Literature update week 08 (2018)

[1] *De Smedt D, De Sutter J, De Pauw M et al.* **Lifestyle behaviour and risk factor control in coronary patients: Belgian results from the cross-sectional EUROASPIRE surveys**. Acta Cardiol 2018:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29458303
ABSTRACT
OBJECTIVE: The aim of this study was to assess lifestyle behaviour as well as risk factor management across Belgian coronary patients who participated in the cross-sectional European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) surveys. METHODS: Analyses are based on a series of coronary patients by combining data from the Belgian participants in the EUROASPIRE III (328 patients; in 2006-2007) and EUROASPIRE IV (343 patients; in 2012-2013) surveys. Four hospitals located in the Ghent area participated in the surveys. Patients included in the analyses were >/=18 years old and had been hospitalised for a coronary event. Information on cardiovascular risk factors, lifestyle behaviour and medical treatment were obtained. RESULTS: Overall, the proportion of smokers was 11% with 40% persistent smokers. Adequate physical activity levels were reported by 17%, 28% of patients were obese, 47% was central obese and known diabetes was prevalent in 21% of patients. Hypertension was observed in 46% of patients and 20% had a total cholesterol >/=5 mmol/L. About 80% had participated in a cardiac rehabilitation programme and the majority of patients were treated with blood pressure (92%) or lipid-lowering drugs (92%). Anxiety and depressive symptoms were reported by 30% and 24%, respectively. Differences between EUROASPIRE III and IV were limited. CONCLUSIONS: Compared to the overall EUROASPIRE results in Europe, Belgian CHD patients seem to do slightly better. However, tackling obesity, physical inactivity, hypertension and psychosocial distress remains an important challenge in the management of coronary patients.

[2] *McCullough PA, Ballantyne CM, Sanganalmath SK et al.* **Efficacy and Safety of Alirocumab in High-Risk Patients With Clinical Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from 5 Placebo-Controlled ODYSSEY Trials)**. The American journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29472008
ABSTRACT
Patients with previous atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH) are at high risk of future cardiovascular events. Despite maximally tolerated doses of statins, many patients still have elevated low-density lipoprotein cholesterol (LDL-C) levels. We evaluated the efficacy and safety of alirocumab in patients with ASCVD and/or HeFH on a maximally tolerated dose of statin (rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg, or simvastatin 80 mg, or lower doses with an investigator-approved reason) +/- other lipid-lowering therapies from 5 placebo-controlled phase 3 trials (52 to 78 weeks). Patients with (n = 2,449) and without (n = 1,050) ASCVD were pooled from the FH I, FH II, HIGH FH, LONG TERM, and COMBO I trials. Patients with HeFH with (n = 575) and without ASCVD (n = 682) were pooled from all trials except COMBO I. High-intensity statins were utilized in 55.7% to 59.0% and in 72.4% to 87.6% of the ASCVD and the HeFH groups, respectively. Efficacy end points included LDL-C percent change from baseline to week 24 stratified by alirocumab dose. Mean baseline demographics and lipid levels were comparable in alirocumab-

and placebo-treated patients. LDL-C reductions from baseline at week 24 ranged from 46.6% to 51.3% for alirocumab 75/150 mg and from 54.1% to 61.9% for alirocumab 150 mg in ASCVD and HeFH groups and were sustained for up to 78 weeks. LDL-C reductions with alirocumab were independent of ASCVD and/or HeFH status (interaction p value >0.05). Concordant results were observed for other lipids analyzed. The overall safety in the subgroups analyzed was similar in both treatment arms. Injection-site reactions were observed more frequently with alirocumab versus placebo.

[3] *Taylor PC, Kremer JM, Emery P et al.* **Lipid profile and effect of statin treatment in pooled phase II and phase III baricitinib studies**. Annals of the rheumatic diseases 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29463520
ABSTRACT
OBJECTIVES: Lipid profiles are altered by active disease in patients with rheumatoid arthritis (RA) and may be further modified by treatment with Janus kinase inhibitors and other disease-modifying antirheumatic drugs. METHODS: Lipid data were analysed from phase II and III studies of 4 mg (n=997) and 2 mg (n=479) oral baricitinib administered once daily in patients with moderate-to-severe active RA. Lipoprotein particle size and number and GlycA were evaluated with nuclear magnetic resonance in one phase III study. The effect of statin therapy on lipid levels was evaluated in patients on statins at baseline and in patients who initiated statins during the study. RESULTS: Treatment with baricitinib was associated with increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides, but no significant change in LDL-C:HDL-C ratio. Lipid levels plateaued after 12 weeks of treatment. Baricitinib treatment increased large LDL and decreased small, dense LDL particle numbers and GlycA. Lipid changes from baseline were not significantly different between baseline statin users and non-users. In patients who initiated statin therapy during the study, LDL-C, triglycerides (baricitinib 4 mg only) and apolipoprotein B decreased to pre-baricitinib levels; HDL-C and apolipoprotein A-I levels remained elevated. CONCLUSIONS: Baricitinib was associated with increased LDL-C, HDL-C and triglyceride levels, but did not alter the LDL-C:HDL-C ratio. Evaluation of cardiovascular event rates during long-term treatment is warranted to further characterise these findings and their possible clinical implications. TRIAL REGISTRATION NUMBER: NCT00902486, NCT01469013, NCT01185353, NCT01721044, NCT01721057, NCT01711359, NCT01710358, NCT01885078.

[4] *de Paula TP, Santos PC, Duque do Nascimento Arifa R et al.* **Treatment with atorvastatin provides additional benefits to imipenem in a model of Gram-negative pneumonia induced by Klebsiella pneumoniae in mice**. Antimicrobial agents and chemotherapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29463546
ABSTRACT
The clinical pathogen Klebsiella pneumoniae is a relevant cause of nosocomial infections and resistance to current treatment with carbapenem antibiotics is becoming a significant problem. Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) used for controlling plasma cholesterol levels. There is clinical evidence showing other effects of statins, including decrease of lung inflammation. In the current study, we show that pretreatment with atorvastatin markedly attenuated lung injury, which was correlated with a reduction in the

cellular influx into the alveolar space and lungs and down-modulation of the production of pro-inflammatory mediators in the initial phase of infection in C57BL/6 mice with K. pneumoniae However, atorvastatin did not alter the number of bacteria in the lungs and blood of infected mice, despite decreasing local inflammatory response. Interestingly, mice that received combined treatment with atorvastatin and imipenem displayed better survival rate than mice treated with vehicle, atorvastatin or imipenem alone. These findings suggest that atorvastatin could be an adjuvant in host-directed therapies for multidrug-resistant K. pneumoniae, based on its powerful pleiotropic immunomodulatory effects. Together with antimicrobial approaches, combination therapy with anti-inflammatory compounds could improve the efficiency of therapy during acute lung infections.

[5] *Koh YK, Kim KH, Choi MS et al.* **Simvastatin reduces adrenal catecholamine secretion evoked by stimulation of cholinergic nicotinic and angiotensinergic AT1 receptors**. Archives of pharmacal research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29460135
ABSTRACT
We investigated the influence of simvastatin, a statin, on the secretion of catecholamines (CA) in rat adrenal glands, and clarified its action mechanism. Simvastatin suppressed acetylcholine (ACh)-evoked CA release in a dose- and time-dependent fashion. In the presence of simvastatin, CA secretion evoked by 1.1-dimethyl-4-phenyl piperazinium iodide (DMPP), angiotensin II, high K(+), veratridine, and Bay-K-8644 was time-dependently inhibited. However, in the simultaneous presence of simvastatin and Nomega-nitro-L-arginine methyl ester hydrochloride, CA secretion evoked by angiotensin II and DMPP recovered to control levels. Adrenal NO release was increased by simvastatin-treatment. Simvastatin-inhibited CA secretion was not affected by treatment with mevalonate. Pravastatin did not influence ACh-evoked CA secretion, while atorvastatin reduced it. In the simultaneous presence of simvastatin and fimasartan, ACh-induced CA release was markedly reduced compared to that of fimasartan-treatment alone. We present the first evidence that simvastatin reduces adrenal CA secretion induced by stimulation of nicotinic and AT1-receptors. Simvastatin-induced inhibition seems to involve reducing the influx of both Ca(2+) and Na(+) into adrenochromaffin cells, partly via the elevation of NO production by NO synthase activation, without inhibition of 3-hydroxy-methylglutaryl coenzyme A reductase. Co-administration of simvastatin and fimasartan may be clinically helpful for the treatment of cardiovascular diseases.

[6] *El-Tantawy WH, Temraz A*. **Natural products for controlling hyperlipidemia: review**. Archives of physiology and biochemistry 2018:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29457523
ABSTRACT
Hyperlipidemia is an abnormality of lipid metabolism, characterized by an elevation of total cholesterol, triglyceride, and low density lipoprotein-cholesterol, and/or a decreasing of high density lipoprotein cholesterol in circulating levels. Hyperlipidemia has been ranked as one of the greatest risk factors contributing to prevalence and severity of coronary heart diseases. Hyperlipidemia-associated lipid disorders are considered the cause of atherosclerotic cardiovascular disease. There has been a growing interest in natural products and their role in

the maintenance and improvement of health and wellness. The cholesterol-lowering effect of dietary plants has been well studied and various natural products were shown to be helpful in lowering plasma cholesterol levels and encouraging safety profile. The main focus of this review is to describe what we know to date of natural products, along with their lipid-lowering mechanisms, which are either through inhibition of cholesterol absorption, inhibition of cholesterol synthesis or antioxidant mechanisms.

[7] *Santos RD*. **Expression of LDLRs (Low-Density Lipoprotein Receptors), Dyslipidemia Severity, and Response to PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) Inhibition in Homozygous Familial Hypercholesterolemia: Connecting the Dots**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:481-483.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29467219
ABSTRACT

[8] *Spacek M, Zemanek D, Hutyra M et al.* **Vulnerable atherosclerotic plaque - review of current concepts and advanced imaging**. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29467545
ABSTRACT
Atherosclerosis is the most common cause of both carotid and coronary steno-occlusive disease. Rupture of an atherosclerotic plaque may lead to the formation of an overlying thrombosis resulting in complete arterial occlusion or downstream embolism. Clinically, this may manifest as a stroke or acute myocardial infarction, the overall leading causes of mortality and disability in developed countries. In this article, we summarize current concepts of the development of vulnerable plaque and provide an overview of commonly used imaging methods that may suggest/indicate atherosclerotic plaque vulnerability.

[9] *Stahel P, Xiao C, Hegele RA, Lewis GF*. **The Atherogenic Dyslipidemia Complex and Novel Approaches to Cardiovascular Disease Prevention in Diabetes**. The Canadian journal of cardiology 2017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29459241
ABSTRACT
Despite the effectiveness of low-density lipoprotein (LDL)-lowering strategies for the treatment of diabetic dyslipidemia, significant residual risk of atherosclerotic cardiovascular disease remains. Residual risk might in part be explained by lipid abnormalities that go beyond LDL cholesterol elevation, collectively termed the "atherogenic dyslipidemia complex (ADC)," consisting of hypertriglyceridemia, elevated small dense LDL particles, reduced high-density lipoprotein cholesterol, and high-density lipoprotein particle numbers, increased remnant lipoproteins, and postprandial hyperlipidemia. In this review, we briefly discuss the pathophysiology of the typical dyslipidemia that occurs in insulin-resistant states including obesity, the metabolic syndrome, and type 2 diabetes. Lipid-modifying strategies including lifestyle modification, ezetimibe, statins, fibrates, niacin, and cholesteryl ester transfer protein inhibitors in treating ADC are discussed. With the advent of novel therapies involving antisense oligonucleotides and monoclonal antibodies, new targets can be specifically downregulated to

potentially promote lipoprotein clearance or suppress production. We review novel approaches currently undergoing clinical testing and we speculate on their suitability for use in treating ADC for the prevention of atherosclerotic cardiovascular disease. In addition, future targets that might be considered for therapeutic development are discussed.

[10] *Ackers I, Szymanski C, Duckett KJ et al.* **Blocking Wnt5a signaling decreases CD36 expression and foam cell formation in atherosclerosis**. Cardiovasc Pathol 2018; 34:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29474941
ABSTRACT
BACKGROUND AND AIMS: Wnt5a is a highly studied member of the Wnt family and recently has been implicated in the pathogenesis of atherosclerosis, but its precise role is unknown. Foam cell development is a critical process to atherosclerotic plaque formation. In the present study, we investigated the role of noncanonical Wnt5a signaling in the development of foam cells. METHODS: Human carotid atherosclerotic tissue and THP-1-derived macrophages were used to investigate the contribution of Wnt5a signaling in the formation of foam cells. Immunohistochemistry was used to evaluate protein expression of scavenger receptors and noncanonical Wnt5a receptors [frizzled 5 (Fz5) and receptor tyrosine kinase-like orphan receptor 2 (Ror2)] in human atherosclerotic macrophages/foam cells. Changes in protein expression in response to Wnt5a stimulation/inhibition were determined by Western blot, and lipid accumulation was evaluated by fluorescent lipid droplet staining. RESULTS: Wnt5a ($P<.05$), Fz5 ($P<.01$), and Ror2 ($P<.01$) were significantly expressed in advanced atherosclerotic lesions compared to less advanced lesions (N=10). Wnt5a, Fz5, and Ror2 were expressed in macrophages/foam cells within the plaque. In vitro studies revealed that Wnt5a significantly increased the expression of the lipid uptake receptor CD36 ($P<.05$) but not the lipid efflux receptor ATP-binding cassette transporter ($P>.05$). rWnt5a also significantly increased lipid accumulation in THP-1 macrophages ($P<.05$). Furthermore, inhibition of Wnt5a signaling with Box5 prevented lipid accumulation ($P<.01$) and prevented CD36 up-regulation ($P<.01$). CONCLUSIONS: These results suggest a direct role for Wnt5a signaling in the pathogenesis of atherosclerosis, specifically the accumulation of lipid in macrophages and the formation of foam cells.

[11] *Quesada I, Cejas J, Garcia R et al.* **Vascular dysfunction elicited by a crosstalk between periaortic adipose tissue and the vascular wall is reversed by pioglitazone**. Cardiovascular therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29464937
ABSTRACT
AIM: Perivascular adipose tissue (PVAT) is in intimate contact with the vessel wall and extravascular PVAT-derived inflammatory mediators may adversely influence atherosclerotic plaque formation and stability through outside-to-inside signalling. We sought to investigate the role of PVAT on the atheroma development in an experimental animal model of Metabolic Syndrome (MS) associated with oxidative stress and low-grade inflammatory state. We also studied the effect of Pioglitazone an insulin sensitizer, on the aortic wall and its surrounding PVAT, considering a bi-directional communication between both layers. METHODS: Apolipoprotein E-deficient mice (ApoE(-/-)) were fed with standard diet (CD, control diet) or

fructose overload (10% w/v) (FD, fructose diet) for 8 weeks and treated with or without Pioglitazone the latest 4 weeks. RESULTS: Biochemical variables show that glycaemia and lipid peroxidation determined by thiobarbituric acid reactive species (TBARS) significantly increased in FD-fed ApoE(-/-) mice. FD significantly increased aortic PVAT expression of oxidative stress associated genes: p22(phox) , Nox1, Nox2, Nox4 and p47(phox) , and pro-inflammatory genes: Visfatin, MCP-1 and MMP-9. Pioglitazone diminished PVAT-oxidative damage elicited by fructose treatment and markedly down-regulated pro-inflammatory markers. Even Pioglitazone did not prevent the development of the aortic atheroma plaques stimulated by FD, significantly diminished VCAM-1 expression, MMP-9 expression and activity in aortic media wall and significantly reduced the accumulation of lipids and macrophages in atheroma plaques. CONCLUSION: Our results support the fact that PVAT contributes to the development and progression of cardiovascular disease by underlying mechanisms elicited by "outside-in" signalling. Treatment with Pioglitazone may offer a new effect on the whole vessel wall, promoting the stability of advanced atherosclerotic plaques. This article is protected by copyright. All rights reserved.

[12] *Liang W, Wang Q, Ma H et al.* **Knockout of Low Molecular Weight FGF2 Attenuates Atherosclerosis by Reducing Macrophage Infiltration and Oxidative Stress in Mice**. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2018; 45:1434-1443.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29466783
ABSTRACT
BACKGROUND/AIMS: Fibroblast growth factor 2 (FGF2) plays a predominant role during angiogenesis in the adventitia and in atherosclerotic plaque. A dilemma exists, however, as to whether angiogenic stimulation by FGF2 for the prevention and treatment of atherogenesis is feasible. The aim of this study is to investigate the effect of the 18-kDa FGF-2 isoform on atherosclerosis progression in high-fat diet-fed apolipoprotein E knockout (ApoE-/-) mice. METHODS: We established a model of atherosclerosis using ApoE and 18-kDa FGF-2 gene double knockout mice. They were randomly divided into three groups depending on the duration of diet: 8 weeks, 12 weeks and 16 weeks. Then, we studied the morphology and inflammatory factor staining in the atherosclerosis plaque of these mice. RESULTS: Knockout of the 18-kDa FGF-2 isoform did not change the metabolic characteristics of the mice. Compared to the control group, knockout of the 18-kDa FGF-2 isoform significantly attenuated atherogenesis, reduced aortic plaques, reduced macrophage infiltration and suppressed oxidative stress in mice fed with a high fat diet at all-time points. CONCLUSIONS: 18-kDa FGF-2 aggravated the inflammatory reaction of atherosclerosis.

[13] *Hashiguchi M, Maruyama J, Shimizu M et al.* **Risk Factor for Diabetes Mellitus and High Blood Glucose With HMG-CoA Reductase Inhibitors Using a Postmarketing Surveillance Database in Japan**. Clinical pharmacology in drug development 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29462515
ABSTRACT
To investigate whether 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) use is associated with an increased risk of diabetes mellitus and hyperglycemia, we performed a

nested case-control study using a postmarketing surveillance database in Japan. The database cohort included 26,849 cases of statin use and 5308 cases of other lipid-lowering drug use in patients with hyperlipidemia. Participants received at least 1 type of statin, had a clear medication history of statin use, and had no complications of diabetes mellitus. Cases were defined as onset of diabetes mellitus or hyperglycemia during statin intake. For each case, 20 controls were randomly selected and matched by time point. The factors associated with an increased risk of diabetes mellitus and hyperglycemia during statin intake examined included sex, age, body mass index, statin use duration, complications, concomitant medication, and clinical laboratory tests. Statin-associated diabetes mellitus or hyperglycemia was identified based on abnormal elevation of blood glucose concentrations beyond the reference range. A total of 19,868 patients met the inclusion criteria, of whom 24 were patients in the case group. Two complicating factors, fatty liver (adjusted odds ratio 16.10) and hyperuricemia (adjusted odds ratio 28.96), were extracted for onset of diabetes mellitus or hyperglycemia. Nonalcoholic fatty liver was associated with diabetes mellitus, obesity, and insulin resistance, and hyperuricemia was associated with lifestyle. This study suggested that the onset of diabetes mellitus or hyperglycemia might be increased with statin use in patients with complications of fatty liver and hyperuricemia.

[14] *Plutzky J, Liao KP*. **Lipids in RA: Is Less Not Necessarily More?** Curr Rheumatol Rep 2018; 20:8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29464513
ABSTRACT
PURPOSE OF REVIEW: In rheumatoid arthritis (RA), lipid levels are dynamic and can fluctuate along with changes in inflammation. A reduction in inflammation, most commonly as a result of disease-modifying anti-rheumatic drug (DMARD) therapy, is associated with increases in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). In this review, we discuss new evidence shedding light on the potential mechanism underlying changes in lipid levels observed with changes in inflammation. RECENT FINDINGS: Measured lipid levels in the blood are a result of a balance between synthesis and catabolism or absorption. Recent human studies in active RA show that the catabolic rates of lipids are higher than expected compared to expected rates in the general population. DMARD therapy appears to allow a return to baseline lower catabolic rates, resulting in an apparent increase in lipids. Increases in lipids observed with control of inflammation and RA treatment suggest a return to homeostasis. Studies are underway to understand the overall impact on cardiovascular risk in RA when lipid levels increase as a result of controlling inflammation.

[15] *Gu A, Kamat S, Argulian E*. **Trends and Disparities in Statin Use and Low-Density Lipoprotein Cholesterol Levels among US Patients with Diabetes, 1999-2014**. Diabetes Res Clin Pract 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29476887
ABSTRACT
AIMS: The 2013 American College of Cardiology/American Heart Association Guideline defined patients with diabetes aged 40-75 years as a major statin benefit group. We explored the temporal trends and disparities in statin utilization and LDL-C levels among patients with

diabetes aged 40-75 years. METHODS: A total of 4860 patients from the National Health and Nutrition Examination Survey 1999 to 2014 were included in this study. Differences in statin use and LDL-C levels were explored by patient characteristics. RESULTS: From 1999-2002 to 2011-2014, the prevalence of statin use increased from 26.2% to 49.5% (Ptrend < 0.001). This was accompanied by a continuous decrease in the mean LDL-C level (from 115.8 mg/dL to 103.3 mg/dL, Ptrend < 0.001). The use of guideline-defined high-potency statin medications (atorvastatin and rosuvastatin) remained largely unchanged (from 14.0% to 17.9%, Ptrend =0.55). Statin utilization increased with age. Women and blacks were 10% and 16% less likely to receive statin treatment compared with men and whites, respectively. In comparison with other statin treatment, use of atorvastatin or rosuvastatin was associated with average LDL-C reduction of 8.0 mg/dL. LDL-C levels were significantly higher among women and black patients. After adjustment for potential confounders, age and Hispanic-white differences in statin use and LDL-C levels were substantially attenuated. CONCLUSIONS: Despite a steady increase in statin use during the 16-year study period, statin therapy remains underutilized in certain subgroups of patients. Confounding factors related to healthcare utilization account for some of the disparities in statin use and LDL-C levels.

[16] *Tirona RG, Kassam Z, Strapp R et al.* **Apixaban and Rosuvastatin Pharmacokinetics in Nonalcoholic Fatty Liver Disease**. Drug metabolism and disposition: the biological fate of chemicals 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29472495
ABSTRACT
There is little known about the impact of nonalcoholic fatty liver disease (NAFLD) on drug metabolism and transport. We examined the pharmacokinetics of oral apixaban (2.5 mg) and rosuvastatin (5 mg) when administered simultaneously in subjects with magnetic resonance imaging-confirmed NAFLD (N=22) and healthy controls (N=12). The areas under the plasma concentration-time curve (AUC0-12) for apixaban were not different between control and NAFLD subjects (671 and 545 ng/mLxhr, respectively; P=0.15). In multivariable linear regression analyses, only participant weight but not NAFLD, age or SLCO1B1/ABCG2/CYP3A5 genotypes, was associated with apixaban and rosuvastatin AUC0-12 (P<0.001 and P=0.06). Similarly, the AUC0-12 for rosuvastatin did not differ between control and NAFLD groups (25.4 and 20.1 ng/mLxhr, respectively; P=0.28). Furthermore, hepatic fibrosis in NAFLD subjects was not associated with differences in apixaban or rosuvastatin pharmacokinetics. Decreased systemic exposures for both apixaban and rosuvastatin were associated with increased body weight (P<0.001 and P<0.05, respectively). NAFLD does not appear to affect the pharmacokinetics of apixaban or rosuvastatin.

[17] *Schwinger RHG*. **[Cardiovascular Medication in Elderly Patients]**. Deutsche medizinische Wochenschrift (1946) 2018; 143:236-243.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29471572
ABSTRACT
Elderly people show increased probability to develop atherosclerotic diseases; in consequence heart failure - most often following coronary heart disease - as well as atrial fibrillation is more common. Following guidelines may lead to polypharmacy, i. e. use of more than 5 drugs daily.

Thus, drug interactions as well as side effects become more likely; especially in elderly patients reduced kidney function has to be taken into account. Only drugs which have shown to prolong life or to reduce symptoms in controlled clinical trials should be used. There is little evidence to use low dose aspirin or lipid lowering agents in primary prevention especially in elderly. ACE inhibitors, beta blocker and MRA are effective to improve symptoms and outcome in HFrEF but not in HFmEF or HFpEF. This also holds true for the elderly. Withdrawal of long term diuretic treatment in the elderly patients may lead to symptoms of heart failure or increase in blood pressure to hypertensive values often. In coronary heart disease ss blocker may be used to control symptoms as well as to reduce the need for coronary intervention following 1 year after myocardial infarction. Because the risk of stroke increases with age more than the risk of bleeding, the absolute benefit of oral anticoagulation in atrial fibrillation patients is highest in the elderly. NOAK appear to be safer and at least as efficacious as warfarin.

[18] *Kojima-Ishii K, Toda N, Okubo K et al.* **Metabolic and immunological assessment of small-for-gestational-age children during one-year treatment with growth hormone: the clinical impact of apolipoproteins**. Endocrine journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29459555
ABSTRACT
Children born small for gestational age (SGA) are at a higher risk for metabolic disorders later in life. In this study, we aimed to characterize young SGA children without catch-up growth and evaluate the effects of GH treatment on endocrinological, metabolic, and immunological parameters. Study design is a one-year single hospital-based study included prospective observation of SGA patients during 12 months of GH treatment. Clinical and laboratory profiles of SGA children at baseline were compared with controls born appropriate size for age. Twenty-six SGA children (median age, 3.4 years) and 26 control children (median age, 3.8 years) were enrolled. Anthropometric, hematologic, biochemical, immunological, and endocrinological parameters were assessed at baseline and 1, 3, 6, 9, and 12 months after the start of GH treatment. As a result, median height SD score (SDS) of SGA children increased by +0.42 with 12-month GH treatment. Body mass index SDS was lower in SGA children than in controls. Serum apolipoprotein A1 increased, whereas apolipoprotein B decreased during GH treatment. Serum leptin and resistin levels, which were lower in SGA children than in controls at baseline, did not change remarkably with GH treatment. Monocyte counts, which were lower in SGA patients at baseline, increased after GH treatment. Neutrophil counts significantly increased after GH treatment. Natural killer cell ratios, which were higher in SGA patients, decreased after GH treatment. In conclusion, there was no evidence suggesting metabolic abnormalities in SGA children. Serum apolipoprotein changes might predict the beneficial role of GH treatment in lowering cardiometabolic risk.

[19] *Gohar A, Schnabel RB, Hughes M et al.* **Underrepresentation of sex in reporting traditional and emerging biomarkers for primary prevention of cardiovascular disease: a systematic review**. European heart journal. Quality of care & clinical outcomes 2016; 2:99-107.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29474623
ABSTRACT

Background: Primary prevention of cardiovascular disease (CVD) relies on the identification of individuals at increased risk of developing cardiovascular events. Circulating biomarkers mirroring the (subclinical) disease process are valuable tools for CVD risk prediction. Evidence is accumulating that the clinical presentation and mechanisms for CVD differ between men and women. A systematic review of sex-specific data was performed on biomarker levels and their association with CVD in primary prevention in order to investigate the availability of sex-specific data and to explore for any differences in the associations between men and women. Methods and results: PubMed MEDLINE and Embase were searched on 2 February 2014 and updated on 15 January 2015. Biomarkers included represented pathophysiological pathways of lipids, inflammation, kidney function, and of the heart. Data on patient characteristics, sex-specific biomarker levels, biomarker association with future CVD events and clinical value were extracted. Only 54 studies of 360 publications provided sex-specific information. Most of the remaining 306 publications not providing sex-specific results only corrected for sex in multivariable models. The additional clinical utility of biomarkers was reported in seven publications, one of which was stratified by sex. Conclusion: Sex-specific data on biomarkers for CVD in the general population exist, but it is underreported. There is inconsistency in sex-specific differences in levels of traditional biomarkers and in their relation to CVD. To improve personalized cardiovascular diagnoses and care for men and women, reporting sex-specific data on clinical utility of biomarkers is crucial and should be encouraged in publications of sufficiently powered studies.

[20] *Law TK, Yan AT, Gupta A et al.* **Primary prevention of cardiovascular disease: global cardiovascular risk assessment and management in clinical practice**. European heart journal. Quality of care & clinical outcomes 2015; 1:31-36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29474565
ABSTRACT
Aims: For the primary prevention of cardiovascular disease, the Framingham Risk Score (FRS) is the most well-known risk prediction method. However, there are limited data regarding physicians' method of risk assessment and guideline adherence in clinical practice. Methods and results: In the PARADIGM (Primary cARe AuDIt of Global risk Management) study (March 2009-10), 105 primary care physicians across Canada prospectively collected data for 3015 patients (mean age 56 years, 59% men) without known cardiovascular disease, diabetes, or lipid-lowering medications at baseline. For each patient, the treating physician determined their cardiovascular risk, and reported the risk stratification method and subsequent treatment decisions. Kappa statistics assessed the agreement between the study-calculated FRS and the treating physician's reported risk assessment. The FRS was the most commonly reported risk assessment method, but was used in only 34.0% of patients. Regardless of the method used (even if the FRS was reportedly used), there was only fair agreement between the risk stratification as reported by the physician and the study-calculated FRS. Moreover, physicians recommended statin initiation in 92% of all patients that they identified as high risk; however, according to the study-calculated FRS, only 56% of the truly high-risk patients were recommended statin therapy. Conclusion: For the primary prevention of cardiovascular disease, these findings indicate a need to improve risk assessment and stratification, as misclassification directly contributes to suboptimal risk factor management in real-world clinical practice. Future

studies should establish the optimal risk stratification method with quality improvement strategies for its subsequent implementation. Clinical Trial Registration: http://clinicaltrials.gov/ct2/show/NCT00950703; NCT00950703.

[21] *Ren T, Yang WS, Lin Y et al.* **A novel PPARalpha/gamma agonist, propane-2-sulfonic acid octadec-9-enyl-amide, ameliorates insulin resistance and gluconeogenesis in vivo and vitro**. European journal of pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29476879
ABSTRACT
Peroxisome proliferator-activated receptor alpha/gamma (PPARalpha/gamma) agonists have emerged as important pharmacological agents for improving insulin action. Propane-2-sulfonic acid octadec-9-enyl-amide (N15) is a novel PPARalpha/gamma dual agonist synthesized in our laboratory. The present study investigates the efficacy and safety of N15 on insulin resistance regulation in high fat diet (HFD)-and streptozotocin (STZ)-induced diabetic mice and in palmitic acid (PA)-induced HepG2 cells. Our results showed that N15 remarkably ameliorated insulin resistance and dyslipidemia in vivo, as well as rectified the glucose consumption and gluconeogenesis in vitro. Moreover, the glucose-lowering effect of N15 was associated with PPARgamma mediated up-regulation of hepatic glucose consumption and down-regulation of gluconeogenesis. Meanwhile, N15 exerted advantageous effects on glucose and lipid metabolism without triggering weight gain and hepatotoxicity in mice. In conclusion, our data demonstrated that by alleviating glucose and lipid abnormalities, N15 could be used as a potential prophylactic and therapeutic agent against type 2 diabetes and related metabolic disorders.

[22] *Wang JM, Ye SD, Li SM, Hu W*. **Correlations of 25(OH)D level with blood lipid, inflammatory factors and vascular endothelial function in diabetic patients**. European review for medical and pharmacological sciences 2018; 22:731-735.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29461603
ABSTRACT
OBJECTIVE: To investigate the correlation between 25-hydroxyvitamin D [25(OH)D] and the lipid profile, inflammatory cytokines, and endothelial function in diabetic patients. PATIENTS AND METHODS: A total of 77 patients with type 2 diabetes mellitus treated in our hospital from January 2015 to March 2017 and 73 healthy volunteers were selected. The 25(OH)D, lipids, inflammatory factors, and endothelial function were compared between the two groups. The levels of 25(OH)D in diabetic patients were also compared to detect the levels of serum lipids and inflammatory cytokines in different groups. According to the inflammatory factors, patients with diabetes mellitus were divided into several groups. In addition, 25(OH)D, endothelial function indicators [nitrogen oxide (NO) and von Willebrand factor (vWF)], serum lipids [triglyceride (TG) and total cholesterol (TC)], high-density lipoprotein (HDL), and inflammatory factor tumor necrosis factor-alpha (TNF-alpha) were compared among different groups. RESULTS: Compared with normal group, the 25(OH)D, NO, and HDL in the diabetic group were significantly lower than those in the normal group ($p<0.05$). Other lipids and inflammatory factors in the former were significantly higher than those in the normal group. Patients have lower HDL in those with less amount of 25(OH)D. Other blood lipid components such as TC and

TG, LDL, and inflammatory factors significantly increased gradually as the 25(OH)D grows ($p<0.05$). For patients with more inflammatory cytokines, levels of 25(OH)D, NO, vWF, and ET-1 were significantly lower than those with normal inflammatory cytokines. Correlation analysis revealed that 25(OH)D was positively correlated with HDL and NO, but negatively correlated with TG, TC, TNF-alpha, and vWF. CONCLUSIONS: In diabetic patients, the level of 25(OH)D is decreased and the inflammatory factors are increased. In patients with proper supplementation of 25(OH)D, the inflammation can be reduced and endothelial function can be improved.

[23] *Escate R, Mata P, Cepeda JM et al.* **miR-505-3p controls chemokine receptor up-regulation in macrophages: role in familial hypercholesterolemia**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018; 32:601-612.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29457550
ABSTRACT
Familial hypercholesterolemia (FH) conveys a high risk of premature atherosclerosis as a result of lifelong exposure to high LDL cholesterol levels that are not fully reduced by standard-of-care lipid-lowering treatment. Inflammatory mediators have played a role in the progression of atherosclerotic lesions. Here, we investigated whether innate immunity cells in patients with FH have a specific proinflammatory phenotype that is distinct from that of cells in normal participants. To this end, miR-505-3p-a microRNA related to chronic inflammation-and its target genes were investigated in monocyte-derived macrophages (MACs) of patients with FH (FH-MACs) and non-FH controls (co-MACs). On the basis of the profiler PCR array analysis of agomiR-505-3p-transfected MACs, we identified the chemokine receptors, CCR3, CCR4, and CXCR1, as genes that are regulated by miR-505-3p via the transcription factor, RUNX1. miR-505-3p was significantly down-regulated, whereas CCR3, CCR4, CXCR, and RUNX1 were increased in FH-MAC compared with co-MAC, with the increase being more evident in the proinflammatory M1-like FH-MAC. Chemokine receptor levels were unrelated to LDL plasma levels at entry, but correlated with age in patients with FH, not in controls. In summary, we demonstrate for first time to our knowledge that MACs from FH-MACs have an inflammatory phenotype that is characterized by the up-regulation of CCR3, CCR4, and CXCR1 under the control of miR-505-3p. These results suggest a chronic inflammatory condition in FH innate immunity cells that is not reverted by standard lipid-lowering treatment.-Escate, R., Mata, P., Cepeda, J. M., Padro, T., Badimon, L. miR-505-3p controls chemokine receptor up-regulation in macrophages: role in familial hypercholesterolemia.

[24] *Soulaidopoulos S, Nikiphorou E, Dimitroulas T, Kitas GD*. **The Role of Statins in Disease Modification and Cardiovascular Risk in Rheumatoid Arthritis**. Frontiers in medicine 2018; 5:24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29473041
ABSTRACT
Rheumatoid arthritis (RA) is an autoimmune, inflammatory disorder associated with excess cardiovascular morbidity and mortality. A complex interplay between traditional risk factors (dyslipidemia, insulin resistance, arterial hypertension, obesity, smoking) and chronic inflammation is implicated in the development of premature atherosclerosis and consequently in the higher incidence of cardiovascular events observed in RA patients. Despite the

acknowledgment of elevated cardiovascular risk among RA individuals, its management remains suboptimal. While statin administration has a crucial role in primary and secondary cardiovascular disease prevention strategies as lipid modulating factors, there are limited data concerning the precise benefit of such therapy in patients with RA. Systemic inflammation and anti-inflammatory treatments influence lipid metabolism, leading to variable states of dyslipidemia in RA. Hence, the indications for statin therapy for cardiovascular prevention may differ between RA patients and the general population and the precise role of lipid lowering treatment in RA is yet to be established. Furthermore, some evidence supports a potential beneficial impact of statins on RA disease activity, attributable to their anti-inflammatory and immunomodulatory properties. This review discusses existing data on the efficacy of statins in reducing RA-related cardiovascular risk as well as their potential beneficial effects on disease activity.

[25] *Chen H, Shen F, Sherban A et al.* **DEPTOR Suppresses Lipogenesis and Ameliorates Hepatic Steatosis and Acute-on-Chronic Liver Injury in Alcoholic Liver Disease**. Hepatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29457836

ABSTRACT

Alcoholic liver disease (ALD) is characterized by lipid accumulation and liver injury. However, how chronic alcohol consumption causes hepatic lipid accumulation remains elusive. The present study demonstrates that activation of the mechanistic target of rapamycin complex 1 (mTORC1) plays a causal role in alcoholic steatosis, inflammation and liver injury. Chronic-plus-binge ethanol feeding led to hyperactivation of mTORC1, as evidenced by increased phosphorylation of mTOR and its downstream kinase S6K1 in hepatocytes. Aberrant activation of mTORC1 was likely attributed to the defects of the DEP-domain containing mTOR-interacting protein (DEPTOR) and the NAD(+) -dependent deacetylase SIRT1 in the liver of chronic-plus-binge ethanol-fed mice and in the liver of patients with ALD. Conversely, adenoviral overexpression of hepatic DEPTOR suppressed mTORC1 signaling and ameliorated alcoholic hepatosteatosis, inflammation and acute-on-chronic liver injury. Mechanistically, the lipid-lowering effect of hepatic DEPTOR was attributable to decreased proteolytic processing, nuclear translocation, and transcriptional activity of the lipogenic transcription factor SREBP-1. DEPTOR-dependent inhibition of mTORC1 also attenuated alcohol-induced cytoplasmic accumulation of the lipogenic regulator lipin 1 and prevented alcohol-mediated inhibition of fatty acid oxidation. Pharmacological intervention with rapamycin alleviated the ability of alcohol to upregulate lipogenesis, to downregulate fatty acid oxidation, and to induce steatogenic phenotypes. Chronic-plus-binge ethanol feeding led to activation of SREBP-1 and lipin 1 through S6K1-dependent and independent mechanisms. Furthermore, hepatocyte-specific deletion of SIRT1 disrupted DEPTOR function, enhanced mTORC1 activity, and exacerbated alcoholic fatty liver, inflammation and liver injury in mice. CONCLUSION: the dysregulation of SIRT1-DEPTOR-mTORC1 signaling is a critical determinant of ALD pathology. Targeting SIRT1 and DEPTOR and selectively inhibiting mTORC1-S6K1 signaling may have therapeutic potential for treating ALD in humans. This article is protected by copyright. All rights reserved.

[26] *Chen Y, Liu L*. **Is the decrease of triglyceride level after acute myocardial infarction within a month by the effect of combination therapy of Ezetimibe and Simvastatin**. International journal of cardiology 2018; 256:21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29454404
ABSTRACT

[27] *Zhang P, Wang XH, Su XJ*. **Comment on the original paper entitled "The effect of Ezetimibe and Simvastatin Combination Therapy on percutaneous coronary intervention patients"**. International journal of cardiology 2018; 256:18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29454400
ABSTRACT

[28] *Gregg S, Li TY, Hetu MF et al.* **Relationship between carotid artery atherosclerosis and bulb geometry**. The international journal of cardiovascular imaging 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29464422
ABSTRACT
The carotid bifurcation is a common site of atherosclerotic plaque. Plaque development is thought to occur preferentially at geometrically predisposed areas such as arterial branch points. The aim of this study was to investigate the geometric and anatomical variables that contribute to the development of carotid plaque using three-dimensional (3D) ultrasound. Sixty-seven consecutive outpatients referred for elective coronary angiography underwent 3D carotid ultrasound scans for the purpose of carotid plaque quantification. Geometric quantification of the left and right carotid bulbs were performed retrospectively on this study population. Geometric values such as angle, area and length of the carotid bulb and the bifurcation were determined using QLAB software (Philips Healthcare). Plaque volume within the carotid bulb and artery branches was quantified using the stacked contour method. Pearson's correlation and linear regression analysis were used to determine the relationship between anatomical variables and plaque volume. The mean age for the total patient population was 65.9 +/- 11.5 years. Carotid bulb inflow area (BIA) ($r = 0.28$, $p = 0.001$), bulb volume (BV) ($r = 0.21$, $p = 0.01$) and bifurcation angle (BifA) ($r = 0.18$, $p = 0.04$) showed a positive linear relationship with plaque volume. In contrast, internal carotid artery angle (ICAA) ($r = - 0.18$, $p = 0.04$) and bulb flare ($r = - 0.20$, $p = 0.02$) displayed a negative linear relationship with plaque volume. When adjusting for age and sex, only the BIA remained significant (beta = 0.18, $p = 0.04$). Geometric variables were identified as potential risk factors associated with plaque volume in the carotid bulb. Further analysis of the evolution of the BIA as well as the relationship to other geometric variables could create a stronger predictive model of atherosclerosis as well as assist in preoperative planning.

[29] *Camera M, Rossetti L, Barbieri SS et al.* **PCSK9 as a Positive Modulator of Platelet Activation**. Journal of the American College of Cardiology 2018; 71:952-954.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29471945
ABSTRACT

[30] *Leite GAA, Sanabria M, Cavariani MM et al.* **Lower sperm quality and testicular and epididymal structural impairment in adult rats exposed to rosuvastatin during prepuberty**. Journal of applied toxicology : JAT 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29460396
ABSTRACT
The increase of obesity, bad eating habits and the lack of physical exercises are highly related to dyslipidemias. Rosuvastatin is a lipid-lowering drug and has been indicated to prevent cardiovascular diseases and to treat dyslipidemias due to its higher efficiency to reduce serum cholesterol concentrations. This study aimed to evaluate the reproductive adverse effects on sexual maturity due to rosuvastatin exposure in juvenile male rats during prepuberty. Three groups were randomly formed with newly weaned rats: control, whose rats received saline solution 0.9% and rosuvastatin at doses of 3 or 10 mg kg(-1) day(-1) , administered orally by gavage, from postnatal day 21 until preputial separation (average of 45 days for controls and 49 days for statin-treated animals), indicative of puberty onset. Male rats were maintained until sexual maturity and were killed on postnatal day 110. In the rosuvastatin-treated groups, the results showed diminished follicle-stimulating hormone, luteinizing hormone and testosterone concentrations, increased estradiol and prolactin concentrations, histopathologic alterations on testis and epididymis and decreased sperm quality. Moreover, statin-exposed groups showed decreased expression of androgen receptor on testis and epididymis and lower expression of aquaporin-9 on epididymal epithelium. In conclusion, administration of rosuvastatin to prepubertal male rats provoked long-term hormonal deregulation and impaired reproduction at adulthood.

[31] *Wagner JB, Abdel-Rahman S, Van Haandel L et al.* **Impact of SLCO1B1 Genotype on Pediatric Simvastatin Acid Pharmacokinetics**. Journal of clinical pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29469964
ABSTRACT
This study investigated the impact of allelic variation in SLCO1B1, a gene encoding for the liver-specific solute carrier organic anion transporter family member 1B1 protein (SLCO1B1), on simvastatin and simvastatin acid (SVA) systemic exposure in children and adolescents. Participants (8-20 years old) with at least 1 variant SLCO1B1 c.521T>C allele (521TC, n = 15; 521CC, n = 2) and 2 wild-type alleles (521TT, n = 15) completed a single oral dose pharmacokinetic study. At equivalent doses, SVA exposure was 6.3- and 2.5-fold greater in 521CC and TC genotypes relative to 521TT (Cmax , 2.1 +/- 0.2 vs 1.0 +/- 0.5 vs 0.4 +/- 0.3 ng/mL; P < .0001; and AUC, 12.1 +/- 0.3 vs 4.5 +/- 2.5 vs 1.9 +/- 1.8 ng.h/mL; P < .0001). The impact of the SLCO1B1 c.521 genotype was more pronounced in children, although considerable interindividual variability in SVA exposure was observed within genotype groups. In addition, SVA systemic exposure was negligible in 25% of pediatric participants. Further investigation of the ontogeny and genetic variation of SVA formation and SLCO1B1-mediated hepatic uptake is necessary to better understand the variability in SVA exposure in children and its clinical consequences.

Literature update week 08 (2018)

[32] *Geng X, Irvin MR, Hidalgo B et al.* **An exome-wide sequencing study of lipid response to high-fat meal and fenofibrate in Caucasians from the GOLDN cohort**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29463568
ABSTRACT
Our understanding of genetic influences on the response of lipids to specific interventions is limited. In this study, we sought to elucidate effects of rare genetic variants on lipid response to a high-fat meal challenge and fenofibrate (FFB) therapy in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) cohort using an exome-wide sequencing-based association study. Our results showed that the rare coding variants in ITGA7, SIPA1L2, and CEP72 are significantly associated with fasting low-density lipoprotein cholesterol (LDL-C) response to FFB (P=1.24E-07), triglyceride postprandial area under the increase (AUI) (P=2.31E-06), and triglyceride postprandial AUI response to FFB (P=1.88E-06) respectively. We sought to replicate the association for SIPA1L2 in the Heredity and Phenotype Intervention (HAPI) Heart Study, which included a high-fat meal challenge but not FFB treatment. The associated rare variants in GOLDN were not observed in the HAPI Heart study and thus the gene-based result was not replicated. For functional validation, we found gene transcript level of SIPA1L2 is associated with triglyceride postprandial AUI (P</=0.05) in GOLDN. Our study suggests unique genetic mechanisms contributing to the lipid response to the high-fat meal challenge and FFB therapy.

[33] *Hong SH, Woo M, Kim M, Song YO*. **Hypolipidemic and Antidiabetic Effects of Functional Rice Cookies in High-Fat Diet-Fed ICR Mice and db/db Mice**. Journal of medicinal food 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29474103
ABSTRACT
We have previously reported the lipid-lowering effects of a Korean rice cookie called dasik (RCD) in comparison with a western style cookie. In this study, Schisandra chinensis (Turcz.) Baill. (Chinese magnolia vine) fruit-supplemented RCD (SRCD) was added to a diet, and the hypolipidemic and antidiabetic effects of different diets were examined by using the ICR and db/db mouse models, respectively. ICR mice were fed the AIN-76 diet, or high-fat diet (HFD), or the RCD- or SRCD-supplemented HFD (10%, w/w) for 9 weeks (n = 7 per group). Compared with the RCD group, plasma and hepatic triglyceride and cholesterol concentrations were decreased in the SRCD group. Hepatic expressions for fatty acid and cholesterol synthesis were downregulated, whereas those for beta-oxidation and cholesterol export were upregulated (P < .05). The antidiabetic effects of SRCD were tested in db/db mice for 10 weeks (n = 7 per group). Glucose tolerance was improved in the SRCD group through the regulation of gluconeogenic enzymes and biomarkers related to the insulin signaling pathway (P < .05). In addition, SRCD increased the expression levels of antioxidative enzymes, and decreased those of inflammatory cytokines (P < .05). Moreover, oxidative stress, leptin, and insulin levels were lower in the SRCD group than in the other groups (P < .05). In conclusion, the lipid-lowering and antidiabetic effects of SRCD were greater than those of RCD with respect to the suppression of lipid synthesis, oxidative stress, and inflammation and the improvement of glucose metabolism.

[34] *Masuda Y, Yamaguchi S, Suzuki C et al.* **Generation and Characterization of a Novel Small Biologic Alternative to PCSK9 Antibodies, DS-9001a, Albumin Binding Domain-Fused Anticalin Protein**. The Journal of pharmacology and experimental therapeutics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29463608
ABSTRACT
Since it was recently reported that an antibody for proprotein convertase subtilisin/kexin type 9 (PCSK9) reduced the risk of cardiovascular events in a clinical context, PCSK9 inhibition is thought to be an attractive therapy for dyslipidemia. In the present study, we created a novel small biologic alternative to PCSK9 antibodies called DS-9001a, comprising an albumin binding domain fused to an artificial lipocalin mutein (ABD-fused Anticalin protein), which can be produced by a microbial production system. DS-9001a strongly interfered with PCSK9 binding to low-density-lipoprotein receptor (LDL-R) and PCSK9-mediated degradation of LDL-R. In cynomolgus monkeys, single administration of DS-9001a reduced the serum LDL-C level by about 62.4% for more than 21 days. Moreover, DS-9001a reduced plasma non-high-density-lipoprotein cholesterol and oxidized LDL levels, and their further reductions were observed when atorvastatin and DS-9001a were administered in combination in human CETP/ApoB double transgenic mice. Additionally, their reductions upon the combination of atorvastatin and DS-9001a were more pronounced than those upon the combination of atorvastatin and anacetrapib. Besides its favorable pharmacological profile, DS-9001a has a lower molecular weight (about 22 kDa), yielding a high stoichiometric drug concentration that might result in a smaller administration volume than that in existing antibody therapy. Since bacterial production systems are viewed as more suited to mass production at low cost, DS-9001a may provide a new therapeutic option to treat a large number of patients with dyslipidemia. In addition, considering the growing demand for antibody-like drugs, ABD-fused Anticalin proteins could represent a promising new class of small biological molecules.

[35] *Egan B*. **The glucose-lowering effects of exogenous ketones: is there therapeutic potential?** The Journal of physiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29473164
ABSTRACT
The ketone bodies acetoacetate, beta-hydroxybutyrate (betaHB) and acetone are small, lipid-derived molecules that are generated during ketogenesis, a process that is amplified during fasting, starvation, ketogenic diets, and prolonged glycogen-depleting exercise. This article is protected by copyright. All rights reserved.

[36] *Kobalava ZD, Villevalde SV, Vorobyeva MA*. **[Effects of High-Dose Statin Therapy on Cognitive Functions and Quality of Life in Very High Cardiovascular Risk Patients]**. Kardiologiia 2017; 57:34-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29466221
ABSTRACT
AIM: To investigate the effects of intensive lipid-lowering therapy on cognitive functions and quality of life in patients (pts) with very high cardiovascular risk. MATERIAL AND METHODS: In 93 pts (58 men, 63.2+/-9.5 years old with history of clinically evident cardiovascular disease and fasting low-density lipoprotein cholesterol (LDL-C) >1.8 mmol/l or non-high-density lipoprotein

cholesterol (non-HDL-C) >2.6 mmol/l the mental status and quality of life were assessed before and after 6 months of therapy with atorvastatin 80 mg/day. The Montreal Cognitive Assessment (MoCA) scale and Questionnaire SF-36 (russian version) were used to evaluate cognitive functions and quality of life. RESULTS: 59 (63%) pts had cognitive dysfunction (less than 26 scores by MoCA scale). We observed significant difference in cognitive status between pts >/=65 and.

[37] *Pogorelova OA, Tripoten MI, Guchaeva DA et al.* **[Carotid Plaque Instability in Patients With Acute Coronary Syndrome as Assessed by Ultrasound Duplex Scanning]**. Kardiologiia 2017; 57:5-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29466206
ABSTRACT
AIM: to study carotid plaques structure in patients with acute coronary syndrome by ultrasound duplex scanning. MATERIALS AND METHODS: We included in this study143 patients with acute coronary syndrome (ACS) aged 32-83 years and 28 patients with documented coronary heart disease (CHD) aged 46-83 years. Duplex scanning of carotid arteries was carried out with Philips iU22 ultrasound system and L9-3 linear array transducer. Atherosclerotic plaques in CCA, CCA bifurcation, and ICA from right and left side were investigated. Off-line analysis of B-mode images and plaque gray scale median (GSM) was performed with computer semiautomated workstation MultiVox. RESULTS: 378 plaques of ACS and 59 plaques of CHD patients were studied. We assessed traditional (heterogenous structure, hypoechogenic component, irregular plaque surface) as well as additional (positive remodeling, "layered" structure of plaque, local calcification) criteria of plaque instability. In ACS compared with CHD group there were more plaques with hypoechogenic component (43.4 and 28.8%, p=0.0459), heterogenous structure (77.8 and 64.4%, p=0.0327), irregular surface including irregularities more than 2.0 mm (22.5 and 6.8%, p=0.0048, respectively). There was significant difference in "layered" structure (55.7 and 35.8%, p=0.0011) and insignificant difference in positive remodeling (16.3 and 7.5%, p=0.06, respectively). There were no differences of GSM value (53.1 and 57.2, p=0.24) and local calcification (23.2 and 24.5%, p=0.23, respectively). CONCLUSION: In our study ultrasound duplex scanning revealed that signs of plaque instability in carotid arteries in patients with ACS were more frequent than in patients with stable CHD. The newly introduced parameter "layered" structure of atherosclerotic plaque was found to be most significant.

[38] *Pogosova NV, Oganov RG, Boytsov SA et al.* **[Efficiency of primary prevention for diseases caused by atherosclerosis in patients at high cardiovascular risk in Russia and other European countries (Part 2)]**. Kardiologiia 2017; 57:5-16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29466184
ABSTRACT
BACKGROUND: The picture of primary prevention obtained from real-life practice makes possible scheduling measures for prevention improvement. AIM: To analyze features of drug and non-drug therapy aimed at decreasing cardiovascular risk in Russian patients with a high risk (HR) of CVD compared with the study general population. MATERIALS AND METHODS: 14 European countries, including the Russian Federation, participated in this cross-sectional study. The study included patients aged 18-80 without clinical signs of atherosclerosis who have

received antihypertensive and/or lipid-lowering therapy and/or therapy for diabetes mellitus (DM) within >6 to.

[39] *Balzan S, Lubrano V*. **LOX-1 receptor: A potential link in atherosclerosis and cancer**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29462603
ABSTRACT
Altered production of reactive oxygen species (ROS), causing lipid peroxidation and DNA damage, contributes to the progression of atherosclerosis and cancer. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a lectin-like receptor for oxidized low-density lipoproteins (ox-LDL) primarily expressed in endothelial cells and vasculature-rich organs. LOX-1 receptors is a marker for atherosclerosis, and once activated by ox-LDL or other ligands, stimulates the expression of adhesion molecules, pro-inflammatory signaling pathways and proangiogenic proteins, including NF-kB and VEGF, in vascular endothelial cells and macrophages. Several different types of cancer reported LOX-1 gene upregulation, and numerous interplays exist concerning LOX-1 in atherosclerosis, metabolic diseases and cancer. One of them involves NF-kB, an oncogenic protein that regulates the transcription of several inflammatory genes response. In a model of cellular transformation, the MCF10A ER-Src, inhibition of LOX-1 gene reduces NF-kB activation and the inflammatory and hypoxia pathways, suggesting a mechanistic connection between cellular transformation and atherosclerosis. The remodeling proteins MMP-2 and MMP-9 have been found increased in angiogenesis in atherosclerotic plaque and also in human prostate cancer cells. In this review, we outlined the role of LOX-1 in atherogenesis and tumorigenesis as a potential link in these diseases, suggesting that LOX-1 inhibition could represent a promising strategy in the treatment of atherosclerosis and tumors.

[40] *Chen Z, Yu R, Xiong Y et al.* **Correction to: A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease**. Lipids in health and disease 2018; 17:33.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29475442
ABSTRACT
Following publication of the original article [1], the corresponding author reported that he had mistyped the first author's unit. The affiliation of Zhonge Chen, "Medical Center of the Graduate School, Nanchang University, China", should be changed to "Department of Gastroenterology, Second Affiliated Hospital, Nanchang University Nanchang, China". All the other authors have agreed to this change. The corrected version should be as follows.

[41] *Olszewska-Banaszczyk M, Jackowska P, Gorzelak-Pabis P et al.* **Comparison of the effects of rosuvastatin monotherapy and atorvastatin-ezetimibe combined therapy on the structure of erythrocyte membranes in patients with coronary artery disease**. Pharmacological reports : PR 2017; 70:258-262.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29475008
ABSTRACT
BACKGROUND: Abnormalities in the physical properties of the red blood cells (RBCs) membranes may underlie the defects that are strongly linked to cardiovascular diseases (CVD).

The aim of the study was to compare the effects of two therapies of equal hipolipemic efficacy on the erythrocyte membrane fluidity, concentration of membrane cholesterol, lipids peroxidation and RBCs distribution witdh in patients with CVD. METHODS: The study included 44 patients with angiographic evidence of CVD, who despite previous 6-month hypolipemic therapy, did not achieve the concentration of LDL-C <70mg/dl. They were randomly assigned to: rosuvastatin 20mg/day (R20) and atorvastatin 10mg/day combined with ezetimibe 10mg/day (A10+E10). The membrane fluidity, the concentration of thiobarbituric acid reactive substances -TBARS, concentration of membrane cholesterol were evaluated after 6 months therapy. RESULTS: An improvement in lipid parameters was observed in each of the groups studied. In R20 the treatment resulted in 33% reduction concentrations of TBARS in serum, as well as in a decrease in membrane cholesterol by 16%, fluorescence anisotropy of TMA-DPH by 17.7%, fluorescence anisotropy of DPH by 2.8%. In A10+E10 the reduction of TBARS by 20.5% in serum, membrane cholesterol by 15.8% as well as a 14.25% increase in RBC membrane fluidity in the superficial layer (TMA-DPH) and decrease fluidity in the deep layer (DPH) were observed. CONCLUSION: Rosuvastatin increases the fluidity of erythrocyte membrane and decreases the TBARS in serum to greater extent than does equal hipolipemic combined therapy atorvastatin with ezetimibe.

[42] *Mandal SR, Bharati A, Haghighi RR et al.* **Non-invasive characterization of coronary artery atherosclerotic plaque using dual energy CT: Explanation in ex-vivo samples**. Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics (AIFB) 2018; 45:52-58.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29472090

ABSTRACT

PURPOSE: In this study non-calcified plaque composition is evaluated by Dual Energy CT (DECT). Energy Dispersive X-ray Spectroscopy (EDS) has been used to study the Plaque composition. An attempt has been made to explain the DECT results with EDS analysis. METHODS: Thirty-two ex-vivo human cadaver coronary artery samples were scanned by DECT and data was evaluated to calculate their effective atomic number and electron density (Zeff & rhoe) by inversion method. Result of DECT was compared with pathology to assess their differentiating capability. The EDS study was used to explain DECT outcome. RESULTS: DECT study was able to differentiate vulnerable plaque from stable with 87% accuracy (area under the curve (AUC):0.85 [95% confidence interval {CI}:0.73-0.98}] and Kappa Coefficient (KC):0.75 with respect to pathology. EDS revealed significant compositional difference in vulnerable and stable plaque at p<.05. The weight percentage of higher atomic number elements like F, Na, Mg, S, Si, P, Cl, K and Ca was found to be slightly more in vulnerable plaques as compared to a stable plaque. EDS also revealed a significantly increased weight percentage of nitrogen in stable plaques. CONCLUSIONS: The EDS results were able to explain the outcomes of DECT study. This study conclusively explains the physics of DECT as a tool to assess the nature of non-calcified plaques as vulnerable and stable. The method proposed in this study allows for differentiation between vulnerable and stable plaque using DECT.

[43] *Susukida R, Nishi D, Kawashima Y et al.* **Generalizability of Findings from a Randomized Controlled Trial of Fish Oil Supplementation for Attenuating Posttraumatic Stress Symptoms among Rescue Workers in Japan**. Psychotherapy and psychosomatics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29462814
ABSTRACT

[44] *He S, Wu C, Xiao J et al.* **Endothelial extracellular vesicles modulate the macrophage phenotype: Potential implications in atherosclerosis**. Scand J Immunol 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29465752
ABSTRACT
OBJECTIVE: Endothelial cells (ECs) and macrophages engage in tight and specific interactions that play critical roles in cardiovascular homeostasis and the pathogenesis of atherosclerosis. Extracellular vesicles (EVs) are circular membrane fragments released from the endosomal compartment as exosomes or shed from the surfaces of the membranes of most cell types. Increasing evidence indicates that EVs play a pivotal role in cell-to-cell communication. However, the contribution of EVs, as determine by oxidized low-density lipoprotein (ox-LDL)-exposed and/or Kruppel-like factor 2 (KLF2)-transduced ECs in the interaction between vascular ECs and monocytes/ macrophages, which is a key event in atherosclerotic plaque development, has remained elusive. APPROACH AND RESULTS: The present study demonstrates the characteristic impact of EVs from ox-LDL-treated and/or KLF2-transduced ECs on the monocyte/macrophage phenotype in vitro and in vivo.Q-PCR showed that both the atherosclerosis inducer ox-LDL and atheroprotective factor KLF2 regulated inflammation-associated microRNA-155 (miR-155) expression in human umbilical vein endothelial cells (HUVECs). Moreover, co-culture, immunofluorescence and flow cytometry revealed that miR-155 was enriched in ox-LDL-induced ECs-EVs and subsequently transferred to human monocytic THP1 cells, in which these vesicles enhance monocyte activation by shifting the monocytes/macrophages balance from anti-inflammatory M2 macrophages towards pro-inflammatory M1 macrophages; EVs from KLF2-expressing ECs suppressed monocyte activation by enhancing immunomodulatory responses and diminishing proinflammatory responses, which indicate the potent anti-inflammatory activities of these cells. Furthermore, oil-red staining showed that atherosclerotic lesions were reduced in mice that received EVs from KLF2-transduced ECs with decreased pro-inflammatory M1 macrophages and increased anti-inflammatory M2 macrophages, and this effect is at least partly due to the decreased expression of inflammation-associated miR-155, confirming our in vitro findings. CONCLUSIONS: In summary, the present study provides novel insights into the pathophysiological effects of altered EV secretion and/or microRNA content and their influence on modulating monocyte activation depending on the environment surrounding EVs-releasing ECs. This article is protected by copyright. All rights reserved.

[45] *Egnot NS, Barinas-Mitchell E, Criqui MH et al.* **An exploratory factor analysis of inflammatory and coagulation markers associated with femoral artery atherosclerosis in the San Diego Population Study**. Thrombosis research 2018; 164:9-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29459247
ABSTRACT

BACKGROUND AND AIMS: Several biomarkers of inflammation and coagulation have been implicated in lower extremity atherosclerosis. We utilized an exploratory factor analysis (EFA) to identify distinct factors derived from circulating inflammatory and coagulation biomarkers then examined the associations of these factors with measures of lower extremity subclinical atherosclerosis, including the ankle-brachial index (ABI), common and superficial femoral intima-media thickness (IMT), and atherosclerotic plaque presence, burden, and characteristics. METHODS: The San Diego Population Study (SDPS) is a prospective, community-living, multi-ethnic cohort of 1103 men and women averaged age 70. Regression analysis was used to assess cross-sectional associations between the identified groupings of biomarkers (factors) and the ABI and femoral artery atherosclerosis measurements. RESULTS: Two biomarker factors emerged from the factor analysis. Factor 1 consisting of C-reactive protein (CRP), interleukin (IL)-6, and fibrinogen was significantly associated with higher odds (OR=1.99, p<0.01) of a borderline ABI value (0.91-0.99), while Factor 2 containing D-dimer and pentraxin (PTX)-3 was significantly associated with higher common femoral artery (CFA) IMT (beta=0.23, p<0.01) and lower ABI (beta=-0.03, p<0.01). CONCLUSIONS: Two groupings of biomarkers were identified via EFA of seven circulating biomarkers of inflammation and coagulation. These distinct groups are differentially associated with markers of lower extremity subclinical atherosclerosis. Our findings suggest that high inflammatory and coagulation burden were better markers of more severe lower-extremity disease as indicated by low ABI rather than early atherosclerotic lesion development in the femoral artery.

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ABSTRACT

[47] *Jing HR, Luo FW, Liu XM et al.* **Fish oil alleviates liver injury induced by intestinal ischemia/reperfusion via AMPK/SIRT-1/autophagy pathway**. World journal of gastroenterology : WJG 2018; 24:833-843.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29467553
ABSTRACT
AIM: To evaluate whether fish oil (FO) can protect liver injury induced by intestinal ischemia/reperfusion (I/R) via the AMPK/SIRT-1/autophagy pathway. METHODS: Ischemia in Wistar rats was induced by superior mesenteric artery occlusion for 60 min and reperfusion for 240 min. One milliliter per day of FO emulsion or normal saline was administered by intraperitoneal injection for 5 consecutive days to each animal. Animals were sacrificed at the end of reperfusion. Blood and tissue samples were collected for analyses. AMPK, SIRT-1, and Beclin-1 expression was determined in lipopolysaccharide (LPS)-stimulated HepG2 cells with or without FO emulsion treatment. RESULTS: Intestinal I/R induced significant liver morphological changes and increased serum alanine aminotransferase and aspartate aminotransferase levels. Expression of p-AMPK/AMPK, SIRT-1, and autophagy markers was decreased whereas tumor necrosis factor-alpha (TNF-alpha) and malonaldehyde (MDA) were increased. FO emulsion blocked the changes of the above indicators effectively. Besides, in LPS-stimulated HepG2 cells, small interfering RNA (siRNA) targeting AMPK impaired the FO induced increase of p-AMPK,

SIRT-1, and Beclin-1 and decrease of TNF-alpha and MDA. SIRT-1 siRNA impaired the increase of SIRT-1 and Beclin-1 and the decrease of TNF-alpha and MDA. CONCLUSION: Our study indicates that FO may protect the liver against intestinal I/R induced injury through the AMPK/SIRT-1/autophagy pathway.