAIN METHODS: Three-months-old female mice C57BL/6 with bilateral ovariectomy (Ovx group, n = 30) or a sham procedure (n = 30) were separated feeding control diet (C, n = 15) or a diet restricted in vitamin D (D-, n = 15) during additional 12 weeks. KEY FINDINGS: Body mass (BM) and blood pressure (BP) were higher in Ovx than in C animals, but highest in Ovx (D-) that also showed glucose intolerance/ insulin resistance. Plasmatic lipids, alanine aspartase transferase, and hepatic steatosis were increased because of the combination of Ovx and D-. However, D- had little implication in the changes of the BM and BP, but affected hepatic steatosis. Gene and protein expressions demonstrated an impaired glucose uptake in the liver because of Ovx and D-, and an increase in lipogenesis and decrease in beta-oxidation in the liver associated more to the Ovx, but also evident in D-. Also, interleukin 6 and tumor necrosis factor alpha showed an enhancement due to dietary restriction of vitamin D. SIGNIFICANCE: The findings demonstrated that ovariectomy and dietary restriction of vitamin D are inducers of harmful effects on the liver of mice, enhancing lipogenesis and inflammation and compromising beta-oxidation. The treatment of vitamin D deficiency is simple and not costly and can reduce the impact of menopause on metabolism and especially the liver.

[11] *Oza MJ, Kulkarni YA*. **Biochanin A improves insulin sensitivity and controls hyperglycemia in type 2 diabetes**. <u>Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie</u> 2018; 107:1119-1127.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30257324
ABSTRACT
Biochanin A (5,7-Dihydroxy-4'-methoxyisoflavone) is an O-methylated isoflavone known for its anti-inflammatory, lipid lowering and anti-cancer activity. The current study was designed to find out antidiabetic efficacy of Biochanin A in type 2 diabetes in rats. Induction of type 2 diabetes mellitus in experimental animals was carried out by manipulation of diet using high fat diet for fourteen days and then administration of streptozotocin at low dose of 35 mg/kg, i.p. The diabetic animals were treated with 10, 20 and 40 mg/kg of Biochanin A for 28 days. The effect of Biochanin A treatment in diabetic animals was evaluated by measuring changes in body weight, biochemical parameters, insulin sensitivity index, Homeostatic model assessment-Insulin resistance (HOMA-IR), oral glucose tolerance test, glycohaemoglobin and hepatic glycogen level. Changes in histopathological characteristics of pancreatic tissue were also evaluated after treatment with Biochanin A. Immunohistochemical analysis of pancreatic tissue was carried out for the expression of SIRT1. The results showed that the selected doses of (10, 20 and 40 mg/kg) Biochanin A significantly decreased blood glucose (p < 0.001). The higher dose (40 mg/kg) of Biochanin A significantly reduced glucose tolerance (p < 0.001) in diabetic animals. Biochanin A treatment significantly reduced insulin resistance (p < 0.001) and improved inulin sensitivity (p < 0.01 for 10 mg/kg, 20 mg/kg, p < 0.001 for 40 mg/kg) at all selected dose levels. It also improved lipid profile significantly (p < 0.001) at lower, middle and higher dose level. Glycohaemoglobin formation was significantly decreased in diabetic animals

(p < 0.001) after treatment with Biochanin A at all three dose levels. Liver glycogen level was also improved significantly after treatment with Biochanin A in diabetic animals at 20 mg/kg and 40 mg/kg dose level. Biochanin A at dose of 40 mg/kg increased SIRT1 expression in pancreatic tissue. In conclusion, Biochanin A has significant effect in type 2 diabetes mellitus which might be linked to its effects on SIRT1.

[12] *Ye G, Fu Q, Jiang L, Li Z*. **Vascular smooth muscle cells activate PI3K/Akt pathway to attenuate myocardial ischemia/reperfusion-induced apoptosis and autophagy by secreting bFGF**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 107:1779-1785.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30257397
ABSTRACT
BACKGROUND: Vascular smooth muscle cells (VSMCs) has been reported to be implicated in atherosclerotic plaque instability and rupture. Recently, it has been demonstrated that VSMCs block the progression of cardiac remodeling and thus promoting cardiac function in a rat myocardial infarction model. However, the detailed molecular mechanism of how VSMCs contributes to recovery in myocardial ischemia/reperfusion remains not fully understood. METHODS: We have isolated, identified and cultured VSMCs from rats to co-culture with rat cardiomyocyte H9C2. To culture H9C2 cells under hypoxia, we utilized CoCl2-containing medium to culture for 8h and then was replaced with normal media for additional 16h. Cell viability was examined by MTT assay and apoptosis was determined by flow cytometry. Infarcted area of myocardial tissue was measured by TTC staining. RESULTS: VSMCs was shown to promote cell viability and inhibit apoptosis of H9C2 cells under hypoxia, which exhibited upregulated anti-apoptotic protein Bcl-2 and autophagy-related protein p62, whereas pro-apoptotic protein cleaved caspase-3 and the level of LC3II/LC3I were downregulated. Then, we confirmed VSMCs played the contributory role in cell viability of H9C2 under hypoxia by secreting bFGF, which exerted its function through PI3K/Akt pathway. Finally, in vivo, the results demonstrated that VSMCs transplantation contributed to recovery of myocardial ischemia. CONCLUSION: We determine that VSMCs promote recovery of infarcted cardiomyocyte through secretion of bFGF, which then activating PI3K/Akt pathway to inhibit apoptosis and autophagy. These findings provide more insights into the molecular mechanism underlying VSMCs contributing to recovery of myocardial I/R and facilitate developing therapeutical strategies for treating heart diseases.

[13] *Tirawanchai N, Supapornhemin S, Somkasetrin A et al.* **Regulatory effect of Phikud Navakot extract on HMG-CoA reductase and LDL-R: potential and alternate agents for lowering blood cholesterol**. BMC complementary and alternative medicine 2018; 18:258.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30249222
ABSTRACT
BACKGROUND: For decades, various cardiovascular symptoms have been relieved by the use of Ya-Hom Navakot, which is a formulation comprising 54 herbal medicines. The Thailand Ministry of Public Health listed Ya-Hom Navakot's nine active principle and nomenclative herbal ingredients and termed them 'Phikud Navakot' (PN). Several reports have confirmed that PN has cardiovascular benefits similar to Ya-Hom Navakot. However, whether PN facilitates lipid-

lowering activity remains unclear. METHODS: The present study investigated an in vitro model for examining the gene expression levels of 3-hydroxyl-3-methylglutaryl-CoA reductase (HMGCR) and low-density lipoprotein receptor (LDL-R) in HepG2 cells using qRT-PCR. The ethanol and water extractions of Ya-Hom Navakot, PN and Ya-Hom Navakot without PN were compared. RESULTS: One mg/ml of both NYEF and NYWF were found to significantly lower cholesterol by either the up-regulation of LDL-R or down-regulation of HMGCR compared with negative controls and 1 mg/ml simvastatin (p < 0.05). PNEF also up-regulated LDL-R gene expression, even more than NYEF (p < 0.05). In addition, the ethanol and water extracts of PN significantly down-regulated HMGCR gene expression compared with those of Ya-Hom Navakot without PN (p < 0.05). CONCLUSION: The use of Ya-Hom Navakot or PN may provide an alternative treatment to lower cholesterol through HMGCR gene inhibition and LDL-R gene enhancement.

[14] *Cherlin S, Wang MH, Bickeboller H, Cantor RM*. **Detecting responses to treatment with fenofibrate in pedigrees**. BMC genetics 2018; 19:64.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255820
ABSTRACT
BACKGROUND: Fenofibrate (Fb) is a known treatment for elevated triglyceride (TG) levels. The Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study was designed to investigate potential contributors to the effects of Fb on TG levels. Here, we summarize the analyses of 8 papers whose authors had access to the GOLDN data and were grouped together because they pursued investigations into Fb treatment responses as part of GAW20. These papers report explorations of a variety of genetics, epigenetics, and study design questions. Data regarding treatment with 160 mg of micronized Fb per day for 3 weeks included pretreatment and posttreatment TG and methylation levels (ML) at approximately 450,000 epigenetic markers (cytosine-phosphate-guanine [CpG] sites). In addition, approximately 1 million single-nucleotide polymorphisms (SNPs) were genotyped or imputed in each of the study participants, drawn from 188 pedigrees. RESULTS: The analyses of a variety of subsets of the GOLDN data used a number of analytic approaches such as linear mixed models, a kernel score test, penalized regression, and artificial neural networks. CONCLUSIONS: Results indicate that (a) CpG ML are responsive to Fb; (b) CpG ML should be included in models predicting the TG level responses to Fb;

[15] *de Andrade M, Warwick Daw E, Kraja AT et al.* **The challenge of detecting genotype-by-methylation interaction: GAW20**. BMC genetics 2018; 19:81.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255819
ABSTRACT
BACKGROUND: GAW20 working group 5 brought together researchers who contributed 7 papers with the aim of evaluating methods to detect genetic by epigenetic interactions. GAW20 distributed real data from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study, including single-nucleotide polymorphism (SNP) markers, methylation (cytosine-phosphate-guanine [CpG]) markers, and phenotype information on up to 995 individuals. In addition, a simulated data set based on the real data was provided. RESULTS: The 7 contributed papers analyzed these data sets with a number of different statistical methods, including

generalized linear mixed models, mediation analysis, machine learning, W-test, and sparsity-inducing regularized regression. These methods generally appeared to perform well. Several papers confirmed a number of causative SNPs in either the large number of simulation sets or the real data on chromosome 11. Findings were also reported for different SNPs, CpG sites, and SNP-CpG site interaction pairs. CONCLUSIONS: In the simulation (200 replications), power appeared generally good for large interaction effects, but smaller effects will require larger studies or consortium collaboration for realizing a sufficient power.

[16] *LeBlanc M, Nustad HE, Zucknick M, Page CM*. **Quality control for Illumina 450K methylation data in the absence of iDat files using correlation structure in pedigrees and repeated measures**. BMC genetics 2018; 19:66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255766
ABSTRACT
BACKGROUND: An important feature in many genomic studies is quality control and normalization. This is particularly important when analyzing epigenetic data, where the process of obtaining measurements can be bias prone. The GAW20 data was from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), a study with multigeneration families, where DNA cytosine-phosphate-guanine (CpG) methylation was measured pre- and posttreatment with fenofibrate. We performed quality control assessment of the GAW20 DNA methylation data, including normalization, assessment of batch effects and detection of sample swaps. RESULTS: We show that even after normalization, the GOLDN methylation data has systematic differences pre- and posttreatment. Through investigation of (a) CpGs sites containing a single nucleotide polymorphism, (b) the stability of breeding values for methylation across time points, and (c) autosomal gender-associated CpGs, 13 sample swaps were detected, 11 of which were posttreatment. CONCLUSIONS: This paper demonstrates several ways to perform quality control of methylation data in the absence of raw data files and highlights the importance of normalization and quality control of the GAW20 methylation data from the GOLDN study.

[17] *Shen X, Lu Q*. **Joint analysis of genetic and epigenetic data using a conditional autoregressive model**. BMC genetics 2018; 19:71.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255769
ABSTRACT
BACKGROUND: Rapidly evolving high-throughput technology has made it cost-effective to collect multilevel omic data in clinical and biological studies. Different types of omic data collected from these studies provide both shared and complementary information, and can be integrated into association analysis to enhance the power of identifying novel disease-associated biomarkers. To model the joint effect of genetic markers and DNA methylation on the phenotype of interest, we propose a joint conditional autoregressive (JCAR) model. A linear score test is used for hypothesis testing and the corresponding p value can be obtained using the Davies method. RESULTS: The JCAR model was applied to the GAW20 data from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study. In our application of the JCAR model, we consider a baseline model and a full model. In the baseline model, we consider 3 different scenarios: a model with only genetic information, a model with only DNA methylation information at visit 2, and a model using both genetic and DNA methylation

information at visit 2. For the full model, we consider both genetic and DNA methylation information at visit 2 and visit 4. The top 10 significant genes are reported for each model. Based on the results, we found that the gene MYO3B was significant as long as the methylation information was considered in the analysis. CONCLUSIONS: JCAR is a useful tool for joint association analysis of genetic and epigenetic data. It is easy to implement and is computationally efficient. It can also be extended to analyze other types of omic data.

[18] *Wang X, Boekstegers F, Brinster R*. **Methods and results from the genome-wide association group at GAW20**. BMC genetics 2018; 19:79.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255814
ABSTRACT

BACKGROUND: This paper summarizes the contributions from the Genome-wide Association Study group (GWAS group) of the GAW20. The GWAS group contributions focused on topics such as association tests, phenotype imputation, and application of empirical kinships. The goals of the GWAS group contributions were varied. A real or a simulated data set based on the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study was employed by different methods. Different outcomes and covariates were considered, and quality control procedures varied throughout the contributions. RESULTS: The consideration of heritability and family structure played a major role in some contributions. The inclusion of family information and adaptive weights based on data were found to improve power in genome-wide association studies. It was proven that gene-level approaches are more powerful than single-marker analysis. Other contributions focused on the comparison between pedigree-based kinship and empirical kinship matrices, and investigated similar results in heritability estimation, association mapping, and genomic prediction. A new approach for linkage mapping of triglyceride levels was able to identify a novel linkage signal. CONCLUSIONS: This summary paper reports on promising statistical approaches and findings of the members of the GWAS group applied on real and simulated data which encompass the current topics of epigenetic and pharmacogenomics.

[19] *Shameer K, Perez-Rodriguez MM, Bachar R et al.* **Pharmacological risk factors associated with hospital readmission rates in a psychiatric cohort identified using prescriptome data mining**. BMC medical informatics and decision making 2018; 18:79.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255805
ABSTRACT

BACKGROUND: Worldwide, over 14% of individuals hospitalized for psychiatric reasons have readmissions to hospitals within 30 days after discharge. Predicting patients at risk and leveraging accelerated interventions can reduce the rates of early readmission, a negative clinical outcome (i.e., a treatment failure) that affects the quality of life of patient. To implement individualized interventions, it is necessary to predict those individuals at highest risk for 30-day readmission. In this study, our aim was to conduct a data-driven investigation to find the pharmacological factors influencing 30-day all-cause, intra- and interdepartmental readmissions after an index psychiatric admission, using the compendium of prescription data (prescriptome) from electronic medical records (EMR). METHODS: The data scientists in the project received a deidentified database from the Mount Sinai Data Warehouse, which was

used to perform all analyses. Data was stored in a secured MySQL database, normalized and indexed using a unique hexadecimal identifier associated with the data for psychiatric illness visits. We used Bayesian logistic regression models to evaluate the association of prescription data with 30-day readmission risk. We constructed individual models and compiled results after adjusting for covariates, including drug exposure, age, and gender. We also performed digital comorbidity survey using EMR data combined with the estimation of shared genetic architecture using genomic annotations to disease phenotypes. RESULTS: Using an automated, data-driven approach, we identified prescription medications, side effects (primary side effects), and drug-drug interaction-induced side effects (secondary side effects) associated with readmission risk in a cohort of 1275 patients using prescriptome analytics. In our study, we identified 28 drugs associated with risk for readmission among psychiatric patients. Based on prescription data, Pravastatin had the highest risk of readmission (OR = 13.10; 95% CI (2.82, 60.8)). We also identified enrichment of primary side effects (n = 4006) and secondary side effects (n = 36) induced by prescription drugs in the subset of readmitted patients (n = 89) compared to the non-readmitted subgroup (n = 1186). Digital comorbidity analyses and shared genetic analyses further reveals that cardiovascular disease and psychiatric conditions are comorbid and share functional gene modules (cardiomyopathy and anxiety disorder: shared genes (n = 37; P = 1.06815E-06)). CONCLUSIONS: Large scale prescriptome data is now available from EMRs and accessible for analytics that could improve healthcare outcomes. Such analyses could also drive hypothesis and data-driven research. In this study, we explored the utility of prescriptome data to identify factors driving readmission in a psychiatric cohort. Converging digital health data from EMRs and systems biology investigations reveal a subset of patient populations that have significant comorbidities with cardiovascular diseases are more likely to be readmitted. Further, the genetic architecture of psychiatric illness also suggests overlap with cardiovascular diseases. In summary, assessment of medications, side effects, and drug-drug interactions in a clinical setting as well as genomic information using a data mining approach could help to find factors that could help to lower readmission rates in patients with mental illness.

[20] *Romanescu RG, Espin-Garcia O, Ma J, Bull SB*. **Integrating epigenetic, genetic, and phenotypic data to uncover gene-region associations with triglycerides in the GOLDN study**. BMC proceedings 2018; 12:57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30263054
ABSTRACT

Background: There has been significant interest in investigating genome-wide and epigenome-wide associations with lipids. Testing at the gene or region level may improve power in such studies. Methods: We analyze chromosome 11 cytosine-phosphate-guanine (CpG) methylation levels and single-nucleotide polymorphism (SNP) genotypes from the original Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study, aiming to explore the association between triglyceride levels and genetic/epigenetic factors. We apply region-based tests of association to methylation and genotype data, in turn, which seek to increase power by reducing the dimension of the gene-region variables. We also investigate whether integrating 2 omics data sets (methylation and genotype) into the triglyceride association analysis helps or hinders detection of candidate gene regions. Results: Gene-region testing identified 1 CpG region that

had been previously reported in the GOLDN study data and another 2 gene regions that are also associated with triglyceride levels. Testing on the combined genetic and epigenetic data detected the same genes as using epigenetic or genetic data alone. Conclusions: Region-based testing can uncover additional association signals beyond those detected using single-variant testing.

[21] *Tintle NL, Fardo DW, de Andrade M et al.* **GAW20: methods and strategies for the new frontiers of epigenetics and pharmacogenomics**. BMC proceedings 2018; 12:26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30263042
ABSTRACT

GAW20 provided a platform for developing and evaluating statistical methods to analyze human lipid-related phenotypes, DNA methylation, and single-nucleotide markers in a study involving a pharmaceutical intervention. In this article, we present an overview of the data sets and the contributions analyzing these data. The data, donated by the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) investigators, included data from 188 families (N = 1105) which included genome-wide DNA methylation data before and after a 3-week treatment with fenofibrate, single-nucleotide polymorphisms, metabolic syndrome components before and after treatment, and a variety of covariates. The contributions from individual research groups were extensively discussed prior, during, and after the Workshop in groups based on discussion themes, before being submitted for publication.

[22] *Fleming RM, Fleming MR, Harrington GM et al.* **Long-term health effects of the three major diets under self-management with advice, yields high adherence and equal weight loss, but very different long-term cardiovascular health effects as measured by myocardial perfusion imaging and specific markers of inflammatory coronary artery disease**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30260004
ABSTRACT

BACKGROUND: Obesity is caused by eating behaviours. Adherence to all diets has been extremely poor, thus, comparative data on health effects of different diets over periods of a year or more are limited. This study was designed to treat the root causes of obesity by modifying the eating behaviours and to compare the long-term (one year) cardiovascular health affects using three major diets under isocaloric conditions. METHODS: 120 obese, otherwise healthy, adults were recruited including 63 men and 57 women with a mean age and BMI of 43.7 years and 42.4 respectively. Participants agreed to follow and self-manage diet with follow-up at six-week intervals to achieve 1500-1600 calorie intake of assigned diet type: low-to-moderate-fat, lowered-carbohydrate, or vegan. Adherence, weight loss, changes in 14 cardiovascular lipids and coronary blood flow health risk indices were measured. RESULTS: One-year body mass changes did not differ by diet (P>.999). Effect sizes (R, R2) were statistically significant for all indices. Coronary blood flow, R (CI95%) = .48 to .69, improved with low-to-moderate-fat and declined with lowered carbohydrate diets. Inflammatory factor Interleukin-6 (R = .51 to .71) increased with lowered carbohydrate and decreased with low-to-moderate-fat diets. CONCLUSIONS: One-year lowered-carbohydrate diet significantly increases cardiovascular risks, while a low-to-moderate-fat diet significantly reduces cardiovascular risk factors. Vegan

diets were intermediate. Lowered-carbohydrate dieters were least inclined to continue dieting after conclusion of the study. Reductions in coronary blood flow reversed with appropriate dietary intervention. The major dietary effect on atherosclerotic coronary artery disease is inflammation and not weight loss.

[23] *Hernandez-Mijares A, Ascaso JF, Blasco M et al.* **Residual cardiovascular risk of lipid origin. Components and pathophysiological aspects**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30262442
ABSTRACT

There is no doubt about the relationship between LDL-c and cardiovascular risk, as well as about the benefits of statin treatment. Once the objective of LDL-c has been achieved, the evidences that demonstrate the persistence of a high cardiovascular risk, a concept called residual risk, are notable. The residual risk of lipid origin is based on atherogenic dyslipidemia, characterized by an increase in triglycerides and triglyceride-rich lipoproteins, a decrease in HDL-c and qualitative alterations in LDL particles. The most commonly used measures to identify this dyslipidemia are based on the determination of total cholesterol, triglycerides, HDL, non-HDL cholesterol and remaining cholesterol, as well as apolipoprotein B100 and lipoprotein (a) in certain cases. The treatment of atherogenic dyslipidemia is based on weight loss and physical exercise. Regarding pharmacological treatment, we have no evidence of cardiovascular benefit with drugs aimed at lowering triglycerides and HDL-c, fenofibrate seems to be effective in situations of atherogenic dyslipidemia.

[24] *Perez Sori Y, Herrera Moya VA, Puig Reyes I et al.* **Histology of atherosclerotic plaque from coronary arteries of deceased patients after coronary artery bypass graft surgery**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30262443
ABSTRACT

BACKGROUND AND AIM: Ischaemic heart disease is an important health problem. The characteristics of atherosclerotic plaques determine patient outcome. The aim of this study was to determine the histological grade of coronary atherosclerotic lesions in deceased patients after coronary artery bypass graft surgery, and to identify the complications of the severe plaques. METHOD: A descriptive, cross-sectional, prospective study was carried out on 21 anatomical pieces of deceased patients over a period of 3 years. The epicardial coronary arteries were sectioned transversally every 1cm, and the odd numbered fragments and the regions of the anastomosis with the grafts were selected. They were embedded in paraffin, stained with haematoxylin-eosin, and the histological slides were studied using an Olympus BHM microscope. RESULTS: An age over 50 years (85.7%), male gender (81.0%), and smoking (66.7%) predominated. Peri-operative infarction (38.1%) and cardiogenic shock (33.3%) were the main direct causes of death. The majority of the grafts were of venous origin (64.6%), and 149 lesions were detected, of which 116 (77.8%) were severe plaques, and 47.4% of them were located in the left anterior descending artery. The large majority (81.9%) of the lesions were located in the arterial segments proximal to the graft. A total of 255 histological complications

were detected in the severe plaques, with 75.0% showing calcification. Hypertensive patients had more plaques with more complications, but no statistically significant association was found between these variables. CONCLUSIONS: Severe plaques predominated, mostly located in the proximal segments of the coronary arteries, and the left anterior descending was the most affected artery. Calcification was the most observed complication in the severe plaques.

[25] *Webb GJ, Hirschfield GM*. **Work in Progress: Drugs in Development**. Clinics in liver disease 2018; 22:501-515.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259849
ABSTRACT
Primary biliary cholangitis is an archetypal autoimmune disease that causes cholestasis, fibrosis, and liver failure. Ursodeoxycholic acid and obeticholic acid are approved for its treatment. Not all patients respond, some are intolerant, many have ongoing symptoms, and new therapies are required. Herein we describe drugs in development and potential future biological targets. We consider compounds acting on the farnesoid X receptor/fibroblast growth factor 19 pathway, fibrates and other agonists of the peroxisome proliferator-activated receptor family, transmembrane-G-protein-receptor-5 agonists, and several immunological agents. We also consider the roles of bile acid reuptake inhibitors, nalfurafine, and fibrates in pruritus management.

[26] *Wong KA, Bahar R, Liu CH, Bowlus CL*. **Current Treatment Options for Primary Biliary Cholangitis**. Clinics in liver disease 2018; 22:481-500.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259848
ABSTRACT
Primary biliary cholangitis is a progressive, autoimmune disease of the interlobular bile ducts, leading to secondary damage of hepatocytes that may progress to cirrhosis and liver failure. Until recently, the only approved treatment was ursodeoxycholic acid. However, 40% of patients do not have an adequate response. Obeticholic acid was approved for treatment as add-on therapy in this group of patients. Off-label use of fibrates has also been reported to be effective. Several new therapies are in development and may further add to the treatment options available to patients with primary biliary cholangitis.

[27] *Cuevas-Tena M, Bermudez JD, Silvestre RLA et al.* **Impact of colonic fermentation on sterols after the intake of a plant sterol-enriched beverage: A randomized, double-blind crossover trial**. Clinical nutrition (Edinburgh, Scotland) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30243503
ABSTRACT
BACKGROUND: Cholesterol microbial transformation has been widely studied using in vitro fermentation assays, but less information is available on the biotransformation of plant sterols (PS). The excretion percentage of animal sterols (AS) (67-73%) is considerably greater than that of PS (27-33%) in feces from healthy humans following a Western diet. However, a lower content of AS in feces from subjects following a vegetarian, vegan or low-fat animal diet has been seen when compared to omnivorous subjects. Although only one human study has reported fecal sterol excretion after the consumption of PS-enriched food (8.6 g PS/day), it was

found that the target group showed an increase in the excretion of cholesterol and a 57% decrease in its metabolites compared to the control group. OBJECTIVE: Evaluation of the impact of a PS-enriched milk based fruit beverage intake on fecal sterol excretion and the microbial conversion of sterols in postmenopausal women with mild hypercholesterolemia. METHODS: Forty postmenopausal women participated in a randomized, double-blind, crossover study with two beverages, with a PS-enriched (2 g PS/day) or without. The women were divided in two groups: 20 women consumed the PS-enriched beverage and the other 20 women consumed a placebo (without PS) beverage for 6 weeks. After a four-week washout period, the type of beverage was exchanged and consumed for another 6 weeks. Feces were collected at the start (0 and 10 weeks) and end of each intervention period (6 and 16 weeks), and fecal sterols were determined by capillary gas chromatography with mass spectrometry. RESULTS: The intake of the PS-enriched beverage modified the fecal sterol excretion profile. A significant increase mainly in PS and their metabolites versus the placebo intervention period was observed. Although the same effect was not observed in the case of AS, a tendency towards increased cholesterol and decreased coprostanol (the main metabolite of cholesterol) was recorded after PS-enriched beverage intake versus placebo. Furthermore, the PS-enriched beverage also modified the microbial conversion of sterols. In this context, an important decrease in the conversion percentage of cholesterol in 16 women (between 11% and 50%) and of sitosterol in 24 women (between 15% and 61%) was observed. CONCLUSIONS: The results obtained suggest that the microbiota could preferably use PS as a substrate, when present in a greater proportion compared with cholesterol. Besides, a lower sitosterol and cholesterol conversion trend would mean that intake of the PS-enriched beverage could modulate the metabolic activity of the gut microbiota. Therefore, further studies on the impact of PS-enriched foods upon gut microbiota modulation are needed. Clinical Trial Registry Number: NCT 02065024 listed on the NIH website: ClinicalTrials.gov. Clinical Trial Registry Name: Food Matrix and Genetic Variability as Determinants of Bioavailability and Biological Effects of Beta-cryptoxanthin and Phytosterols (foodmagenpol). The full trial protocol is available upon request to the corresponding author.

[28] *Smolders EJ, Ter Horst PJG, Wolters S, Burger DM*. **Cardiovascular Risk Management and Hepatitis C: Combining Drugs**. Clinical pharmacokinetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259390
ABSTRACT
Direct-acting antivirals (DAAs) are known victims (substrate) and perpetrators (cause) of drug-drug interactions (DDIs). These DAAs are used for the treatment of hepatitis C virus (HCV) infections and are highly effective drugs. Drugs used for cardiovascular risk management are frequently used by HCV-infected patients, whom also are treated with DAAs. Therefore, the aim of this review was to describe DDIs between cardiovascular drugs (CVDs) and DAAs. An extensive literature search was performed containing search terms for the marketed DAAs and CVDs (beta-blocking agents, ACE inhibitors, angiotensin II antagonists, renin inhibitors, diuretics, calcium channel blockers, statins/ezetimibe, fibrates, platelet aggregation inhibitors, vitamin K antagonists, heparins, direct Xa inhibitors, nitrates, amiodarone, and digoxin). In particular, the drug labels from the European Medicines Agency and the US Food and Drug Administration were used. A main finding of this review is that CVDs are mostly victims of DDIs

with DAAs. Therefore, when possible, monitoring of pharmacodynamics is recommended when coadministering these drugs with DAAs. Nevertheless, it is sometimes better to discontinue a drug on a temporary basis (statins, ezetimide). The DAAs are victims of DDIs in combination with bisoprolol, carvedilol, labetalol, verapamil, and gemfibrozil. Despite there are many DDIs predicted in this review, most of these DDIs can be managed by monitoring the efficacy and toxicity of the victim drug or by switching to another CVD/DAA.

[29] *Adiwidjaja J, Boddy AV, McLachlan AJ*. **A Strategy to Refine the Phenotyping Approach and Its Implementation to Predict Drug Clearance: A Physiologically-Based Pharmacokinetic Simulation Study**. CPT: pharmacometrics & systems pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30260092
ABSTRACT

Phenotyping approach to predict drug metabolism activity is often hampered by a lack of correlation between the probe and the drug of interest. In this paper we present a strategy to refine the phenotyping approach based on a physiologically-based pharmacokinetic simulation (implemented in Simcyp Simulator v.17) using previously published models. The CL/F of erlotinib was better predicted by the sum of caffeine and i.v. midazolam CL/F (r(2) = 0.60) compared to that of either probe drug alone. The clearance of atorvastatin and repaglinide had a strong correlation (r(2) = 0.70 and 0.63, respectively) with that of pitavastatin (a SLCO1B1 probe). Use of multiple probes for drugs that are predominantly metabolised by more than one CYP enzyme should be considered. In a case where hepatic uptake transporters play a significant role in the disposition of a drug, the pharmacokinetic of a transporter probe will provide better predictions of the drug clearance.

[30] *Iqbal U, Perumpail BJ, John N et al.* **Judicious Use of Lipid Lowering Agents in the Management of NAFLD**. Diseases (Basel, Switzerland) 2018; 6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30249980
ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the Western world. NAFLD encompasses a spectrum of histological features, including steatosis, steatohepatitis with balloon degeneration, and hepatic fibrosis leading to cirrhosis. In patients with advanced liver damage, NAFLD is associated with an increased risk of hepatocellular carcinoma. Diabetes mellitus, hypertension, and dyslipidemia are components of metabolic syndrome and are commonly associated with NAFLD. Cardiovascular disease is the leading cause of mortality in patients with NAFLD. Therefore, it is important to pre-emptively identify and proactively treat conditions like hyperlipidemia in an effort to favorably modify the risk factors associated with cardiovascular events in patients with NAFLD. The management of hyperlipidemia has been shown to reduce cardiovascular mortality and improve histological damage/biochemical abnormalities associated with non-alcoholic steatohepatitis (NASH), a subset of NAFLD with advance liver damage. There are no formal guidelines available regarding the use of anti-hyperlipidemic drugs, as prospective data are lacking. The focus of this article is to discuss the utility of lipid-lowering drugs in patients with NAFLD.

[31] *Emmer BT, Hesketh GG, Kotnik E et al.* **The cargo receptor SURF4 promotes the efficient cellular secretion of PCSK9**. eLife 2018; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30251625
ABSTRACT

PCSK9 is a secreted protein that regulates plasma cholesterol levels and cardiovascular disease risk. Prior studies suggested the presence of an ER cargo receptor that recruits PCSK9 into the secretory pathway, but its identity has remained elusive. Here, we apply a novel approach that combines proximity-dependent biotinylation and proteomics together with genome-scale CRISPR screening to identify SURF4, a homologue of the yeast cargo receptor Erv29p, as a primary mediator of PCSK9 secretion in HEK293T cells. The functional contribution of SURF4 to PCSK9 secretion was confirmed with multiple independent SURF4-targeting sgRNAs, clonal SURF4-deficient cell lines, and functional rescue with SURF4 cDNA. SURF4 was found to localize to the early secretory pathway where it physically interacts with PCSK9. Deletion of SURF4 resulted in ER accumulation and decreased extracellular secretion of PCSK9. These findings support a model in which SURF4 functions as an ER cargo receptor mediating the efficient cellular secretion of PCSK9.

[32] *Gilowski W, Krysiak R, Marek B, Okopien B*. **The effect of short-term perindopril and telmisartan treatment on circulating levels of anti-inflammatory cytokines in hypertensive patients**. Endokrynol Pol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259507
ABSTRACT

INTRODUCTION: Both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were found to reduce plasma levels of proinflammatory cytokines. No previous study has compared their effect on production of anti-inflammatory cytokines. MATERIAL AND METHODS: The study enrolled 52 patients with grade 1 and grade 2 arterial hypertension. The participants were divided into two groups treated with either perindopril (4 mg daily) or telmisatran (40 mg daily). Blood pressure, plasma lipids, glucose homeostasis markers, as well as plasma levels of uric acid, interleukin-4, interleukin-10, interleukin-13 and high sensitivity C-reactive protein (hsCRP) were measured at the beginning of the study and six weeks later. RESULTS: Both perindopril and telmisartan reduced systolic and diastolic blood pressure. Although both agents increased serum levels of interleukin-10, this effect was more pronounced in patients treated with telmisartan. Neither telmisartan nor perindopril affected circulating levels of uric acid, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, interleukin-4, interleukin-13 and hsCRP. The effect of telmisartan on interleukin-10 slightly correlated with an improvement in insulin sensitivity. Treatment-induced changes in interleukin-10 did not correlate with hypotensive properties of perindopril and telmisartan. CONCLUSIONS: The obtained results indicate that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers administered for a short period of time produce a relatively week effect on anti-inflammatory cytokines, limited to interleukin-10 and stronger for telmisartan than for perindopril.

[33] *Krysiak R, Drosdzol-Cop AB, Skrzypulec-Plinta V, Okopien B*. **The effect of atorvastatin on sexual function and depressive symptoms in young women with elevated cholesterol levels: a pilot study**. Endokrynol Pol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259501
ABSTRACT

INTRODUCTION: Statins were found to improve erectile function in men. No previous study has investigated prospectively sexual functioning in women receiving these agents. AIM: The aim of this study was to evaluate the impact of atorvastatin therapy on female sexual functions and depressive symptoms in young women with elevated cholesterol levels. METHODS: The study included 14 women with elevated cholesterol levels and 14 matched women with normal plasma lipids. Hypercholesterolemic women were then treated with atorvastatin (20-40 mg daily) for 24 weeks. Apart from measuring plasma lipids, at the beginning and at the end of the study, all participants of the study completed questionnaires evaluating sexual function (Female Sexual Function Index - FSFI) and the presence and severity of depressive symptoms (Beck Depression Inventory-Second Edition - BDI-II). RESULTS: The mean total FSFI score was insignificantly lower, while the BDI-II score higher in women with hypercholesterolemia than in the control group. Both groups significantly differed in domain scores for arousal and orgasm. Atorvastatin decreased the domain score for desire, increased the domain score for orgasm, but did not affect the total FSFI score and the remaining domain scores. Moreover, atorvastatin tended to reduce the BDI-II score. Treatment-induced changes in desire, orgasm and the BDI-II did not correlate with the effect of atorvastatin on plasma lipids. CONCLUSIONS: Atorvastatin treatment produces a relatively mild effect on sexual functioning and mood in women, affecting only selected elements of female sexual behavior.

[34] *Cao S, Yu S, Cheng L et al.* **9-O-benzoyl-substituted berberine exerts a triglyceride-lowering effect through AMPK signaling pathway in human hepatoma HepG2 cells**. Environmental toxicology and pharmacology 2018; 64:11-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30268048
ABSTRACT

Berberine is an isoquinoline alkaloid extracted from Rhizoma coptidis and shows anti-hyperlipidemia effect in vivo and in vitro. We previously found that berberine could decrease the intracellular triglyceride content in human hepatoma HepG2 cells through activation of AMP-activated protein kinase (AMPK), a major regulator of lipid metabolism. Herein, to find a more effective agent, several berberine analogues (A1-A13) were isolated and synthesized, and the triglyceride-lowering effects and potential mechanisms were investigated in HepG2 cells. Among these berberine analogues, 9-O-benzoyl-substituted berberine (A13) showed strong affinity to AMPK and significantly up-regulated the levels of phospho-Thr172 AMPK alpha subunit. Meanwhile, A13 reduced the cellular triglyceride levels. Furthermore, A13 could mediate the mRNA levels of downstream proteins involved in triglyceride synthesis and fatty acid oxidation of AMPK signaling pathway. These results suggested that A13 exerts a triglyceride-lowering effect via stimulation of AMPK pathway, which may be beneficial to regulate hyperlipidemia.

[35] *Navarese EP, Andreotti F, Raggi P et al.* **Baseline low-density lipoprotein cholesterol to predict the extent of cardiovascular benefit from lipid-lowering therapies: A Review**. <u>European heart journal. Cardiovascular pharmacotherapy</u> 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30247574
ABSTRACT

Importance: Lipid-lowering therapies have been shown to improve cardiovascular outcome in a wide range of patients. The current guidelines recommend a graded approach to reduction in low-density lipoprotein cholesterol (LDL-C) proportional to the patient's risk, with the goal of achieving either a certain magnitude of reduction or a specific threshold of final LDL-C. Observations: Recent findings from a meta-analysis of numerous randomized trials suggest that more attention should be given to the baseline LDL-C of an individual patient. In this review we discuss how the baseline LDL-C level may provide a means to better understand the results of recent cardiovascular outcome trials and the expected benefits of lipid-lowering therapies. Conclusions and Relevance: The exact quantification of the clinical benefit associate with an intensified lipid-lowering therapy depends on the baseline LDL-C. Mortality is reduced in a log-linear fashion only when LDL-C >100 mg/dl.

[36] *Vahdaninia M, Mackenzie H, Dean T, Helps S*. **The effectiveness of omega-3 polyunsaturated fatty acid interventions during pregnancy on obesity measures in the offspring: an up-to-date systematic review and meta-analysis**. <u>European journal of nutrition</u> 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30251019
ABSTRACT

BACKGROUND: The potential role of omega-3 long chain polyunsaturated fatty acid (LCPUFA) supplementation during pregnancy on subsequent risk of obesity outcomes in the offspring is not clear and there is a need to synthesise this evidence. OBJECTIVE: A systematic review and meta-analysis of randomised controlled trials (RCTs), including the most recent studies, was conducted to assess the effectiveness of omega-3 LCPUFA interventions during pregnancy on obesity measures, e.g. BMI, body weight, fat mass in offspring. METHODS: Included RCTs had a minimum of 1-month follow-up post-partum. The search included CENTRAL, MEDLINE, SCOPUS, WHO's International Clinical Trials Reg., E-theses and Web of Science databases. Study quality was evaluated using the Cochrane Collaboration's risk of bias tool. RESULTS: Eleven RCTs, from ten unique trials, (3644 children) examined the effectiveness of omega-3 LCPUFA maternal supplementation during pregnancy on the development of obesity outcomes in offspring. There were heterogeneities between the trials in terms of their sample, type and duration of intervention and follow-up. Pooled estimates did not show an association between prenatal intake of fatty acids and obesity measures in offspring. CONCLUSION: These results indicate that maternal supplementation with omega-3 LCPUFA during pregnancy does not have a beneficial effect on obesity risk. Due to the high heterogeneity between studies along with small sample sizes and high rates of attrition, the effects of omega-3 LCPUFA supplementation during pregnancy for prevention of childhood obesity in the long-term remains unclear. Large high-quality RCTs are needed that are designed specifically to examine the effect of prenatal intake of fatty acids for prevention of childhood obesity. There is also a need to determine specific sub-groups in the population that might get a greater benefit and whether different

omega-3 LCPUFA, i.e. eicosapentaenoic (EPA) vs. docosahexanoic (DHA) acids might potentially have different effects.

[37] *Panfoli I, Santucci L, Bruschi M et al.* **Microvesicles as promising biological tools for diagnosis and therapy**. Expert review of proteomics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30253662
ABSTRACT

INTRODUCTION: Shed by most cells, in response to a myriad of stimuli, extracellular vesicles (EVs) carry proteins, lipids and various nucleic acids. EVs encompass diverse subpopulations differing for biogenesis and content. Among these, microvesicles (MVs) derived from plasma membrane, are key regulators of physio-pathological cellular processes including cancer, inflammation and infection. MVs. This review is unique in that it focuses specifically on the MV as a mediator of information transfer. In fact, few proteomic studies have rigorously distinguished MVs from exosomes. Areas covered: Aim of this review is to discuss the proteomic analyses of the MVs. Many studies have examined mixed populations containing both exosomes and MVs. We discuss MVs role in cell specific interactions. We also show their emerging roles in therapy and diagnosis. Expert commentary: We see MVs as therapeutic tools for potential use in precision medicine. They may also have potential for allowing the identification of new biomarkers. MVs represent an invaluable tool for studying the cell of origin, which they closely represent, but it is critical to build a repository with data from MVs to deepen our understanding of their molecular repertoire and biological functions.

[38] *Helmke A, Casper J, Nordlohne J et al.* **Endothelial-to-mesenchymal transition shapes the atherosclerotic plaque and modulates macrophage function**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201801238R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30260706
ABSTRACT

Endothelial cells can acquire a mesenchymal phenotype upon irritation [endothelial-to-mesenchymal transition (EndMT)]. Macrophages accumulate in the atherosclerotic plaque. This study addressed whether macrophages modulate EndMT and delineated a reciprocal effect of EndMT on macrophage functions in atherosclerosis. In atherosclerotic murine and human aortas, endothelial cells with mesenchymal markers were elevated by confocal microscopy and flow cytometric analysis. Increased EndMT master transcription factor Snai1 expression and extracellular matrix are consistent with enhanced EndMT in this condition. Hypoxia was detected in individual aortic EndMT cells in vivo and rapidly induced a similar EndMT phenotype in vitro. As a novel inducer of EndMT, macrophages, which are abundant in the atherosclerotic lesions, enhance mesothelial marker expression during coculture in vitro. In the reverse relationship, EndMT altered endothelial colony-stimulating factor expression. Functionally, EndMT cell-conditioned media attenuated macrophage proliferation, antigen-presenting cell marker expression, and TNF-alpha production in response to oxidized LDL but increased oxidized LDL uptake and scavenger receptor expression. These experiments demonstrate that macrophages promote partial EndMT. In turn, EndMT cells modulate macrophage phenotype and lipid uptake. Our data suggest that EndMT shapes macrophage and endothelial cell

phenotypes, thus affecting internal atherosclerotic plaque in addition to surface structure.- Helmke, A., Casper, J., Nordlohne, J., David, S., Haller, H., Zeisberg, E., von Vietinghoff, S. Endothelial-to-mesenchymal transition shapes the atherosclerotic plaque and modulates macrophage function.

[39] *Hu YB, Hu ED, Fu RQ.* **Statin Use and Cancer Incidence in Patients with Type 2 Diabetes Mellitus: A Network Meta-Analysis**. Gastroenterology research and practice 2018; 2018:8620682.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30254671
ABSTRACT
Background: Type 2 diabetes mellitus (T2DM) patients are involved closely with cancer. This work aims to conduct a systematic review and network meta-analysis (NMA) to examine the effect of different types of statins on cancer incidence in patients with T2DM. Methods: We systematically searched the Cochrane Library, PubMed, Embase, and Wanfang databases from January 1999 to March 2017. We performed a pairwise meta-analysis to estimate the pooled ratios (ORs) and 95% confidence intervals (CIs). A NMA was performed to compare different types of statins. Results: Seven publications were included. In pairwise meta-analysis, the incidence of cancer in T2DM patients was reduced when simvastatin, atorvastatin, pravastatin, fluvastatin, lovastatin, rosuvastatin, and pitavastatin were used. In the result of NMA, the usage of simvastatin (RR 0.30 and 95% CI 0.16-0.56), atorvastatin (RR 0.29 and 95% CI 0.09-0.88), pravastatin (RR 0.34 and 95% CI 0.12-0.93), fluvastatin (RR 0.27 and 95% CI 0.09-0.83), rosuvastatin (RR 0.22 and 95% CI 0.10-0.49), and pitavastatin (RR 0.33 and 95% CI 0.20-0.57) was superior to the nonstatin groups. When compared with six other statins, rosuvastatin appeared to be the best one. Conclusions: Different statins can reduce the risk of cancer in patients with T2DM. Our analyses suggest that rosuvastatin may be more effective than others.

[40] *Waskowicz LR, Zhou J, Landau DJ et al.* **Bezafibrate induces autophagy and improves hepatic lipid metabolism in glycogen storage disease type Ia**. Human molecular genetics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30256948
ABSTRACT
Glucose-6-phosphatase alpha (G6Pase) deficiency, also known as von Gierke's Disease or GSD Ia, is characterized by decreased ability of the liver to convert glucose-6-phosphate (G6P) to glucose leading to glycogen accumulation and hepatosteatosis. Long-term complications of GSD Ia include hepatic adenomas and carcinomas, in association with the suppression of autophagy in the liver. The G6pc-/- mouse and canine models for GSD Ia were treated with the pan-peroxisomal proliferator-activated receptor (PPAR) agonist, bezafibrate, to determine the drug's effect on liver metabolism and function. Hepatic glycogen and triglyceride concentrations were measured and Western blotting was performed to investigate pathways affected by the treatment. Bezafibrate decreased liver triglyceride and glycogen concentrations and partially reversed the autophagy defect previously demonstrated in GSD Ia models. Changes in medium-chain acyl-CoA dehydrogenase expression and acylcarnintine flux suggested that fatty acid oxidation was increased, and fatty acid synthase expression associated with lipogenesis was decreased in G6pc-/- mice treated with bezafibrate. In summary, bezafibrate induced autophagy in the liver while increasing fatty acid oxidation and decreasing

lipogenesis in G6pc-/- mice. It represents a potential therapy for glycogen overload and hepatosteatosis associated with GSD Ia, with beneficial effects that have implications for non-alcoholic fatty liver disease.

[41] *Pedro JM, Brito M, Barros H*. **Cardiovascular Risk Assessment in Angolan Adults: A Descriptive Analysis from CardioBengo, a Community-Based Survey**. International journal of hypertension 2018; 2018:2532345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30258655
ABSTRACT

From a community-based survey conducted in Angola, 468 individuals aged 40 to 64 years and not using drug therapy were evaluated according to the World Health Organisation STEPwise Approach to Chronic Disease Risk Factor Surveillance. Using data from tobacco use, blood pressure, blood glucose, and total cholesterol levels, we estimated the 10-year risk of a fatal or nonfatal major cardiovascular event and computed the proportion of untreated participants eligible for pharmacological treatment according to clinical values alone and total cardiovascular risk. The large majority of participants were classified as having a low (<10%) 10-year cardiovascular risk (87.6%), with only 4.5% having a high (>/= 20%) cardiovascular risk. If we consider the single criteria for hypertension, 48.7% of the population should be considered for treatment. This value decreases to 22.0% if we apply the risk prediction chart. The use of hypoglycaemic drugs does not present any differences (19.0% in both situations). The use of lipid-lowering drugs (3.8%) is only recommended by the risk prediction chart. This study reveals the need of integrated approaches for the treatment of cardiovascular disorders in this population. Risk prediction charts can be used as a way to promote a better use of limited resources.

[42] *Lee EJ, Oh H, Kang BG et al.* **Lipid-lowering effects of medium-chain triglyceride-enriched coconut oil in combination with licorice extracts in experimental hyperlipidemic mice**. Journal of agricultural and food chemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30244576
ABSTRACT

Coconut oil has gained in popularity over recent years as healthy oil due to its potential cardiovascular benefits. Coconut oil contains medium chain triglycerides (MCT) including lauric acid and capric acid that display beneficial properties in human health. Licorice (Glycyrrhiza uralensis) is used as a sweetener and in traditional Chinese medicine with anti-inflammatory, anti-microbial and antioxidant activities. This study investigated the in vivo effects of medium chain-triglycerides (MCT)-coconut oil (MCO) and its combination with licorice extract (LE-MCO) on serum lipid profile, hepatic steatosis, and local fat pad proteins in diet-induced obese mice. No liver toxicity was observed in 45% fat diet (HFD)-fed mice orally treated with LE, MCO and LE-MCO for 12 weeks. Their supplementation reduced HFD-enhanced body weight, blood glucose and insulin in mice. Plasma levels of both PLTP and LCAT were boosted in LE-MCO-administrated mice. Supplementation of LE-MCO diminished plasma levels of TG and TC with concomitant reduction of the LDL-C level and tended to raise blood HDL-C level, compared to that of HFD alone-mice. Treatment of LE-MCO encumbered the hepatic induction of hepatosteatosis-related proteins of SREBP2, SREBP1c FAS, ACC and CD36 in HFD-fed mice. 6)

Substantial suppression of this induction was also observed in the liver of mice treated with MCO. Oral administration of LE-MCO to HFD mice boosted hepatic activation of AMPK and the induction of UCP-1 and FATP1 in brown fat. Conversely, LE-MCO disturbed hepatic PPAR-LXR-RXR signaling in HFD-fed animals and reversed HFD-elevated epididymal PPARgamma. Collectively, oral administration of LE-MCO may impede hyperlipidemia and hepatosteatosis through curtailing hepatic lipid synthesis.

[43] *Orkaby AR, Rich MW, Sun R et al.* **Pravastatin for Primary Prevention in Older Adults: Restricted Mean Survival Time Analysis**. <u>J Am Geriatr Soc </u>2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30251369
ABSTRACT
OBJECTIVES: To use restricted mean survival time, which summarizes treatment effects in terms of event-free time over a fixed time period, to evaluate the benefit of pravastatin therapy for primary prevention of cardiovascular disease in older adults. DESIGN: Secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT). SETTING: Ambulatory setting. PARTICIPANTS: Individuals aged 65 and older (mean aged 71, 49% female) free of cardiovascular disease (N=2,867). INTERVENTION: Pravastatin 40 mg/d (n=1,467) versus usual care (n=1,400). MEASUREMENTS: We estimated the difference in RMST for total and coronary heart disease (CHD)-free survival between the pravastatin and usual care groups over the 6-year trial period and used parametric survival models to estimate RMST differences projected over 10 years. RESULTS: Over 6 years, individuals treated with pravastatin lived (RMST 2,008.1 days), on average, 33.7 fewer days than those receiving usual care (RMST 2,041.8 days) (difference -33.7 days, 95% confidence interval (CI)=-67.0 to -0.5 days, p=.047). Pravastatin-treated individuals lived RMST 2,088.1 days), on average, 18.7 more days free of CHD over 6 years than those receiving usual care (RMST 2,069.4 days), but this difference was not statistically significant (difference 18.7 days, 95% CI=-10.4-47.8 days, p=.21). The 10-year projection showed that pravastatin-treated individuals would live 108.1 fewer days (95% CI=-204.5 to -14.1, p=.03) than those receiving usual care, although treated individuals would gain 77.9 days (95% CI=3.8-159.6, p=.046) of CHD-free survival. CONCLUSION: RMST provides an intuitive and explicit way to express the effect of pravastatin therapy on CHD-free and overall survival in older adults free of cardiovascular disease. This measure allows a more personalized interpretation than hazard ratios of the benefits and risks of a medical intervention for decision-making.

[44] *Nohara A, Otsubo Y, Yanagi K et al.* **Safety and Efficacy of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolemia (HoFH): Results from the AEGR-733-301 Long-Term Extension Study**. <u>Journal of atherosclerosis and thrombosis </u>2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259883
ABSTRACT
AIM: Lomitapide is an approved lipid-lowering agent indicated as adjunct to low-fat diet and standard lipid-lowering therapies (LLTs) including lipoprotein apheresis for the treatment of homozygous familial hypercholesterolemia (HoFH). Clinical data from Phase 3 studies have demonstrated the prolonged lipid-lowering capacity of lomitapide in patients with HoFH. We assessed the long-term lipid-lowering capacity of daily oral lomitapide in a cohort of Japanese

patients with HoFH enrolled in a Phase 3 extension study. METHODS: Five of 8 Japanese HoFH patients completing a 56-week Phase 3 dose-escalation and safety study of lomitapide continued their maximum tolerated dose (MTD) until study drug was approved or commercially available or until treatment was discontinued. Lipid parameters were measured at Day 1 and at 12-week intervals through study end. Safety and tolerability were assessed. RESULTS: Daily lomitapide treatment with permitted LLTs maintained approximately 50% mean reductions in plasma low-density lipoprotein cholesterol (LDL-C) levels from baseline for 60 weeks. Reductions in LDL-C levels varied across patients and were not associated with the HoFH genotype. Four patients achieved 25% reductions and 1 patient achieved 50% reduction in LDL-C; 2 patients achieved reduction in LDL-C to 100 mg/d. Lomitapide significantly reduced total cholesterol (26.5%), triglycerides (54.8%), and non-high-density lipoprotein cholesterol (non-HDL-C) (37.4%). All 5 patients continued their individual MTD of lomitapide throughout the extension study with acceptable safety and tolerability, and no deaths were reported. CONCLUSION: Results from this extension study support the long-term safety and efficacy of lomitapide in significantly reducing plasma levels of atherosclerotic lipids in patients with HoFH.

[45] *Sakata K, Gamou T, Tada H et al.* **Low Baseline High-Sensitive C-Reactive Protein is Associated with Coronary Atherosclerosis Regression: Insights from the MILLION Study**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30249940
ABSTRACT

AIM: The prospective, randomized, multicenter Myocardial Ischemia Treated with Percutaneous Coronary Intervention and Plaque Regression by Lipid Lowering & Blood Pressure Controlling assessed by Intravascular Ultrasonography (MILLION) study demonstrated that combined treatment with atorvastatin and amlodipine enhanced coronary artery plaque regression. Although the baseline high-sensitive C-reactive protein (hs-CRP) reportedly plays an important role in atherogenesis, few data exist regarding the relationship between hs-CRP and plaque regression in patients receiving a combined atorvastatin and amlodipine therapy. METHODS: A total of 68 patients (male, 55; mean age, 64.2 years) with baseline and follow-up 3-dimensional intravascular ultrasound examinations in the MILLION study were stratified by baseline hs-CRP level quartiles. The serial measurements of lipid, blood pressure, and percentage changes in the plaque volume were compared between the groups, and the factors associated with the percentage change in the plaque volume were assessed. RESULTS: There were no significant between-group differences in the extent of change in low-density lipoprotein cholesterol (LDL-C) or systolic and diastolic blood pressure after 18-24 months of treatment. The percentage change in the plaque volume showed a linear association with the baseline hs-CRP (p for trend 0.05); however, there was no correlation with changes in LDL-C or systolic and diastolic blood pressure. In the multiple regression analysis, the baseline hs-CRP level was independently associated with the percentage change in the plaque volume (beta=0.29, p=0.022). CONCLUSIONS: Coronary plaque regression was associated with the baseline hs-CRP level in patients treated with a combined lipid- and blood pressure-lowering therapy.

[46] *Shakour N, Bianconi V, Pirro M et al.* **In silico evidence of direct interaction between statins and beta-amyloid**. Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30260016
ABSTRACT

INTRODUCTION: Aggregation of amyloid-beta (Abeta) peptides represents a crucial step in the pathogenesis of Alzheimer disease (AD). Compelling evidence from preclinical studies has established that statins may reduce amyloidogenesis and Abeta-mediated neurodegeneration, supporting a potential role of statin treatment in the prevention of AD. Different statins have been shown to interfere indirectly with Abeta production and clearance through either cholesterol-dependent or cholesterol-independent mechanisms. However, whether there may be a direct interaction between statins and Abeta metabolism is still unclear. MATERIALS AND METHODS: To test the possible direct interaction between statins and Abeta, we performed an in silico study by testing the orientation of different ligands, including statins and sulindac (the standard ligand of Abeta), in the Abeta active site using molecular operating environment (MOE) software. RESULTS: Docking experiments showed that all the tested statins could directly interact with Abeta protofibrils. Among statins, pitavastatin had the strongest interaction with Abeta (pki = 7.66), followed by atorvastatin (pk i = 7.63), rosuvastatin (pk i = 6.99), fluvastatin (pk i = 6.96), pravastatin (pk i = 6.46), lovastatin (pk i = 6.37), and simvastatin (pk i = 5.90). According to the above-mentioned results, pitavastatin, atorvastatin, rosuvastatin, and fluvastatin had a stronger binding to Abeta compared with the standard ligand sulindac (pk i = 6.62). CONCLUSION: This study showed a direct interaction between statins and Abeta protofibrils, which may underlie the protective role of this widely used class of drugs against amyloidogenesis and Abeta-mediated neurodegeneration.

[47] *Tang ZH, Li TH, Peng J et al.* **PCSK9: A novel inflammation modulator in atherosclerosis?** Journal of cellular physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30246446
ABSTRACT

Proprotein convertase subtilisin/kexin 9 (PCSK9) is the ninth member of the secretory serine protease family. It binds to low-density lipoprotein receptor (LDLR) for endocytosis and lysosome degradation in the liver, resulting in an increasing in circulating LDL-cholesterol (LDL-c) level. Since a PCSK9 induced increase in plasma LDL-c contributes to atherosclerosis, PCSK9 inhibition has become a new strategy in preventing and treating atherosclerosis. However, in addition to the effect of PCSK9 on elevating blood LDL-c levels, accumulating evidence shows that PCSK9 plays an important role in inflammation, likely representing another major mechanism for PCSK9 to promote atherosclerosis. In this review, we discuss the association of PCSK9 and inflammation, and highlight the specific effects of PCSK9 on different vascular cellular components involved in the atherosclerotic inflammation. We also discuss the clinical evidence for the association between PCSK9 and inflammation in atherosclerotic cardiovascular disease. A better understanding of the direct association of PCSK9 with atherosclerotic inflammation might help establish a new role for PCSK9 in vascular biology and identify a novel molecular mechanism for PCSK9 therapy.

[48] *Herrera-Martinez AD, Pedraza-Arevalo S, F LL et al.* **Type 2 diabetes in neuroendocrine tumors: are biguanides and statins part of the solution?** The Journal of clinical endocrinology and metabolism 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30265346
ABSTRACT

Background: Biguanides and statins have been reported to exert beneficial effects on various cancer types. However, their precise effects and underlying molecular mechanisms are still poorly understood. Materials and Methods: We analyzed the relation between metabolic-syndrome, i.e., presence of type-2 diabetes (T2DM), hyperlipidemia and their treatment, with histological, epidemiological, and prognosis variables in two patient cohorts with neuroendocrine-tumors [NETs: lung-carcinoids (LCs; n=81) and gastro-entero-pancreatic (GEP-NET; n=100)]. Additionally, we investigated the antitumoral effects of different biguanides and statins by evaluating proliferation/migration/secretion/gene-expression and involved molecular pathways using BON1/QGP1-cell cultures. Results: In T2DM patients, pleura invasion was higher (LCs group; p<0.05) and tumor diameter tended to be increased (GEP-NET group). mRNA levels of somatostatin and ghrelin systems were different in tumor tissue of T2DM patients with and without metformin. Biguanides (metformin/buformin/phenformin) decreased proliferation rate in BON1/QGP1-cells (24-72h). However, the effects of statins on proliferation-rate were dependent of the statin-type, cell-type, and time. Specifically, only simvastatin/atorvastatin decreased proliferation in BON1-cells (48/72h and 72h, respectively), while all statins decreased proliferation rate in QGP1-cells (48/72h). Remarkably, metformin and simvastatin decreased migration capacity in BON1-cells and biguanides decreased serotonin secretion in BON1-cells. Phenformin increased apoptosis in BON1/QGP1-cells, and simvastatin in QGP1-cells. These antitumor effects likely involved altered expression of key genes related to cancer aggressiveness (i.e. GLUT4, INSR). Altogether, our results reveal a clear inhibitory effect of biguanides and statins on NET-cell aggressiveness. Conclusion: Given the demonstrated clinical safety of these drugs, our results invite to further explore their potential therapeutic role for the treatment of NET patients. Precis: Clinical/molecular changes in patients with T2DM and NETs reversed in metformin treated patients. Biguanides/statins altered aggressiveness features (proliferation, apoptosis, etc.) in NET cells.

[49] *van Capelleveen JC, Lee SR, Verbeek R et al.* **Relationship of lipoprotein-associated apolipoprotein C-III with lipid variables and coronary artery disease risk: The EPIC-Norfolk prospective population study**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30249512
ABSTRACT

BACKGROUND: Plasma apolipoprotein C-III (apoC-III) levels are associated with coronary artery disease (CAD) risk. OBJECTIVE: To assess whether lipoprotein-associated apoC-III levels predict risk of CAD events. METHODS: apoC-III associated with apoB, apoAI, and Lp(a) (apoCIII-apoB, apoCIII-apoAI, and apoCIII-Lp(a), respectively) were measured using high-throughput chemiluminescent enzyme-linked immunoassays in 2711 subjects (1879 controls and 832 cases with CAD) in the European Prospective Investigation into Cancer and Nutrition-Norfolk prospective population study with 7.4 years of follow-up. These measures were correlated with a variety of lipid measurements and the presence of CAD. The indices of "total apoCIII-apoB"

and "total apoCIII-apoAI" were derived by multiplying plasma apoB and apoAI, respectively. RESULTS: apoCIII-apoB (P = .001), apoCIII-Lp(a) (P < .001), apoCIII-apoAI (P = .005) were higher in cases vs controls; tended to correlate positively with body mass index, hsCRP, apoC-III, low-density lipoprotein (LDL) cholesterol, triglycerides, remnant cholesterol, very low density lipoprotein, LDL and high-density lipoprotein particle number and very low density lipoprotein size; but negatively with LDL and high-density lipoprotein particle size (P < .001 for all). apoCIII-apoB, apoCIII-apoAI, apoCIII-Lp(a), total apoCIII-Lp(a), and total apoCIII-apoB were predictors of CAD after adjustment of age, sex, body mass index, smoking, diabetes, hypertensive and lipid-lowering drug use, but they lost their significance after further adjustment of lipid and lipoprotein variables. CONCLUSIONS: This study suggests that enzyme-linked immunoassay-measured lipoprotein-associated apoC-III markers reflect atherogenic lipid particles but do not independently predict risk of CAD events.

[50] *Iizuka Y, Kim H, Hirako S et al.* **Benefits of combination low-dose pioglitazone plus fish oil on aged type 2 diabetes mice**. Journal of food and drug analysis 2018; 26:1265-1274.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30249325
ABSTRACT

The elderly patients with type 2 diabetes suffer more adverse drug events than young adults due to pharmacokinetic and pharmacodynamic changes associated with aging. Reducing the risks of these medication-related problems are equally important for the clinical care of older type 2 diabetes patients. Pioglitazone is used for treating type 2 diabetes as an oral antidiabetic drug. Despite pioglitazone is used helpful insulin sensitizers, the accumulation of subcutaneous fat is considered a major adverse effect of pioglitazone therapy. We investigated to reduce the adverse effect of pioglitazone by combination with fish oil rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in aged diabetic KK mice. The accumulation of subcutaneous fat associated with high-dose pioglitazone is reduced by fish oil, suppressing lipogenesis and stimulating fatty acid beta-oxidation in the liver. Our data suggest that adding fish oil to low-dose pioglitazone results in antidiabetic efficacy similar to that of the high-dose without concomitant body weight gain.

[51] *Zhang X, Rimbert A, Balder W et al.* **Use of Plasma Metabolomics to Analyze Phenotype-Genotype Relationships in Young Hypercholesterolemic Females**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30266833
ABSTRACT

Hypercholesterolemia is characterized by high plasma low density lipoprotein (LDL) cholesterol and often caused by genetic mutations in LDLR, APOB or PCSK9. However, a substantial proportion of hypercholesterolemic subjects do not have any mutations in these canonical genes, leaving the underlying pathobiology to be determined. In this study, we investigated whether combining plasma metabolomics with genetic information increases insight in the biology of hypercholesterolemia. For this proof of concept study, we combined plasma metabolites from 119 hypercholesterolemic females with genetic information on the LDL canonical genes. Using hierarchical clustering we identified four subtypes of hypercholesterolemia, which could be distinguished along two axes represented by triglyceride

and large LDL particle concentration. Subjects with mutations in LDLR or APOB preferentially clustered together suggesting that patients with defects in the LDL receptor pathway show a distinctive metabolomics profile. In conclusion, we show the potential of using metabolomics to segregate hypercholesterolemic subjects in different clusters, which may help in targeting genetic analysis.

[52] *Shan J, Qian W, Kang A et al.* **Lipid profile perturbations in the plasma and lungs of mice with LPS-induced acute lung injury revealed by UHPLC-ESI-Q Exactive HF MS analysis**. Journal of pharmaceutical and biomedical analysis 2018; 162:242-248.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30268025
ABSTRACT
An UHPLC-ESI-Q Exactive HF MS-based lipidomics method was successfully applied to profile various lipids from the plasma and lungs of mice intranasally challenged with lipopolysaccaride (LPS). Response trends of lipids to LPS were graphically represented by variable importance in projection (VIP) plot, heat map, and bar plot. As a result, 77 differential lipids in the lung and 13 differential lipids in the plasma were identified by comparison between healthy and LPS-induced mice. These results revealed the correlation between inflammation and lipids metabolism. The differentially regulated lipids could also be potentially used as biomarkers for inflammation.

[53] *Hua H, Yang J, Lin H et al.* **PPARalpha-independent action against metabolic syndrome development by fibrates is mediated by inhibition of STAT3 signalling**. The Journal of pharmacy and pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30251457
ABSTRACT
OBJECTIVES: Metabolic syndrome (MS) is the concurrence of at least three of five medical conditions: obesity, high blood pressure, insulin resistance, high serum triglyceride (TG) and low serum high-density lipoprotein levels. While fibrates are used to treat disorders other than the lowering serum TG, the mechanism by which fibrates decrease MS has not been established. METHODS: In this study, wild-type and Ppara-null mice fed a medium-fat diet (MFD) were administered gemfibrozil and fenofibrate for 3 months respectively, to explore the effect and action mechanism. KEY FINDINGS: In Ppara-null mice, MFD treatment increased body weight, adipose tissue, serum TG and impaired glucose tolerance. These phenotypes were attenuated in two groups treated with gemfibrozil and fenofibrate. The STAT3 pathway was activated in adipose and hepatic tissues in positive control, and inhibited in groups treated with gemfibrozil and fenofibrate. The above phenotypes and inflammation were not observed in any wild-type group. In 3T3-L1 adipogenic stem cells treated with high glucose, STAT3 knockdown greatly decreased the number of lipid droplets. CONCLUSIONS: Low dose of clinical fibrates was effective against MS development independent of PPARalpha, and this action was mediated by STAT3 signalling inhibition in adipose tissue and, to a lesser extent, in hepatic tissues.

[54] *Lopes RD, de Barros ESPGM, de Andrade Jesuino I et al.* **Timing of Loading Dose of Atorvastatin in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes: Insights From the SECURE-PCI Randomized Clinical Trial**. JAMA cardiology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30264159
ABSTRACT

Importance: Loading doses of atorvastatin did not show reduction on clinical outcomes in the overall population of patients with acute coronary syndrome (ACS) enrolled in the Statins Evaluation in Coronary Procedures and Revascularization (SECURE-PCI) trial, but a potential benefit was identified in patients who subsequently underwent percutaneous coronary intervention (PCI). Objectives: To determine whether periprocedural loading doses of atorvastatin are associated with decreased 30-day major adverse cardiovascular events (MACE) in patients with ACS undergoing PCI according to type of ACS and timing of atorvastatin administration before PCI. Design, Setting, and Participants: Secondary analysis of a multicenter, double-blind, placebo-controlled, randomized clinical trial conducted at 53 sites that enrolled 4191 patients with ACS intended to be treated with PCI between April 18, 2012, and October 06, 2017. Interventions: Patients were randomized to 2 loading doses of 80 mg of atorvastatin or matching placebo before and 24 hours after a planned PCI. By protocol, all patients (regardless of treatment group) received 40 mg of atorvastatin for 30 days starting 24 hours after the second dose of study medication. Main Outcomes and Measures: The primary outcome was MACE through 30 days, composed by all-cause mortality, myocardial infarction, stroke, and unplanned coronary revascularization. Cox regression models adjusting for key baseline characteristics were used to assess the association between atorvastatin and MACE in patients undergoing PCI. Results: From the overall trial population, 2710 (64.7%) underwent PCI (650 women [24.0%]; mean [SD] age, 62 [11.3] years). Loading atorvastatin was associated with reduced MACE at 30 days by 28% in the PCI group (adjusted hazard ratio [HR], 0.72; 95% CI 0.54-0.97; P = .03). Loading dose of atorvastatin was administered less than 12 hours before PCI in 2548 patients (95.3%) (45.1% < 2 hours and 54.3% between 2 and 12 hours). There was no significant interaction between treatment effect and timing of study drug administration. The treatment effect of loading atorvastatin was more pronounced in patients with ST-segment elevation myocardial infarction than in patients with non-ST-segment elevation ACS (adjusted HR, 0.59; 95% CI, 0.38-0.92; P = .02; HR, 0.85; 95% CI, 0.58-1.27; P = .43, respectively). Conclusions and Relevance: In patients with ACS undergoing PCI, periprocedural loading doses of atorvastatin appeared to reduce the rate of MACE at 30 days, primarily in patients with ST-segment elevation myocardial infarction. This beneficial effect seemed to be preserved and consistent, regardless of timing of atorvastatin administration, including within 2 hours before PCI. Trial Registration: clinicaltrials.gov Identifier: NCT01448642.

[55] *Nam CW, Kim DS, Li J et al.* **Efficacy and safety of alirocumab in Korean patients with hypercholesterolemia and high cardiovascular risk: subanalysis of the ODYSSEY-KT study**. The Korean journal of internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30257549
ABSTRACT

Background/Aims: Efficacy and safety data of alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is not yet well established in the Korean population. We assessed them in ODYSSEY-KT through the pre-specified Korean subanalysis. Methods: In the ODYSSEY-KT study, South Korean and Taiwanese patients with hypercholesterolemia and high cardiovascular risks were randomized (1:1) to alirocumab or

placebo. Alirocumab was self-administered subcutaneously at 75 mg every 2 weeks with a maximally tolerated statin dose with or without other lipid-modifying therapies. Alirocumab dose was increased to 150 mg every 2 weeks at week 12 if low density lipoprotein cholesterol (LDL-C) >/= 70 mg/dL at week 8. Primary endpoint was percent change in LDL-C from baseline to week 24. Results from Korean cohort (n = 83: 40 for alirocumab and 43 for placebo, respectively) analyses are reported here. Results: In alirocumab group, the least square of mean change percent in LDL-C levels was -65.7% (placebo: 11.1%; p < 0.0001) and 92.0% of them achieved LDL-C < 70 mg/dL (placebo: 12.7%; p < 0.0001) at week 24. Alirocumab also showed significantly greater improvements in high density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, lipoprotein(a), and apolipoprotein B than placebo (p < 0.05). Two consecutive calculated LDL-C values < 25 mg/dL were observed in 37.5% of alirocumab-treated patients. Overall, 45.0% alirocumab-treated and 51.2% placebo-treated patients experienced treatment-emergent adverse events (TEAEs) without discontinuation of treatment due to TEAEs. Conclusions: Alirocumab has demonstrated to be effective in improvement of LDL-C and related lipid profiles in Korean cohort. Alirocumab was generally well tolerated with no significant safety signals.

[56] *Liland NS, Pittman K, Whatmore P et al.* **Fucosterol Causes Small Changes in Lipid Storage and Brassicasterol Affects some Markers of Lipid Metabolism in Atlantic Salmon Hepatocytes**. Lipids 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30259993
ABSTRACT

Several feeding trials with Atlantic salmon fed naturally high phytosterol concentrations due to dietary rapeseed oil inclusion have shown changes in lipid metabolism and increased hepatic lipid storage in the fish. An in vitro trial with Atlantic salmon hepatocytes was, therefore, performed to study the possible direct effects of phytosterols on lipid storage and metabolism. The isolated hepatocytes were exposed to seven different sterol treatments and gene expression, as well as lipid accumulation by Oil Red O dyeing, was assessed. Fucosterol, a sterol found in many algae species, had an effect on the size of individual lipid droplets, leading to smaller lipid droplets than in the control without added sterols. A sterol extract from soybean/rapeseed led to an increase in the percentage of hepatocytes with visible lipid droplets at 20x magnification, while hepatocytes of both the sterol extract-treated groups and fucosterol-treated groups had a larger proportion of their area covered with lipids compared to control cells. Brassicasterol, a sterol characteristic of rapeseed oil, was the only sterol treatment leading to a change in gene expression, affecting the expression of the nuclear receptors, peroxisome proliferator-activated receptor gamma (pparg) and retinoid X receptor (rxr). The current study thus shows that phytosterols can have direct, although subtle, effects on both hepatic lipid storage and gene expression of Atlantic salmon in vitro.

[57] *Sid V, Shang Y, Siow YL et al.* **Folic Acid Supplementation Attenuates Chronic Hepatic Inflammation in High-Fat Diet Fed Mice**. Lipids 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30252139
ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease worldwide. Hepatic inflammation is an important pathogenic mediator of NAFLD. There is currently no pharmacological agent approved for the treatment of NAFLD. Folic acid is a water-soluble B vitamin that has been shown to have lipid-lowering and antioxidant effects. The objective of this study was to investigate the effect of folic acid supplementation on hepatic inflammation and to identify the underlying mechanisms. Male C57BL/6 J mice were fed a control diet (10% kcal fat), a high-fat diet (HFD) (60% kcal fat), or a HFD supplemented with folic acid (26 mg/kg diet) for 8 weeks. HFD feeding led to increased body mass gain, lipid accumulation, activation of transcription factor nuclear factor-kappaB (NF-kappaB), and elevation of inflammatory cytokine gene expression in the liver. Folic acid supplementation attenuated hepatic lipid accumulation and aggregation of inflammatory foci induced by HFD feeding. This was associated with a significant reduction of NF-kappaB activation and inflammatory cytokine expression. These results suggest that the hepatoprotective effect of folic acid in NAFLD may be attributed, in part, to its anti-inflammatory action.

[58] *Pelusi S, Valenti L*. **Hepatic fat as clinical outcome and therapeutic target for nonalcoholic fatty liver disease**. Liver international : official journal of the International Association for the Study of the Liver 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30248234
ABSTRACT
Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the leading cause of advanced liver disease in Western countries. NAFLD is defined in the presence of increased hepatic fat content, which is mainly stored under the form of neutral lipids within intracellular droplets and is not explained by at risk alcohol intake. In order to understand the pathogenesis, monitor the progression and find novel treatments for this condition, previous research efforts mainly addressed the role of inflammation. However, very recent data seem to suggest that hepatic lipid accumulation may be involved in NAFLD pathogenesis by driving secondary inflammation and fibrosis progression. Here we will briefly review the novel results derived from natural history, genetics, imaging studies and therapeutic trials that support the notion that hepatic fat accumulation may represent a major clinical outcome and therapeutic target for NAFLD. Indeed, prospective and genetic data are consistent with hepatic fat being a driver of NAFLD progression. Furthermore, new technologies will render possible to monitor hepatic fat content without the need of invasive assessment, thereby allowing to identify patients at higher risk, and to monitor the response to drugs that act by decreasing hepatic lipid accumulation. This article is protected by copyright. All rights reserved.

[59] *Turk Veselic M, Erzen B, Hanzel J et al.* **Improving Arterial Wall Characteristics in Patients After Myocardial Infarction with a Very Low Dose of Fluvastatin and Valsartan: A Proof-of-Concept Study**. Medical science monitor : international medical journal of experimental and clinical research 2018; 24:6892-6899.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30266894
ABSTRACT
BACKGROUND We tested the concept of improving arterial wall characteristics by treatment with a very low-dose combination of fluvastatin and valsartan (low-flu/val) in stable, post-

myocardial infarction (MI) patients. MATERIAL AND METHODS We enrolled 36 post-MI middle-aged males in the treatment (n=20) or control (n=16) group receiving low-flu/val (10 mg/20 mg) or placebo, respectively. The parameters of endothelial function (flow-mediated dilatation (FMD), reactive hyperemia index), and arterial stiffness (carotid-femoral pulse wave velocity (cf-PWV), local carotid PWV, and beta stiffness coefficient) were measured before and after 30 days of therapy, and 10 weeks later. RESULTS Treatment with low-flu/val improved FMD from 3.1+/-1.3% to 4.8+/-1.5% (p<0.001; by 54.8%) and cf-PWV from 7.8+/-1.1 to 6.7+/-1.5 m/s (p<0.01; by 14.1%) without affecting either lipids or blood pressure. In the treatment group, FMD and/or cf-PWV significantly improved in 17 patients, but the improvements did not correlate. The benefits obtained were still detectable 10 weeks after complete treatment cessation. No changes were obtained in the control group. No other vascular parameters changed. CONCLUSIONS Low-flu/val added "on top of" optimal therapy substantially improves endothelial function and arterial stiffness in post-MI patients. Since these improved parameters are well-known predictors of future coronary events, such treatment could decrease cardiovascular risk. Further studies are therefore warranted.

[60] *Millar CL, Norris GH, Jiang C et al.* **Long-Term Supplementation of Black Elderberry Promotes Hyperlipidemia, but Reduces Liver Inflammation and Improves HDL Function and Atherosclerotic Plaque Stability in Apolipoprotein E-Knockout Mice**. Molecular nutrition & food research 2018:e1800404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30267603
ABSTRACT

SCOPE: HDL particles are protective against atherosclerosis but may become dysfunctional during inflammation and chronic disease progression. Anthocyanin-rich foods, such as black elderberry, may improve HDL function and prevent disease development via antioxidant and/or anti-inflammatory effects. Therefore, we investigated whether long-term consumption of black elderberry extract (BEE) influenced HDL function and atherosclerosis in apolipoprotein (apo) E(-/-) mice. METHODS AND RESULTS: ApoE(-/-) mice (n = 12/group) were fed a low-fat diet, supplemented with 0, 0.25%, or 1% (by weight) BEE (approximately 37.5-150 mg anthocyanins/kg body weight) for 24 weeks. Feeding 1% BEE increased total serum cholesterol (+31%) and non-HDL cholesterol (+32%) compared to control diet. PON1 arylesterase (+32%) and lactonase (+45%) activities also increased with the 1% BEE diet. Both 0.25% BEE and 1% BEE diets strongly increased HDL cholesterol efflux capacity (CEC) by 64% and 85%, respectively. Further, BEE dose-dependently lowered serum liver enzymes and hepatic inflammatory gene expression. Although there was no change in neutral lipid accumulation in atherosclerotic lesions, BEE promoted connective tissue deposition in the aortic root. CONCLUSIONS: Chronic BEE supplementation in apoE(-/-) mice dose-dependently improved HDL function. Despite BEE promoting hyperlipidemia, which likely offset HDL effects, BEE increased connective tissue content, suggesting improved atherosclerotic plaque stability. This article is protected by copyright. All rights reserved.

[61] *Nowak C, Arnlov J*. **A Mendelian randomization study of the effects of blood lipids on breast cancer risk**. Nature communications 2018; 9:3957.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30262900

ABSTRACT
Observational studies have reported inconsistent associations between circulating lipids and breast cancer risk. Using results from >400,000 participants in two-sample Mendelian randomization, we show that genetically raised LDL-cholesterol is associated with higher risk of breast cancer (odds ratio, OR, per standard deviation, 1.09, 95% confidence interval, 1.02-1.18, P = 0.020) and estrogen receptor (ER)-positive breast cancer (OR 1.14 [1.05-1.24] P = 0.004). Genetically raised HDL-cholesterol is associated with higher risk of ER-positive breast cancer (OR 1.13 [1.01-1.26] P = 0.037). HDL-cholesterol-raising variants in the gene encoding the target of CETP inhibitors are associated with higher risk of breast cancer (OR 1.07 [1.03-1.11] P = 0.001) and ER-positive breast cancer (OR 1.08 [1.03-1.13] P = 0.001). LDL-cholesterol-lowering variants mimicking PCSK9 inhibitors are associated (P = 0.014) with lower breast cancer risk. We find no effects related to the statin and ezetimibe target genes. The possible risk-promoting effects of raised LDL-cholesterol and CETP-mediated raised HDL-cholesterol have implications for breast cancer prevention and clinical trials.

[62] *Del Rio Sola ML, Vaquero Puerta C.* **A Unique Case of Horner's Syndrome Following Subintimal Haematoma Within an Atherosclerotic Plaque**. Neuro-ophthalmology (Aeolus Press) 2018; 42:299-301.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30258476

ABSTRACT
Background and Importance We describe a patient with Horner's syndrome caused by an extensive intraparietal hematoma in the wall of the internal carotid artery confused with an arterial dissection. Detection of such pathology instead of dissection or arteritis is important as the management is different. As far as the authors know, it is the first case in which a haematoma within an atherosclerotic plaque is clinically related Horner's syndrome. Clinical Presentation A 81-year-old man presented with acute right hemiplegia and loss of vision of the left eye due to a central retinal artery occlusion. The patient underwent a computerised angiotomography which demonstrated left internal carotid artery occlusion with recanalisation after carotid bifurcation. Clinically, the patient developed a syndrome of Claude-Bernard Horner which replaced the diagnosis on the suspicion that it was a carotid artery dissection. The patient had miosis and ptosis of left eye. In the magnetic resonance angiography, an intramural of a possible hematoma was observed. It was decided to perform surgical treatment of the carotid lesion. Conclusion As this clinical case shows, there are symptomatic courtships that must be studied in detail so as not to confuse the carotid dissection with critical stenosis of the internal carotid artery.

[63] *Ueland T, Kleveland O, Michelsen AE et al.* **Serum PCSK9 is modified by interleukin-6 receptor antagonism in patients with hypercholesterolaemia following non-ST-elevation myocardial infarction**. Open heart 2018; 5:e000765.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30258647

ABSTRACT
Objective: It is unclear if activation of inflammatory pathways regulates proprotein convertase subtilisin-kexin type 9 (PCSK9) levels. Approach: We evaluated (1) the temporal course of serum PCSK9 during hospitalisation following acute coronary syndrome and associations with markers

of inflammation (leucocyte counts, interleukin (IL)-6, C-reactive protein) and lipid levels and (2) the effect of inhibition of IL-6 signalling with the IL-6 receptor antibody tocilizumab on PCSK9 levels in a randomised, double-blind, placebo-controlled trial release in patients with non-ST-elevation myocardial infarction. Results: Serum PCSK9 increased during the acute phase and this response was modestly associated with neutrophil counts (r=0.24, p=0.009) and presence of hypercholesterolaemia (r=0.019, p=0.045), but was not modified by tocilizumab. However, a modifying effect of tocilizumab on PCSK9 levels was observed in patients with hypercholesterolaemia (p=0.024, repeated measures analysis of variance) and this effect was strongly correlated with the decrease in neutrophils (r=0.66, p=0.004). Conclusions: Our study suggests that patients with a more atherogenic profile may benefit from anti-IL-6 therapy with regard to PCSK9. Trial registration number: NCT01491074.

[64] *Kozijn AE, Tartjiono MT, Ravipati S et al.* **Human C-reactive protein aggravates osteoarthritis development in mice on a high-fat diet**. Osteoarthritis and cartilage 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30248505
ABSTRACT
OBJECTIVE: C-reactive protein (CRP) levels can be elevated in osteoarthritis (OA) patients. In addition to indicating systemic inflammation, it is suggested that CRP itself can play a role in OA development. Obesity and metabolic syndrome are important risk factors for OA and also induce elevated CRP levels. Here we evaluated in a human CRP (hCRP)-transgenic mouse model whether CRP itself contributes to the development of 'metabolic' OA. DESIGN: Metabolic OA was induced by feeding 12-week-old hCRP-transgenic males (hCRP-tg, n=30) and wild-type littermates (n=15) a 45 kcal% high-fat diet (HFD) for 38 weeks. Cartilage degradation, osteophytes and synovitis were graded on Safranin O-stained histological knee joint sections. Inflammatory status was assessed by plasma lipid profiling, flow cytometric analyses of blood immune cell populations and immunohistochemical staining of synovial macrophage subsets. RESULTS: Male hCRP-tg mice showed aggravated OA severity and increased osteophytosis compared with their wild-type littermates. Both classical and non-classical monocytes showed increased expression of CCR2 and CD86 in hCRP-tg males. HFD-induced effects were evident for nearly all lipids measured and indicated a similar low-grade systemic inflammation for both genotypes. Synovitis scores and synovial macrophage subsets were similar in the two groups. CONCLUSIONS: Human CRP expression in a background of HFD-induced metabolic dysfunction resulted in the aggravation of OA through increased cartilage degeneration and osteophytosis. Increased recruitment of classical and non-classical monocytes might be a mechanism of action through which CRP is involved in aggravating this process. These findings suggest interventions selectively directed against CRP activity could ameliorate metabolic OA development.

[65] *Zhang QS, Deater M, Phan N et al.* **Combination therapy with atorvastatin and celecoxib delays tumor formation in a Fanconi anemia mouse model**. Pediatric blood & cancer 2018:e27460.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30255556
ABSTRACT
BACKGROUND: Fanconi anemia is an inherited bone marrow failure disorder associated with a high incidence of leukemia and solid tumors. Currently, no interventions to prevent or delay the

formation of solid tumors are available. PROCEDURE: Two of the most important hallmarks of Fanconi anemia are inflammation and oxidative stress. In this study, we administrated the antioxidant atorvastatin and the anti-inflammatory drug celecoxib to cohorts of Fancd2(-/-) /Trp53(+/-) mice, a model of Fanconi anemia. Treatment started at weaning and continued until the mice developed a palpable mass or suffered from >20% weight loss. Tumor samples and selected tissues were subjected to histopathological examination. chi(2) test was performed to analyze tumor incidence, and Kaplan-Meier survival curves were evaluated with log-rank test. In addition, a small cohort of mice was monitored for the safety of the drugs. RESULTS: The combined oral administration of both drugs significantly delayed tumor onset in Fancd2(-/-) /Trp53(+/-) mice. Specifically, the treatment delayed the onset of ovarian tumors in Fancd2(-/-) /Trp53(+/-) mice and increased the mean ovarian tumor-free survival time by 17%, whereas this combinatorial drug regimen did not have a significant effect on other tumor types. In addition, no detrimental effects on hematopoiesis from the drug treatment were observed during a 12-month safety monitoring. CONCLUSIONS: The data presented here suggest that a combination of atorvastatin and celecoxib may be a good candidate for chemoprevention in Fanconi anemia.

[66] *Xiang Q, Chen SQ, Ma LY et al.* **Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis**. The pharmacogenomics journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30250148
ABSTRACT

Numerous studies have illustrated the relationship between SLCO1B1 T521C polymorphism and statin-induced myopathy risk; however, this association is not consistent. Three electronic databases (PubMed, EMBASE, and the Cochrane Library) were searched from inception to October 2017 to identify potential studies. The summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated from different genetic models by using a random-effects model. Fourteen studies comprising 3265 myopathy patients and 7743 controls were included. The summary ORs suggested that 521CC (OR: 2.31; 95% CI: 1.15-4.63; P = 0.019), 521TC (OR: 1.34; 95% CI: 1.02-1.76; P = 0.034), and 521CC + TC (OR: 1.82; 95% CI: 1.32-2.51; P < 0.001) were associated with a greater risk of statin-induced myopathy than 521TT. The higher incidence of statin-induced myopathy was found to be significantly correlated with the C allele compared with the T allele (OR: 1.89; 95% CI: 1.36-2.62; P < 0.001). In addition, we observed that 521CC + TC was associated with an increased risk of myopathy in individuals who received simvastatin (OR: 2.35; 95% CI: 1.08-5.12; P = 0.032) or rosuvastatin (OR: 1.69; 95% CI: 1.07-2.67; P = 0.024) when compared with 521TT. The 521C allele was associated with a greater risk of cerivastatin-induced myopathy than the T allele (OR: 1.95; 95% CI: 1.47-2.57; P < 0.001). The findings of this study indicated that SLCO1B1 T521C was associated with a significantly higher risk of statin-induced myopathy, especially for simvastatin, rosuvastatin, and cerivastatin. Future studies should be conducted in subjects receiving specific types of drugs, and any potential adverse events need to be explored.

[67] *Gendy MNS, Di Ciano P, Kowalczyk WJ et al.* **Testing the PPAR hypothesis of tobacco use disorder in humans: A randomized trial of the impact of gemfibrozil (a partial PPARalpha agonist) in smokers**. PloS one 2018; 13:e0201512.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30260990

ABSTRACT
Previous pre-clinical studies demonstrated a promising role of alpha-type peroxisome proliferator-activated receptors (PPARalpha) agonists in decreasing nicotine self-administration and nicotine-seeking behavior in animals. Our goal was to investigate the potential of gemfibrozil, a PPARalpha agonist, on reducing tobacco smoking in humans. METHODS: This was a double-blind, placebo-controlled, crossover study evaluating the effects of gemfibrozil (1200 mg/day) on smoking in 27 treatment-seeking smokers. The study had two 2-week phases separated by a washout period of at least 1 week. In each phase and after 1 week on medication, participants underwent a lab session where cue reactivity and forced choice paradigms were conducted. Physiological responses and self-reported craving were monitored during the presentation of smoking and neutral cues. In addition, two types of cigarettes were used in the forced choice paradigms: the Nicotinized cigarettes (Nic) and the Denicotinized cigarettes (Denic). The goal of the forced choice was to calculate the percentage of choice of Nic cigarettes while taking gemfibrozil or placebo. The number of quit days was calculated during the two quit attempts weeks (one while taking gemfibrozil and one while taking placebo) of the study. RESULTS: There were no significant differences between gemfibrozil and placebo groups in the percentage of choice of Nic cigarettes, the cue-reactivity (both physiological and subjective measures), or in the number of days of abstinence. CONCLUSIONS: Although preclinical studies with PPAR alpha agonists showed promising results, this preliminary study did not demonstrate positive effect of gemfibrozil on tobacco use and cessation indices.

[68] *Grosjean F, Yubero-Serrano EM, Zheng F et al.* **Pharmacologic control of oxidative stress and inflammation determines whether diabetic glomerulosclerosis progresses or decreases: A pilot study in sclerosis-prone mice**. PloS one 2018; 13:e0204366.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30252878

ABSTRACT
Diabetic kidney disease (DKD) is characterized by progressive glomerulosclerosis (GS). ROP mice have a sclerosis-prone phenotype. However, they develop severe, rapidly progressive GS when rendered diabetic. Since GS also develops in aged C57Bl6 mice, and can be reversed using bone marrow from young mice which have lower oxidative stress and inflammation (OS/Infl), we postulated that this might also apply to DKD. Therefore, this pilot study asked whether reducing OS/Infl in young adult sclerosis-prone (ROP) diabetic mice leads to resolution of existing GS in early DKD using safe, FDA-approved drugs.After 4 weeks of stable streptozotocin-induced hyperglycemia 8-12 week-old female mice were randomized and treated for 22 weeks as follows: 1) enalapril (EN) (n = 8); 2) pyridoxamine (PYR)+EN (n = 8); 3) pentosan polysulfate (PPS)+EN (n = 7) and 4) PPS+PYR+EN (n = 7). Controls were untreated (non-DB, n = 7) and hyperglycemic (DB, n = 8) littermates. PPS+PYR+EN reduced albuminuria and reversed GS in DB. Treatment effects: 1) Anti-OS/Infl defenses: a) PPS+PYR+EN increased the levels of SIRT1, Nrf2, estrogen receptor alpha (ERalpha) and advanced glycation endproduct-receptor1 (AGER1) levels; and b) PYR+EN increased ERalpha and AGER1 levels. 2) Pro-OS/Infl factors: a) PPS+PYR+EN reduced sTNFR1, b) all except EN reduced MCP1, c) RAGE was reduced by all treatments. In summary, PYR+PPS+EN modulated GS in sclerosis-prone hyperglycemic mice. PYR+PPS+EN also decreased albuminuria, OS/Infl and the sclerosis-prone phenotype. Thus,

reducing OS/Infl may reverse GS in early diabetes in patients, and albuminuria may allow early detection of the sclerosis-prone phenotype.

[69] *Bilen B, Gokbulut B, Kafa U et al.* **Scanning Acoustic Microscopy and Time-Resolved Fluorescence Spectroscopy for Characterization of Atherosclerotic Plaques**. Scientific reports 2018; 8:14378.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30258115
ABSTRACT

Atherosclerotic plaques constitute the primary cause of heart attack and stroke. However, we still lack a clear identification of the plaques. Here, we evaluate the feasibility of scanning acoustic microscopy (SAM) and time-resolved fluorescence spectroscopy (TRFS) in atherosclerotic plaque characterization. We perform dual-modality microscopic imaging of the human carotid atherosclerotic plaques. We first show that the acoustic impedance values are statistically higher in calcified regions compared with the collagen-rich areas. We then use CdTe/CdS quantum dots for imaging the atherosclerotic plaques by TRFS and show that fluorescence lifetime values of the quantum dots in collagen-rich areas are notably different from the ones in calcified areas. In summary, both modalities are successful in differentiating the calcified regions from the collagen-rich areas within the plaques indicating that these techniques are confirmatory and may be combined to characterize atherosclerotic plaques in the future.

[70] *Lee MW, Song JW, Kang WJ et al.* **Comprehensive intravascular imaging of atherosclerotic plaque in vivo using optical coherence tomography and fluorescence lifetime imaging**. Scientific reports 2018; 8:14561.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30267024
ABSTRACT

Comprehensive imaging of both the structural and biochemical characteristics of atherosclerotic plaque is essential for the diagnosis and study of coronary artery disease because both a plaque's morphology and its biochemical composition affect the level of risk it poses. Optical coherence tomography (OCT) and fluorescence lifetime imaging (FLIm) are promising optical imaging methods for characterizing coronary artery plaques morphologically and biochemically, respectively. In this study, we present a hybrid intravascular imaging device, including a custom-built OCT/FLIm system, a hybrid optical rotary joint, and an imaging catheter, to visualize the structure and biochemical composition of the plaque in an atherosclerotic rabbit artery in vivo. Especially, the autofluorescence lifetime of the endogenous tissue molecules can be used to characterize the biochemical composition; thus no exogenous contrast agent is required. Also, the physical properties of the imaging catheter and the imaging procedures are similar to those already used clinically, facilitating rapid translation into clinical use. This new intravascular imaging catheter can open up new opportunities for clinicians and researchers to investigate and diagnose coronary artery disease by simultaneously providing tissue microstructure and biochemical composition data in vivo without the use of exogenous contrast agent.

[71] *Zhang XF, Yang Y, Yang XY, Tong Q.* **MiR-188-3p upregulation results in the inhibition of macrophage proinflammatory activities and atherosclerosis in ApoE-deficient mice**.
<u>Thrombosis research </u>2018; 171:55-61.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30253270
ABSTRACT

BACKGROUND: Atherosclerosis occurs as a result of a chronic inflammatory response in the arterial wall associated with an increased uptake of low-density lipoprotein by macrophages and the subsequent transformation of this lipoprotein into foam cells. It has been found that miR-188-3p can suppress autophagy and myocardial infarction. Therefore, we conducted the present study with determining the suppressive role played by miR-188-3p in atherosclerosis. METHODS: The atherosclerosis model was established using ApoE knockout mice. The healthy C57BL/6J wide-type mice were used as control, while miR-188-3p mimics or inhibitors were applied for the elevation or the depletion of the miR-188-3p expression in mice. The macrophage content was observed in atherosclerotic plaque. Once the miR-188-3p expression was determined, the effects of the over-expression of miR-188-3p on the lipid accumulation and macrophage inflammatory response were accessed. The plasma levels of pro-inflammatory factors and serum RANTES level, as well as OLR1, iNOS, ABCA1 and KLF2 expression were determined in order to evaluate the potential anti-inflammatory and antioxidative activities of miR-188-3p. RESULTS: ApoE knockout mice with atherosclerosis presented with increased lipid accumulation and macrophage content. MiR-188-3p was found to reduce intravascular lipid accumulation in atherosclerotic mice. In addition to the alleviation of macrophage inflammatory response, the upregulation of miR-188-3p also leads to the suppression of oxidation with reduced macrophage accumulation, plasma expression of pro-inflammatory factors and serum RANTES level, OLR1 and iNOS, while it increases ABCA1 and KLF2. CONCLUSIONS: In conclusion, the findings from our study found a new potential therapy for atherosclerosis by investigating the inhibitory effects of miR-188-3p on macrophage inflammatory response and oxidation.

[72] *Mohajeri M, Banach M, Atkin SL et al.* **MicroRNAs: Novel Molecular Targets and Response Modulators of Statin Therapy**. <u>Trends in pharmacological sciences </u>2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30249403
ABSTRACT

Cardiovascular disease (CVD) is a major cause of death globally. Addressing cardiovascular risk factors, particularly dyslipidemia, represents the most robust clinical strategy towards reducing the CVD burden. Statins inhibit 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and represent the main therapeutic approach for lowering cholesterol and reducing plaque formation/rupture. The protective effects of statins extend beyond lowering cholesterol. MicroRNAs (miRNAs or miRs), small noncoding regulatory RNAs, likely mediate the positive pleiotropic effects of statins via modulation of lipid metabolism, enhancement of endothelial function, inhibition of inflammation, improvement of plaque stability, and immune regulation. miRNAs are implicated in statin-related interindividual variations in therapeutic response, directly via HMG-CoA reductase, or indirectly through targeting cytochrome P450 3A (CYP3A) functionality and proprotein convertase subtilisin/kexin type9 (PCSK9) biology.

Literature update week 39 (2018)

[73] *Takahashi EA, Kinsman KA, Neidert NB, Young PM*. **Guiding peripheral arterial disease management with magnetic resonance imaging**. VASA. Zeitschrift fur Gefasskrankheiten 2018:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30251924
ABSTRACT

Peripheral arterial disease (PAD) management is exceptionally challenging. Despite advances in diagnostic and therapeutic technologies, long-term vessel patency and limb salvage rates are limited. Patients with PAD frequently require extensive workup with noninvasive tests and imaging to delineate their disease and help guide appropriate management. Ultrasound and computed tomography are commonly ordered in the workup of PAD. Magnetic resonance imaging (MRI), on the other hand, is less often acknowledged as a useful tool in this disease. Nevertheless, MRI is an important test that can effectively characterize atherosclerotic plaque, assess vessel patency in highly calcified disease, and measure lower extremity perfusion.

[74] *Li CH, Gao BL, Wang JW et al.* **Hemodynamic factors affecting carotid sinus atherosclerotic stenosis**. World neurosurgery 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30261386
ABSTRACT

PURPOSE: Carotid atherosclerotic plaque occurs predominantly at the outer wall of carotid sinus, and computational fluid dynamics (CFD) plays important roles in explaining plaque formation. This study was to investigate the hemodynamic factors in affecting carotid atherosclerotic stenosis. MATERIALS AND METHODS: Sixteen patients with normal carotid artery and 16 patients with symptomatic stenotic carotid sinus had three-dimensional angiographic imaging evaluation and were studied with CFD to simulate the complete three-dimensional blood flow and hemodynamic parameter distribution in the carotid bifurcations. The hemodynamic parameters including wall shear stress (WSS), dynamic and total pressure, gradient of total pressure, strain rate, velocity, and velocity angle were investigated. RESULTS: The atherosclerosis-prone outer lateral walls of the carotid sinus and the external carotid artery at its start had significantly ($P<0.05$) low dynamic pressure, WSS, strain rate and gradient of total pressure but high static pressure. The blood flow near these walls with flow separation had significantly ($P<0.05$) decreased velocity and dynamic pressures but high velocity angle. The carotid divider had significantly ($P<0.05$) elevated dynamic and total pressure, WSS, strain rate and gradient of total pressure but reduced static pressure. Further stenosis took place at the downstream area of stenosis with significantly ($P<0.05$) decreased dynamic pressure, WSS, strain rate, and gradient of total pressure similar to the wall at the sinus and the start of the external carotid artery. CONCLUSION: Significantly decreased vascular wall shear stress, dynamic pressure, strain rate and gradient of total pressure are the key to atherosclerotic plaque formation at the carotid sinus.