Literature update week 43 (2018)

[1] *Hermans MP, Gevaert S, Descamps O et al.* **Frequency and predictors of cholesterol target attainment in patients with stable coronary heart disease in Belgium: results from the Dyslipidemia International Study II (DYSIS II CHD)**. Acta clinica Belgica 2018:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30355016

ABSTRACT
OBJECTIVES: To document the frequency and predictors of low-density lipoprotein cholesterol (LDL-C) target value attainment among patients with coronary heart disease (CHD) in Belgium. METHODS: The second Dyslipidemia International Study (DYSIS II) was an observational study of the prevalence of dyslipidemias and lipid target value attainment. Patients in this analysis were aged >/= 18, had documented CHD, and had a full lipid profile. Use of lipid-lowering therapy (LLT), lipid profile, and LDL-C target value attainment (< 70 mg/dL) were assessed cross-sectionally at the enrollment visit. The distribution of LLTs was assessed among treated patients. Multivariate logistic regression was used to identify variables predictive of LDL-C target value attainment in treated patients. RESULTS: We identified 409 patients with CHD in Belgium, 387 (94.6%) of whom were on LLT at the time of the lipid profile. Among treated patients, the rate of LDL-C target value attainment was 40.6%, and statin monotherapy was the most commonly used LLT (79.3%). Among users of statin monotherapy or combination therapy, simvastatin was the most commonly used treatment (41.6% of patients). Diabetes was associated with higher odds of LDL-C target value attainment (OR 2.29, 95% CI 1.33-3.93), and female gender was associated with lower odds (OR 0.48, 95% CI 0.24-0.97). CONCLUSION: Rates of LDL-C target value attainment are low in patients with CHD in Belgium. Intensifying statin therapy or combining it with non-statins is essential in Belgian patients for optimal LDL-C reduction.

[2] *Kalbacher D, Waldeyer C, Blankenberg S, Westermann D*. **Beyond conventional secondary prevention in coronary artery disease-what to choose in the era of CANTOS, COMPASS, FOURIER, ODYSSEY and PEGASUS-TIMI 54? A review on contemporary literature**. Annals of translational medicine 2018; 6:323.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30364059

ABSTRACT
Patients with established cardiovascular (CV) disease remain at dramatic residual risk for subsequent events, despite growing evidence in secondary prevention and wider dissemination of intensive treatment. This review focuses on new options in secondary risk prevention as presented by these five major randomized controlled trials (RCT): PEGASUS-TIMI 54, COMPASS, FOURIER, ODYSSEY and CANTOS. Three main therapeutic targets are addressed: residual cholesterol, residual inflammatory and residual thrombotic risk. All of the trials reviewed included patients with stable CV disease on optimal medical treatment with a surprising similar mortality. As of now, evolocumab, alirocumab and ticagrelor are on the market, while rivaroxaban and canakinumab are not yet licensed for the treatment of secondary prevention in CV disease. Although life-style modifications and better utilization of established medical treatment options will remain first-line strategy, new medication is just about to enter the market. Secondary prevention in coronary artery disease (CAD) holds a strong potential to reduce subsequent CV events, even CV death. It seems that a combination of an aggressive lipid-lowering treatment in combination with antithrombotic therapy could improve prognosis

significantly (at least for distinct subgroups). Against this background, individual efficacy, risk, and costs have to be considered when identifying patients for each new regime.

[3] *Dourado PMM*. **Rosuvastatin Decreases the Formation of Neointima by Increasing Apo J, Reducing Restenosis after Balloon Injury in Rats**. Arquivos brasileiros de cardiologia 2018; 111:569-570.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30365679
ABSTRACT

[4] *Radaelli G, Sausen G, Cesa CC et al.* **Statin Treatments And Dosages In Children With Familial Hypercholesterolemia: Meta-Analysis**. Arquivos brasileiros de cardiologia 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30365601
ABSTRACT
BACKGROUND: Children with familial hypercholesterolemia may develop early endothelial damage leading to a high risk for the development of cardiovascular disease (CVD). Statins have been shown to be effective in lowering LDL cholesterol levels and cardiovascular events in adults. The effect of statin treatment in the pediatric population is not clearly demonstrated. OBJECTIVE: To systematically review the literature to evaluate the effects of different statins and dosages in total cholesterol levels in children and adolescents with familial hypercholesterolemia. We also aimed to evaluate statin safety in this group. METHODS: PubMed, EMBASE, Bireme, Web of Science, Cochrane Library, SciELO and LILACS databases, were searched for articles published from inception until February 2016. Two independent reviewers performed the quality assessment of the included studies. We performed a meta-analysis with random effects and inverse variance, and subgroup analyses were performed. RESULTS: Ten trials involving a total of 1543 patients met the inclusion criteria. Our study showed reductions in cholesterol levels according to the intensity of statin doses (high, intermediate and low): (-104.61 mg/dl, -67.60 mg/dl, -56.96 mg/dl) and in the low-density lipoprotein cholesterol level: [-105.03 mg/dl (95% CI -115.76, -94.30), I2 19.2%], [-67.85 mg/dl (95% CI -83.36, -52.35), I2 99.8%], [-58.97 mg/dl (95% CI -67.83, -50.11), I2 93.8%. The duration of statin therapy in the studies ranged from 8 to 104 weeks, precluding conclusions about long-term effects. CONCLUSION: Statin treatment is efficient in lowering lipids in children with FH. There is need of large, long-term and randomized controlled trials to establish the long-term safety of statins.

[5] *Schneider LSV, Ciarlariello VB, Miranda R et al.* **Get With The Guidelines(R)-Stroke performance indicators in patients with transient ischemic attack**. Arquivos de neuro-psiquiatria 2018; 76:599-602.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30365623
ABSTRACT
OBJECTIVE: Get With The Guidelines(R)-Stroke is an in-hospital program for improving stroke care by promoting adherence to scientific guidelines. Of the patients with transient ischemic attack (TIA), 10-15% have a stroke within three months, and many patients do not receive the recommended interventions to prevent this outcome. The goal of this study was to assess the adherence to stroke quality indicators in patients with TIA. METHODS: This retrospective

observational study evaluated consecutive patients admitted to a primary stroke center with TIA or acute ischemic stroke (AIS) from August 2008 to December 2013. Six quality indicators applicable to both TIA and AIS were analyzed and compared between groups. RESULTS: A total of 357 patients with TIA and 787 patients with AIS were evaluated. Antithrombotic medication use within 48 hours of admission, discharge use of anticoagulation for atrial fibrillation and counseling for smoking cessation were similar between groups. In the TIA group, discharge use of antithrombotic medication (95% versus 98%; p = 0.01), lipid-lowering treatment (57.7% versus 64.1%; p < 0.01) and stroke education (56.5% versus 74.5%; p < 0.01) were all less frequently observed compared with patients with AIS. CONCLUSIONS: The adherence to some of the Get With The Guidelines(R)-Stroke quality indicators was lower in patients with TIA than in patients with AIS. Measures should be undertaken to reinforce the importance of such clinical interventions in patients with TIA.

[6] *Al-Yafeai Z, Yurdagul A, Jr., Peretik JM et al.* **Endothelial FN (Fibronectin) Deposition by alpha5beta1 Integrins Drives Atherogenic Inflammation**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2601-2614.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354234
ABSTRACT
Objective- Alterations in extracellular matrix quantity and composition contribute to atherosclerosis, with remodeling of the subendothelial basement membrane to an FN (fibronectin)-rich matrix preceding lesion development. Endothelial cell interactions with FN prime inflammatory responses to a variety of atherogenic stimuli; however, the mechanisms regulating early atherogenic FN accumulation remain unknown. We previously demonstrated that oxLDL (oxidized low-density lipoprotein) promotes endothelial proinflammatory gene expression by activating the integrin alpha5beta1, a classic mediator of FN fibrillogenesis. Approach and Results- We now show that oxLDL drives robust endothelial FN deposition and inhibiting alpha5beta1 (blocking antibodies, alpha5 knockout cells) completely inhibits oxLDL-induced FN deposition. Consistent with this, inducible endothelial-specific alpha5 integrin deletion in ApoE knockout mice significantly reduces atherosclerotic plaque formation, associated with reduced early atherogenic inflammation. Unlike TGFbeta (transforming growth factor beta)-induced FN deposition, oxLDL does not induce FN expression (mRNA, protein) or the endothelial-to-mesenchymal transition phenotype. In addition, we show that cell-derived and plasma-derived FN differentially affect endothelial function, with only cell-derived FN capable of supporting oxLDL-induced VCAM-1 (vascular cell adhesion molecule 1) expression, despite plasma FN deposition by oxLDL. The inclusion of alternative exon EIIIA (EDA) of FN (EIIIA) and alternative exon EIIIB (EDB) of FN (EIIIB) domains in cell-derived FN mediates this effect, as EIIIA/EIIIB knockout endothelial cells show diminished oxLDL-induced inflammation. Furthermore, our data suggest that EIIIA/EIIIB-positive cellular FN is required for maximal alpha5beta1 recruitment to focal adhesions and FN fibrillogenesis. Conclusions- Taken together, our data demonstrate that endothelial alpha5 integrins drive oxLDL-induced FN deposition and early atherogenic inflammation. Additionally, we show that alpha5beta1-dependent endothelial FN deposition mediates oxLDL-dependent endothelial inflammation and FN fibrillogenesis.

Literature update week 43 (2018)

[7] *Chai JT, Ruparelia N, Goel A et al.* **Differential Gene Expression in Macrophages From Human Atherosclerotic Plaques Shows Convergence on Pathways Implicated by Genome-Wide Association Study Risk Variants**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2718-2730.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354237

ABSTRACT
Objective- Plaque macrophages are intricately involved in atherogenesis and plaque destabilization. We sought to identify functional pathways in human plaque macrophages that are differentially regulated in respect of (1) plaque stability and (2) lipid content. We hypothesized that differentially regulated macrophage gene sets would relate to genome-wide association study variants associated with risk of acute complications of atherosclerosis. Approach and Results- Forty patients underwent carotid magnetic resonance imaging for lipid quantification before endarterectomy. Carotid plaque macrophages were procured by laser capture microdissection from (1) lipid core and (2) cap region, in 12 recently symptomatic and 12 asymptomatic carotid plaques. Applying gene set enrichment analysis, a number of gene sets were found to selectively upregulate in symptomatic plaque macrophages, which corresponded to 7 functional pathways: inflammation, lipid metabolism, hypoxic response, cell proliferation, apoptosis, antigen presentation, and cellular energetics. Predicted upstream regulators included IL-1beta, TNF-alpha, and NF-kappaB. In vivo lipid quantification by magnetic resonance imaging correlated most strongly with the upregulation of genes of the IFN/ STAT1 pathways. Cross-interrogation of gene set enrichment analysis and meta-analysis gene set enrichment of variant associations showed lipid metabolism pathways, driven by genes coding for APOE and ABCA1/G1 coincided with known risk-associated SNPs (single nucleotide polymorphisms) from genome-wide association studies. Conclusions- Macrophages from recently symptomatic carotid plaques show differential regulation of functional gene pathways. There were additional quantitative relationships between plaque lipid content and key gene sets. The data show a plausible mechanism by which known genome-wide association study risk variants for atherosclerotic complications could be linked to (1) a relevant cellular process, in (2) the key cell type of atherosclerosis, in (3) a human disease-relevant setting.

[8] *Di Bartolo BA, Psaltis PJ, Bursill CA, Nicholls SJ*. **Translating Evidence of HDL and Plaque Regression**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:1961-1968.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354261

ABSTRACT
Considerable evidence from preclinical and population studies suggests that HDLs (high-density lipoproteins) possess atheroprotective properties. Reports from HDL infusion studies in animals and early clinical imaging trials reported evidence of plaque regression. These findings have stimulated further interest in developing new agents targeting HDL. However, the results of more recent imaging studies in the setting of high-intensity statin use have been disappointing. As the concept of plaque changes with HDL therapeutics evolves and imaging technology to evaluate these effects advances, there will become increasing opportunity to determine the effects of HDL agents on atherosclerotic plaque (Graphic Abstract).

[9] *Nishino T, Horie T, Baba O et al.* **SREBF1/MicroRNA-33b Axis Exhibits Potent Effect on Unstable Atherosclerotic Plaque Formation In Vivo**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2460-2473.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354203
ABSTRACT
Objective- Atherosclerosis is a common disease caused by a variety of metabolic and inflammatory disturbances. MicroRNA (miR)-33a within SREBF2 (sterol regulatory element-binding factor 2) is a potent target for treatment of atherosclerosis through regulating both aspects; however, the involvement of miR-33b within SREBF1 remains largely unknown. Although their host genes difference could lead to functional divergence of miR-33a/b, we cannot dissect the roles of miR-33a/b in vivo because of lack of miR-33b sequences in mice, unlike human. Approach and Results- Here, we analyzed the development of atherosclerosis using miR-33b knock-in humanized mice under apolipoprotein E-deficient background. MiR-33b is prominent both in human and mice on atheroprone condition. MiR-33b reduced serum high-density lipoprotein cholesterol levels and systemic reverse cholesterol transport. MiR-33b knock-in macrophages showed less cholesterol efflux capacity and higher inflammatory state via regulating lipid rafts. Thus, miR-33b promotes vulnerable atherosclerotic plaque formation. Furthermore, bone marrow transplantation experiments strengthen proatherogenic roles of macrophage miR-33b. Conclusions- Our data demonstrated critical roles of SREBF1-miR-33b axis on both lipid profiles and macrophage phenotype remodeling and indicate that miR-33b is a promising target for treating atherosclerosis.

[10] *Rinne P, Guillamat-Prats R, Rami M et al.* **Palmitoylethanolamide Promotes a Proresolving Macrophage Phenotype and Attenuates Atherosclerotic Plaque Formation**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2562-2575.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354245
ABSTRACT
Objective- Palmitoylethanolamide is an endogenous fatty acid mediator that is synthetized from membrane phospholipids by N-acyl phosphatidylethanolamine phospholipase D. Its biological actions are primarily mediated by PPAR-alpha (peroxisome proliferator-activated receptors alpha) and the orphan receptor GPR55. Palmitoylethanolamide exerts potent anti-inflammatory actions but its physiological role and promise as a therapeutic agent in chronic arterial inflammation, such as atherosclerosis remain unexplored. Approach and Results- First, the polarization of mouse primary macrophages towards a proinflammatory phenotype was found to reduce N-acyl phosphatidylethanolamine phospholipase D expression and palmitoylethanolamide bioavailability. N-acyl phosphatidylethanolamine phospholipase D expression was progressively downregulated in the aorta of apolipoprotein E deficient (ApoE(-/-)) mice during atherogenesis. N-acyl phosphatidylethanolamine phospholipase D mRNA levels were also downregulated in unstable human plaques and they positively associated with smooth muscle cell markers and negatively with macrophage markers. Second, ApoE(-)(/-) mice were fed a high-fat diet for 4 or 16 weeks and treated with either vehicle or palmitoylethanolamide (3 mg/kg per day, 4 weeks) to study the effects of palmitoylethanolamide on early established and pre-established atherosclerosis. Palmitoylethanolamide treatment reduced plaque size in early atherosclerosis, whereas in pre-

established atherosclerosis, palmitoylethanolamide promoted signs of plaque stability as evidenced by reduced macrophage accumulation and necrotic core size, increased collagen deposition and downregulation of M1-type macrophage markers. Mechanistically, we found that palmitoylethanolamide, by activating GPR55, increases the expression of the phagocytosis receptor MerTK (proto-oncogene tyrosine-protein kinase MER) and enhances macrophage efferocytosis, indicative of proresolving properties. Conclusions- The present study demonstrates that palmitoylethanolamide protects against atherosclerosis by promoting an anti-inflammatory and proresolving phenotype of lesional macrophages, representing a new therapeutic approach to resolve arterial inflammation.

[11] *Sakai K, Nagashima S, Wakabayashi T et al.* **Myeloid HMG-CoA (3-Hydroxy-3-Methylglutaryl-Coenzyme A) Reductase Determines Atherosclerosis by Modulating Migration of Macrophages**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2590-2600.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354246
ABSTRACT
Objective- Inhibition of HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) is atheroprotective primarily by decreasing plasma LDL (low-density lipoprotein)-cholesterol. However, it is unknown whether inhibition of HMGCR in myeloid cells contributes to this atheroprotection. We sought to determine the role of myeloid HMGCR in the development of atherosclerosis. Approach and Results- We generated mice with genetically reduced Hmgcr in myeloid cells (Hmgcr (m-) (/m)(-)) using LysM (Cre) and compared various functions of their macrophages to those of Hmgcr (fl/fl) control mice. We further compared the extent of atherosclerosis in Hmgcr (m-/ m-) and Hmgcr (fl/fl) mice in the absence of Ldlr (LDL receptor). Hmgcr (m-/ m-) macrophages and granulocytes had significantly lower Hmgcr mRNA expression and cholesterol biosynthesis than Hmgcr (fl/fl) cells. In vitro, Hmgcr (m-/ m-) monocytes/macrophages had reduced ability to migrate, proliferate, and survive compared with Hmgcr (fl/fl) monocytes/macrophages. However, there was no difference in ability to adhere, phagocytose, store lipids, or polarize to M1 macrophages between the 2 types of macrophages. The amounts of plasma membrane-associated small GTPase proteins, such as RhoA (RAS homolog family member A), were increased in Hmgcr (m-/ m-) macrophages. In the setting of Ldlr deficiency, Hmgcr (m-/ m-) mice developed significantly smaller atherosclerotic lesions than Hmgcr (fl/fl) mice. However, there were no differences between the 2 types of mice either in plasma lipoprotein profiles or in the numbers of proliferating or apoptotic cells in the lesions in vivo. The in vivo migration of Hmgcr (m-/ m-) macrophages to the lesions was reduced compared with Hmgcr (fl/fl) macrophages. Conclusions- Genetic reduction of HMGCR in myeloid cells may exert atheroprotective effects primarily by decreasing the migratory activity of monocytes/macrophages to the lesions.

[12] *Sukhanov S, Higashi Y, Shai SY et al.* **SM22alpha (Smooth Muscle Protein 22-alpha) Promoter-Driven IGF1R (Insulin-Like Growth Factor 1 Receptor) Deficiency Promotes Atherosclerosis**. Arteriosclerosis, thrombosis, and vascular biology 2018; 38:2306-2317.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354209
ABSTRACT

Objective- IGF-1 (insulin-like growth factor 1) is a major autocrine/paracrine growth factor, which promotes cell proliferation, migration, and survival. We have shown previously that IGF-1 reduced atherosclerosis and promoted features of stable atherosclerotic plaque in Apoe(-/)(-) mice-an animal model of atherosclerosis. The aim of this study was to assess effects of smooth muscle cell (SMC) IGF-1 signaling on the atherosclerotic plaque. Approach and Results- We generated Apoe(-/-) mice with IGF1R (IGF-1 receptor) deficiency in SMC and fibroblasts (SM22alpha [smooth muscle protein 22 alpha]-CreKI/IGF1R-flox mice). IGF1R was decreased in the aorta and adventitia of SM22alpha-CreKI/IGF1R-flox mice and also in aortic SMC, embryonic, skin, and lung fibroblasts isolated from SM22alpha-CreKI/IGF1R-flox mice. IGF1R deficiency downregulated collagen mRNA-binding protein LARP6 (La ribonucleoprotein domain family, member 6) and vascular collagen, and mice exhibited growth retardation. The high-fat diet-fed SM22alpha-CreKI/IGF1R-flox mice had increased atherosclerotic burden and inflammatory responses. alpha-SMA (alpha-smooth muscle actin)-positive plaque cells had reduced proliferation and elevated apoptosis. SMC/fibroblast-targeted decline in IGF-1 signaling decreased atherosclerotic plaque SMC, markedly depleted collagen, reduced plaque fibrous cap, and increased plaque necrotic cores. Aortic SMC isolated from SM22alpha-CreKI/IGF1R-flox mice had decreased cell proliferation, migration, increased sensitivity to apoptosis, and these effects were associated with disruption of IGF-1-induced Akt signaling. Conclusions- IGF-1 signaling in SMC and in fibroblast is a critical determinant of normal vascular wall development and atheroprotection.

[13] *Fuhrmann A, Weingartner O, Meyer S et al.* **Plasma levels of the oxyphytosterol 7alpha-hydroxycampesterol are associated with cardiovascular events**. Atherosclerosis 2018; 279:17-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30366187
ABSTRACT
BACKGROUND AND AIMS: There are safety issues regarding plant sterol ester-enriched functional food. Oxidized plant sterols, also called oxyphytosterols, are supposed to contribute to plant sterol atherogenicity. This study aimed to analyze associations of plasma oxyphytosterol levels with cardiovascular events. METHODS: Plasma cholesterol was measured by gas chromatography-flame ionization detection. Plasma campesterol and sitosterol and their 7-oxygenated metabolites were analyzed by gas chromatography-mass selective detection. RESULTS: In 376 patients admitted for elective coronary angiography, who were not on lipid-lowering drugs, 82 cardiovascular events occurred during a follow-up period of 4.2+/-1.8 years. Patients with cardiovascular events had significantly higher 7alpha-hydroxycampesterol plasma levels (median, 0.46; [interquartile range (IQR) 0.22-0.81] nmol/L vs. median, 0.25 [IQR, 0.17-0.61] nmol/L; p=0.003) and 7alpha-hydroxycampesterol-to-cholesterol ratios (median 0.08 [IQR, 0.04-0.14] nmol/mmol vs. median, 0.05 [IQR 0.03-0.11] nmol/mmol; p=0.005) than controls without such events. Patients above the median were characterized by higher cumulative event rates in Kaplan-Meier-analysis (Logrank-test p=0.084 and p=0.025) for absolute and cholesterol corrected 7alpha-hydroxycampesterol, respectively. After adjustment for influencing factors and related lipids, the hazard ratios per one standard deviation of the log-transformed variables (HR) were 1.19 [95% confidence interval (CI), 0.95-1.48], p=0.132 for 7alpha-hydroxycampesterol and HR, 1.18 [95% CI, 0.94-1.48], p=0.154 for 7alpha-

hydroxycampesterol-to-cholesterol ratio. None of the other investigated oxyphytosterols showed an association with cardiovascular events. CONCLUSIONS: In patients not on lipid-lowering drugs, absolute plasma levels of 7alpha-hydroxycampesterol and their ratios to cholesterol are associated with cardiovascular events. Further research is required to elucidate the role of OPS in cardiovascular diseases.

[14] *Yamashita S, Ruscica M, Macchi C et al.* **Cholesteryl ester transfer protein: An enigmatic pharmacology - Antagonists and agonists**. Atherosclerosis 2018; 278:286-298.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30347344
ABSTRACT
The cholesteryl ester transfer protein (CETP) system moves cholesteryl esters (CE) from high density lipoproteins (HDL) to lower density lipoproteins, i.e. very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) in exchange for triglycerides (TGs). This shuttle process will ultimately form complexes facilitating a bidirectional exchange of CE and TGs, the end process being CE delivery to catabolic sites. The CETP system is generally characteristic of higher animal species; lower species, not provided with this system, have higher and enlarged HDL enriched with apo E, suitable for tissue receptor interaction. Discovery of the CETP system has led to the development of agents interfering with CETP, thus elevating HDL-C and potentially preventing cardiovascular (CV) disease. Activation of CETP leads instead to reduced HDL-C levels, but also to an enhanced removal of CE from tissues. CETP antagonists are mainly small molecules (torcetrapib, anacetrapib, evacetrapib, dalcetrapib) and have provided convincing evidence of a HDL-C raising activity, but disappointing results in trials of CV prevention. In contrast, the CETP agonist probucol leads to HDL-C lowering followed by an increment of tissue cholesterol removal (reduction of xanthomas, xanthelasmas) and positive findings in secondary prevention trials. The drug has an impressive anti-inflammatory profile (markedly reduced interleukin-1beta expression). Newer agents, some of natural origin, have additional valuable pharmacodynamic properties. The pharmacological approach to the CETP system remains enigmatic, although the failure of CETP antagonists has dampened enthusiasm. Studies on the system, a crossroad for any investigation on cholesterol metabolism, have however provided crucial contributions and will still be confronting any scientist working on CV prevention.

[15] LeBlanc EL, Patnode CD, Webber EM *et al.* U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. In: Behavioral and Pharmacotherapy Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults: An Updated Systematic Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018.
[16] *Harms MH, van Buuren HR, van der Meer AJ*. **Improving prognosis in primary biliary cholangitis - Therapeutic options and strategy**. Best practice & research. Clinical gastroenterology 2018; 34-35:85-94.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30343714
ABSTRACT
Overall survival in primary biliary cholangitis is diminished. As patients are often asymptomatic, the disease may silently progress towards cirrhosis and liver failure. Timely diagnosis and effective treatment options are of vital importance to improve the prognosis of affected

patients. Ursodeoxycholic acid is the standard of care first-line therapy and is associated with a reduced risk of liver transplantation and death. Treatment with UDCA is relevant for all patients, irrespective of disease stage or biochemical response. In case of incomplete biochemical response according to internationally accepted criteria, second-line treatment should be considered to improve long-term prognosis. Ursodeoxycholic acid has been the only accepted treatment for PBC during the last decades. Recent research, however, has identified a number of new therapeutic targets and agents, including obeticholic acid, fibrates and budesonide. While these agents all qualify as potentially beneficial second-line treatment, obeticholic acid is currently the only drug specifically approved for the treatment of PBC. Although long-term follow-up studies for these agents are mostly lacking, improvement of biochemical surrogate markers of clinical outcome induced by these drugs suggests a therapeutic benefit. The authors of this review aim to provide a summary of the results of previous and current studies evaluating medical treatments, and propose a treatment strategy based on the evidence available today.

[17] *Chidwick K, Strongman H, Matthews A et al.* **Statin use in cancer survivors versus the general population: cohort study using primary care data from the UK clinical practice research datalink**. BMC Cancer 2018; 18:1018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30348123
ABSTRACT
BACKGROUND: Cancer survivors may be at increased risk of cardiovascular diseases, but little is known about whether prescribing guidelines for the primary prevention of cardiovascular disease are adequately implemented in these patients. We compared levels of statin initiation and cessation among cancer survivors compared to the general population to determine differences in uptake of pharmaceutical cardiovascular risk prevention measures in these groups. METHODS: The study population included individuals aged >/=40 during 2005-13 within the UK Clinical Practice Research Datalink primary care database. Within this population we identified cancer survivors who were alive and under follow-up at least 1 year after diagnosis, and controls with no cancer history. Follow-up time prior to cancer diagnosis was included in the control cohort. Using logistic regression, we compared these groups with respect to uptake of statins within 1 month of a first high recorded cardiovascular risk score. Then, we used Cox modelling to compare persistence on statin therapy (time to statin cessation) between cancer survivors and controls from the main study population who had initiated on a statin. RESULTS: Among 4202 cancer survivors and 113,035 controls with a record indicating a high cardiovascular risk score, 23.0% and 23.5% respectively initiated a statin within 1 month (adjusted odds ratio 0.98 [91.8-1.05], p = 0.626). Cancer survivors appeared more likely to discontinue statin treatment than controls (adjusted hazard ratio 1.07 [1.01-1.12], p = 0.02). This greater risk of discontinuing was only evident after the first year of therapy (p-interaction < 0.001). INTERPRETATION: Although cardiovascular risk is thought to be higher in cancer survivors compared to the general population, cancer survivors were no more likely to receive statins, and marginally more likely to cease long-term therapy, than general population controls. There may be an opportunity to mitigate the suspected higher cardiovascular risk in the growing population of cancer survivors by improving uptake of lipid-lowering treatment and persistence on therapy.

[18] *Yu P, Yang X, Qi Z*. **Letter to the editor: The sole and combined effect of simvastatin and platelet rich fibrin as a filling material in induced bone defect in tibia of albino rats**. Bone 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30366110
ABSTRACT

[19] *Valkova M, Lazurova I, Petrasova D et al.* **Humoral predictors of ankle-brachial index in patients with peripheral arterial disease and controls**. Bratislavske lekarske listy 2018; 119:646-650.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30345773
ABSTRACT
INTRODUCTION: Peripheral arterial disease (PAD) is a common condition due to atherosclerosis with high prevalence in population over 55 years. Although its pathophysiology is well recognized, the role of inflammatory markers is still not fully known. OBJECTIVES: The aim of the study was to assess the relation of C-reactive protein (CRP), tumor necrosis factors-alpha (TNF-alpha) and interleukin-6 (IL-6) to ankle-brachial index (ABI) and metabolic variables in patients with PAD. The second aim was to find the most significant humoral predictor of ABI. PATIENTS AND METHODS: The study groups consisted of 55 patients (36 men and 19 women) diagnosed with PAD (age 63.65 +/- 6.11 years) and 34 control subjects (7 men, 27 women) of average age 59.88 +/- 6.10 years with ABI > 0.9. Blood samples were analyzed for glycaemia, lipid profile and inflammatory markers (CRP, TNF-alpha and IL-6). RESULTS: A significantly higher serum total cholesterol ($p = 0.04$), triglycerides ($p = 0.005$) and lower HDL cholesterol ($p < 0.0001$) were found in the PAD group as compared to controls. Patients with PAD had significantly higher serum glucose ($p = 0.008$), CRP ($p = 0.0044$), IL-6 ($p < 0.0001$) and TNF-alpha ($p < 0.0001$) in comparison to controls. In a multiple linear regression analysis among variables log IL-6 and log HDL cholesterol were most significantly related to ABI (LW 4.75 for log IL-6, LW 4.016 for log HDL cholesterol, respectively, $p < 0.01$) in all subjects. CONCLUSIONS: We conclude that among traditional and humoral risk factors IL-6 is the strongest predictor of ABI. HDL cholesterol is also significant and strong predictor of decreased ABI and could be a potential biomarker of PAD in patients using lipid lowering drugs (Tab. 1, Ref. 31).

[20] *Nativel M, Potier L, Alexandre L et al.* **Lower extremity arterial disease in patients with diabetes: a contemporary narrative review**. Cardiovascular diabetology 2018; 17:138.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30352589
ABSTRACT
Lower-extremity arterial disease (LEAD) is a major endemic disease with an alarming increased prevalence worldwide. It is a common and severe condition with excess risk of major cardiovascular events and death. It also leads to a high rate of lower-limb adverse events and non-traumatic amputation. The American Diabetes Association recommends a widespread medical history and clinical examination to screen for LEAD. The ankle brachial index (ABI) is the first non-invasive tool recommended to diagnose LEAD although its variable performance in patients with diabetes. The performance of ABI is particularly affected by the presence of peripheral neuropathy, medial arterial calcification, and incompressible arteries. There is no

strong evidence today to support an alternative test for LEAD diagnosis in these conditions. The management of LEAD requires a strict control of cardiovascular risk factors including diabetes, hypertension, and dyslipidaemia. The benefit of intensive versus standard glucose control on the risk of LEAD has not been clearly established. Antihypertensive, lipid-lowering, and antiplatelet agents are obviously worthfull to reduce major cardiovascular adverse events, but few randomised controlled trials (RCTs) have evaluated the benefits of these treatments in terms of LEAD and its related adverse events. Smoking cessation, physical activity, supervised walking rehabilitation and healthy diet are also crucial in LEAD management. Several advances have been achieved in endovascular and surgical revascularization procedures, with obvious improvement in LEAD management. The revascularization strategy should take into account several factors including anatomical localizations of lesions, medical history of each patients and operator experience. Further studies, especially RCTs, are needed to evaluate the interest of different therapeutic strategies on the occurrence and progression of LEAD and its related adverse events in patients with diabetes.

[21] *Gayam V, Mandal AK, Garlapati P et al.* **Moderate Hypertriglyceridemia Causing Recurrent Pancreatitis: A Case Report and the Literature Review**. Case reports in gastrointestinal medicine 2018; 2018:8714390.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30345124
ABSTRACT
Recurrent acute pancreatitis secondary to hypertriglyceridemia (HTG) with levels below 1000 mg/dL has been rarely reported in the literature. HTG is the third most common cause of acute pancreatitis and has been established in the literature as a risk factor when levels are greater than 1000 mg/dL. A 43-year-old patient presented to the hospital with severe epigastric abdominal pain. Initial laboratory investigations were significant for a lipase level of 4143 U/L and a triglyceride level of 600 mg/dL. Computed tomography (CT) of the abdomen showed diffuse enlargement of the pancreas consistent with pancreatitis. A diagnosis of severe acute pancreatitis secondary to high triglycerides was made based on the revised Atlanta classification 2012. The patient was initially managed with intravenous boluses of normal saline followed by continuous insulin infusion. Diabetic Ketoacidosis (DKA) was ruled out due to a past medical history of diabetes. Her clinical course was complicated by acute respiratory distress syndrome requiring intubation and mechanical ventilation. During the course, she improved symptomatically and was extubated. She was started on nasogastric feeding initially and subsequently switched to oral diet as tolerated. After initial management of HTG with insulin infusion, oral gemfibrozil was started for long-term treatment of HTG. Emerging literature implicates HTG as an independent indicator of poor prognosis in acute pancreatitis (AP). Despite the paucity of data, the risk of developing AP must be considered even at triglyceride levels lower than 1000 mg/dL.

[22] *Obreja E, Sequeira P, Girnita D*. **When Should a Patient with Statin-Induced Myopathy Be Re-challenged? A Case of Necrotizing Autoimmune Myopathy**. Case Rep Rheumatol 2018; 2018:1215653.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30364043
ABSTRACT

Statins are notorious for causing myalgia and sometimes mild elevation of CPK (creatine phosphokinase). Herein, we present a case of necrotizing autoimmune myopathy induced by statins. The patient was on therapy with atorvastatin for about six years before she started developing myalgia and mild elevation in CPK that resolved after discontinuation of therapy. Since her cardiovascular risk was high and she had hypercholesterolemia, three months after CPK levels normalization, she was re-challenged with pravastatin. Few months later, she again presented severe myalgia, weakness, and elevated CPK levels. Hence, medication was discontinued, and she undergone an extensive workup for possible causes of inflammatory myopathies that revealed necrotizing autoimmune myopathy. Our case report offers an excellent source of "identification patterns" of muscular autoimmune disease which can be easily mistaken as common side effect of a drug.

[23] *Jones LK, Kulchak Rahm A, Manickam K et al.* **Healthcare Utilization and Patients' Perspectives After Receiving a Positive Genetic Test for Familial Hypercholesterolemia**. Circulation. Genomic and precision medicine 2018; 11:e002146.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354341
ABSTRACT
BACKGROUND: The MyCode Community Health Initiative (MyCode) is returning actionable results from whole exome sequencing. Familial hypercholesterolemia (FH) is an inherited condition characterized by premature cardiovascular disease. METHODS: We used multiple methods to assess care in 28 MyCode participants who received FH results. Chart reviews were conducted on 23 individuals in the sample and 7 individuals participated semistructured interviews. RESULTS: Chart reviews for 23 individuals with a Geisinger primary care provider found that 4 individuals (17% of 23) were at LDL-C (low-density lipoprotein cholesterol) goal (of either LDL-C <100 mg/dL for primary prevention and LDL-C <70 mg/dL for secondary prevention) and 17 individuals (74% of 23) were prescribed lipid-lowering therapy before genetic result disclosure. After disclosure of the genetic test result, 5 individuals (22% of 23) met their LDL-C goal and 18 individuals (78% of 23) were prescribed lipid-lowering therapy. Follow-up care about this result was not documented for 4 individuals (17% of 23). Changes to intensity of medication management were made for 8 individuals (47% of 17 individuals previously prescribed lipid-lowering therapy). Interviewed individuals (n=7) were not surprised by their result as all knew they had high cholesterol; however, individuals did not seem to discern FH as a separate condition from their high cholesterol. CONCLUSIONS: Among individuals receiving genetic diagnosis of FH, >25% had no changes to lipid-lowering therapy, despite not being at LDL-C goal and learning their high cholesterol is related to a genetic condition requiring more aggressive treatment. Individuals and clinicians may have an inadequate understanding of FH as a distinct condition requiring enhanced medical management.

[24] *Siemelink MA, van der Laan SW, Haitjema S et al.* **Smoking is Associated to DNA Methylation in Atherosclerotic Carotid Lesions**. Circulation. Genomic and precision medicine 2018; 11:e002030.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354327
ABSTRACT

BACKGROUND: Tobacco smoking is a major risk factor for atherosclerotic disease and has been associated with DNA methylation (DNAm) changes in blood cells. However, whether smoking influences DNAm in the diseased vascular wall is unknown but may prove crucial in understanding the pathophysiology of atherosclerosis. In this study, we associated current tobacco smoking to epigenome-wide DNAm in atherosclerotic plaques from patients undergoing carotid endarterectomy. METHODS: DNAm at commonly methylated sites (cytosine-guanine nucleotide pairs separated by a phospho-group [CpGs]) was assessed in atherosclerotic plaque samples and peripheral blood samples from 485 carotid endarterectomy patients. We tested the association of current tobacco smoking with DNAm corrected for age and sex. To control for bias and inflation because of cellular heterogeneity, we applied a Bayesian method to estimate an empirical null distribution as implemented by the R package bacon. Replication of the smoking-associated methylated CpGs in atherosclerotic plaques was executed in the second sample of 190 carotid endarterectomy patients, and results were meta-analyzed using a fixed-effects model. RESULTS: Tobacco smoking was significantly associated to differential DNAm in atherosclerotic lesions of 4 CpGs (false discovery rate <0.05) mapped to 2 different genes (AHRR, ITPK1) and 17 CpGs mapped to 8 genes and RNAs in blood. The strongest associations were found for CpGs mapped to the gene AHRR, a repressor of the aryl hydrocarbon receptor transcription factor involved in xenobiotic detoxification. One of these methylated CpGs were found to be regulated by local genetic variation. CONCLUSIONS: The risk factor tobacco smoking associates with DNAm at multiple loci in carotid atherosclerotic lesions. These observations support further investigation of the relationship between risk factors and epigenetic regulation in atherosclerotic disease.

[25] *Tuteja S, Rader DJ*. **SLCO1B1 and Statin Therapy**. Circulation. Genomic and precision medicine 2018; 11:e002320.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354338
ABSTRACT

[26] *van der Laan SW, Siemelink MA, Haitjema S et al.* **Genetic Susceptibility Loci for Cardiovascular Disease and Their Impact on Atherosclerotic Plaques**. Circulation. Genomic and precision medicine 2018; 11:e002115.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354329
ABSTRACT
BACKGROUND: Atherosclerosis is a chronic inflammatory disease in part caused by lipid uptake in the vascular wall, but the exact underlying mechanisms leading to acute myocardial infarction and stroke remain poorly understood. Large consortia identified genetic susceptibility loci that associate with large artery ischemic stroke and coronary artery disease. However, deciphering their underlying mechanisms are challenging. Histological studies identified destabilizing characteristics in human atherosclerotic plaques that associate with clinical outcome. To what extent established susceptibility loci for large artery ischemic stroke and coronary artery disease relate to plaque characteristics is thus far unknown but may point to novel mechanisms. METHODS: We studied the associations of 61 established cardiovascular risk loci with 7 histological plaque characteristics assessed in 1443 carotid plaque specimens from the Athero-Express Biobank Study. We also assessed if the genotyped cardiovascular risk loci

impact the tissue-specific gene expression in 2 independent biobanks, Biobank of Karolinska Endarterectomy and Stockholm Atherosclerosis Gene Expression. RESULTS: A total of 21 established risk variants (out of 61) nominally associated to a plaque characteristic. One variant (rs12539895, risk allele A) at 7q22 associated to a reduction of intraplaque fat, P=5.09x10(-6) after correction for multiple testing. We further characterized this 7q22 Locus and show tissue-specific effects of rs12539895 on HBP1 expression in plaques and COG5 expression in whole blood and provide data from public resources showing an association with decreased LDL (low-density lipoprotein) and increase HDL (high-density lipoprotein) in the blood. CONCLUSIONS: Our study supports the view that cardiovascular susceptibility loci may exert their effect by influencing the atherosclerotic plaque characteristics.

[27] *Imamura T, Nguyen A, Rodgers D et al.* **Omega-3 Therapy Is Associated With Reduced Gastrointestinal Bleeding in Patients With Continuous-Flow Left Ventricular Assist Device**. Circ Heart Fail 2018; 11:e005082.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354397
ABSTRACT
Background Gastrointestinal bleeding (GIB) is a common complication seen in patients supported with left ventricular assist devices (LVADs) and is related to increased inflammation and angiogenesis. Omega-3 is an unsaturated fatty acid that possesses anti-inflammatory and antiangiogenic properties. This study aims to assess the prophylactic efficacy of treatment with omega-3 on the incidence of GIB in LVAD patients. Methods and Results Among consecutive 166 LVAD patients enrolled in this analysis, 30 patients (49 years old and 26 male) received 4 mg/d of omega-3 therapy for 310+/-87 days and 136 patients in the control group (58 years old and 98 male) were observed for 302+/-102 days. One-year GIB-free rate was significantly higher in the omega-3 group as compared with the control group (97% versus 73%; P=0.02). Omega-3 therapy was associated with the occurrence of GIB in both the univariate (hazard ratio, 0.12; 95% CI, 0.02-0.91; P=0.040) and multivariate Cox proportional hazard ratio analyses (hazard ratio, 0.13; 95% CI, 0.02-0.98; P=0.047). The frequency of GIB was significantly lower in the omega-3 group (0.08+/-0.42 versus 0.37+/-0.93 events/y; P=0.01), accompanied by significantly lower blood product transfusion and shorter days in the hospital. The frequency of GIB remained lower among the omega-3 group after matching for patient background characteristics (96% versus 73%, P=0.028). Conclusions LVAD patients treated with omega-3 had a significant increase in freedom from GIB. A randomized controlled study is warranted to evaluate the use of omega-3 in LVAD patients.

[28] *Donzelli A, Schivalocchi A, Giudicatti G*. **Letter by Donzelli et al Regarding Article, "Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 138:1912-1913.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354663
ABSTRACT

Literature update week 43 (2018)

[29] *Koh KK*. **Letter by Koh Regarding Article, "PCSK9 Variants, Low-Density Lipoprotein Cholesterol, and Neurocognitive Impairment: Reasons for Geographic and Racial Differences in Stroke Study (REGARDS)"**. Circulation 2018; 138:1283-1284.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354438
ABSTRACT

[30] *Koh KK*. **Letter by Koh Regarding Article, "Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 138:1914-1915.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354661
ABSTRACT

[31] *Mottl AK, Buse JB, Ismail-Beigi F et al.* **Long-Term Effects of Intensive Glycemic and Blood Pressure Control and Fenofibrate Use on Kidney Outcomes**. Clinical journal of the American Society of Nephrology : CJASN 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30361335
ABSTRACT
BACKGROUND AND OBJECTIVES: In people with type 2 diabetes, aggressive control of glycemia, BP, and lipids have resulted in conflicting short-term (<5 years) kidney outcomes. We aimed to determine the long-term kidney effects of these interventions. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a multifactorial intervention study in people with type 2 diabetes at high risk for cardiovascular disease (n=10,251), to examine the effects of intensive glycemic control (hemoglobin A1c <6.0% versus 7%-7.9%), BP control (systolic BP <120 mm Hg versus <140 mm Hg) or fenofibrate versus placebo added to simvastatin on cardiovascular events and death. The glycemia trial lasted 3.7 years and participants were followed for another 6.5 years in ACCORDION, the ACCORD Follow-On Study. The post hoc primary composite kidney outcome was defined as incident macroalbuminuria, creatinine doubling, need for dialysis, or death by any cause. Cox proportional hazards regression estimated the effect of each intervention on the composite outcome and individual components. In secondary outcome analyses, competing risk regression was used to account for the risk of death in incident kidney outcomes. Analyses were adjusted for sociodemographics, randomization groups, and clinical factors. RESULTS: There were 988 cases of incident macroalbuminuria, 954 with doubling of creatinine, 351 requiring dialysis, and 1905 deaths. Hazard ratios (HRs) for the composite outcome with intensive glycemic, BP control, and fenofibrate use compared with standard therapy were 0.92 (95% confidence interval [95% CI], 0.86 to 0.98), 1.16 (95% CI, 1.05 to 1.28), and 1.16 (95% CI, 1.06 to 1.27). Multivariable, secondary outcome analyses showed that in the glycemia trial, only macroalbuminuria was significantly decreased (HR, 0.68; 95% CI, 0.59 to 0.77). In the BP and lipid trials, only creatinine doubling was affected (HR, 1.64; 95% CI, 1.30 to 2.06 and HR, 2.00; 95% CI, 1.61 to 2.49, respectively). CONCLUSIONS: In people with type 2 diabetes at high risk for cardiovascular disease, intensive glycemic control may result in a long-term reduction in macroalbuminuria; however, intensive BP control and fenofibrates may increase the risk for adverse kidney events.

[32] *Vassy JL, Brunette CA, Majahalme N et al.* **The Integrating Pharmacogenetics in Clinical Care (I-PICC) Study: Protocol for a point-of-care randomized controlled trial of statin pharmacogenetics in primary care**. Contemporary clinical trials 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30367991

ABSTRACT
BACKGROUND: The association between the SLCO1B1 rs4149056 variant and statin-associated muscle symptoms (SAMS) is well validated, but the clinical utility of its implementation in patient care is unknown. DESIGN: The Integrating Pharmacogenetics in Clinical Care (I-PICC) Study is a pseudo-cluster randomized controlled trial of SLCO1B1 genotyping among statin-naive primary care and women's health patients across the Veteran Affairs Boston Healthcare System. Eligible patients of enrolled primary care providers are aged 40-75 and have elevated risk of cardiovascular disease by American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Patients give consent by telephone in advance of an upcoming appointment, but they are enrolled only if and when their provider co-signs an order for SLCO1B1 testing, performed on a blood sample already collected in clinical care. Enrolled patients are randomly allocated to have their providers receive results through the electronic health record at baseline (PGx+arm) versus after 12months (PGx- arm). The primary outcome is the change in low-density lipoprotein cholesterol (LDL-C) after one year. Secondary outcomes are concordance with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for simvastatin prescribing, concordance with ACC/AHA guidelines for statin use, and incidence of SAMS. With 408 patients, the study has >80% power to exclude a between-group LDL-C difference of 10mg/dL (non-inferiority design) and to detect between-group differences of 15% in CPIC guideline concordance (superiority design). CONCLUSION: The outcomes of the I-PICC Study will inform the clinical utility of preemptive SLCO1B1 testing in the routine practice of medicine, including its proposed benefits and unforeseen risks.

[33] *Krysiak R, Szkrobka W, Okopien B*. **Atorvastatin potentiates the effect of selenomethionine on thyroid autoimmunity in euthyroid women with Hashimoto's thyroiditis**. Current medical research and opinion 2018:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30354702

ABSTRACT
OBJECTIVE: In many studies, selenium supplementation decreased serum titers of thyroid antibodies. The aim of the study was to investigate whether statin therapy determines selenium action on thyroid autoimmunity. METHODS: This prospective case-control study enrolled 42 euthyroid women with Hashimoto's thyroiditis and normal vitamin D status, 20 of whom had been treated atorvastatin (40 mg daily) for at least 6 months. All patients received selenomethionine (200 microg daily) for 6 months. Plasma levels of lipids, serum titers of thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) antibodies, as well as serum levels of thyrotropin, free thyroid hormones and 25-hydroxyvitamin D were determined at the beginning and at the end of the study. RESULTS: At baseline, there were no differences between both treatment arms in plasma lipids, titers of thyroid antibodies, serum levels of thyrotropin, free thyroid hormones and 25-hydroxyvitamin D. Selenometionine decreased titers of TPOAb (from 843 +/- 228 to 562 +/- 189 U/mL) and TgAb (from 795 +/- 286 to 501 +/- 216 U/mL) in

atorvastatin-treated women, as well as titers of TPOAb (from 892 +/- 247 to 705 +/- 205 U/mL) and TgAb (from 810 +/- 301 to 645 +/- 224 U/mL) in statin-naive women. The changes in antibody titers were more pronounced in women receiving atorvastatin (between-group difference: 94 [32, 156] [TPOAb]; 129 [52, 206] [TgAb]). Treatment-induced changes in TPOAb and TgAb correlated positively with baseline thyroid antibody titers. Circulating levels of lipids, free thyroxine, free triiodothyronine and 25-hydroxyvitamin D remained at similar levels throughout the study. CONCLUSIONS: The obtained results indicate that the decrease in titers of thyroid antibodies was potentiated by atorvastatin use.

[34] *Stefanutti C, Zenti MG*. **Lipoprotein Apheresis And Pcsk9-Inhibitors. Impact On Atherogenic Lipoproteins And Anti-Inflammatory Mediators In Familial Hypercholesterolaemia**. Current pharmaceutical design 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30360706
ABSTRACT
BACKGROUND: A combination therapy with PCSK9-inhibitors (PCSK9-I) and lipoprotein-apheresis (LA) may have synergistic effects on circulating lipid and lipoprotein levels, in particular in Homozygous Familial Hypercholesterolaemic (HoFH) subjects. The relationships between the above mentioned novel therapeutic approaches as highly effective treatment option for Dyslipidemia in Heterozygous Familial Hypercholesterolaemic (HeFH) patients deserve further investigation in larger datasets. OBJECTIVE: This review aims to present the role of lipoprotein apheresis in the management of falilial hypercholesterolemia and discuss the potential advantages and disadvantages of its combination with PCSK9 inhibitors. METHODS: A comprehensive literature search regarding lipoprotein apheresis in patients with familial hypercholesterolemia and its combination with PCSK9 inhibitors has been performed. RESULTS: LA is also a potent therapeutic player having impact on inflammation and related mediators. A large body of evidence on this is available. On the contrary, only few observations are available on PCSK9-I effects on inflammation. CONCLUSIONS: It is quite clear that further investigation on possible direct and/or indirect pleiotropic effects of PCSK9-I on inflammatory molecules is necessary and to be expected. Evidence on both arguments with regard to HoFH and HeFH, are reported in short.

[35] *Moore N, Duret S, Grolleau A et al.* **Previous Drug Exposure in Patients Hospitalised for Acute Liver Injury: A Case-Population Study in the French National Healthcare Data System**. Drug Saf 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30361989
ABSTRACT
INTRODUCTION: Acute liver injury (ALI) is a major reason for stopping drug development or removing drugs from the market. Hospitalisation for ALI is relatively rare for marketed drugs, justifying studies in large-scale databases such as the nationwide Systeme National des Donnees de Sante (SNDS), which covers 99% of the French population. METHODS: SNDS was queried over 2010-2014 for all hospital admissions for acute toxic liver injuries not associated with a possible other cause, using a case-population approach. Exposures of interest were drugs dispensed from 7 to 60 days before date of admission. Individual drugs were analysed by their frequency (if five or more cases) and by the ratio of exposed cases to the number of

exposed subjects and to exposed patient-time in the general population over the same timeframe. RESULTS: Over 5 years, 4807 cases of ALI were identified, mean age 54.5, 59% women, 76% exposed to at least one of 249 different drugs. Drugs most commonly identified were non-overdose paracetamol (31% of cases), esomeprazole or omeprazole (18%), phloroglucinol, domperidone, co-amoxiclav, furosemide, and atorvastatin (more than 250 cases each). When compared to population exposures, the highest per-person risks were observed with antimycobacterial antibiotics, with one case for 1000 or fewer users, followed by colestyramine and erythromycin (around 1/5300), antiepileptic drugs, anticoagulants, and anti-Alzheimer drugs (1/6000-1/10,000 users). When a person-time approach was considered, the drugs with the highest per-tablet risk were still the antituberculosis drugs, followed by a number of other antibiotics. CONCLUSIONS: This nationwide study describes drugs associated with ALI, according to absolute population burden and per-patient and per-tablet risk. Some of these associations may be spurious, others causal, and others yet were unexpected. Systematic analysis of drug classes will look for outliers within each class that could raise signals of unexpected hepatic toxicity.

[36] *Nehme MA, Upadhyay A*. **Ezetimibe in the Treatment of Patients with Metabolic Diseases**. European endocrinology 2013; 9:55-60.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30349611
ABSTRACT
Dyslipidemia is an established risk factor for cardiovascular disease. While statin therapy remains the most important component of dyslipidemia management, a substantial proportion of patients on statin monotherapy fails to achieve guideline-recommended lipid levels. Ezetimibe is a second-line lipid-lowering agent that reduces sterol absorption, and has a favorable effect on lipid profile. This article reviews studies examining the role of ezetimibe on lipid profile, metabolic biomarkers, and cardiovascular outcomes in individuals with metabolic diseases. Special focus is given to studies in patients with dyslipidemia, Type 2 diabetes, and the metabolic syndrome. The controversy surrounding the role of ezetimibe in mitigating atherosclerosis is also highlighted. The article concludes that the ezetimibe-statin combination improves lipid parameters and helps attain guideline-recommended lipid goals in patients with metabolic diseases. However, further research is needed to better understand the role of ezetimibe monotherapy, and the impact of ezetimibe on clinical cardiovascular outcomes.

[37] *Casey C, Woodside JV, McGinty A et al.* **Factors associated with serum 25-hydroxyvitamin D concentrations in older people in Europe: the EUREYE study**. European journal of clinical nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30367156
ABSTRACT
BACKGROUND/OBJECTIVES: We aimed to describe serum 25-hydroxyvitamin D (25OHD) concentrations in older Europeans and to investigate associations between 25OHD and lifestyle factors, including dietary intake and supplement use. SUBJECTS/METHODS: Men and women aged >/= 65 years were recruited from seven centres across north to south Europe. Serum 25OHD2 and 25OHD3 concentrations were measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) in 4495 samples and total 25OHD (25OHD2 + 25OHD3) was adjusted

for season of blood collection. RESULTS: The mean (25th, 75th quartile) of seasonally adjusted 25OHD was 46 (34, 65) nmol/L, with the highest concentration of 25OHD in Bergen [61 (49, 79) nmol/L], and the lowest in Paris [36 (24, 57) nmol/L)]. Vitamin D deficiency (25-50 nmol/L) and vitamin D insufficiency (50-75 nmol/L) were found in 41 and 33% of the population, respectively. In multivariable analysis controlled for confounders, seasonally adjusted 25OHD concentrations were significantly ($p < 0.05$) lower in smokers and participants with self-reported diabetes and higher with increasing dietary vitamin D, and supplement use with fish liver oil, omega-3, and vitamin D. Additionally, in further analysis excluding Bergen, 25OHD was associated with higher intakes of oily fish and increasing UVB exposure. We observed low concentrations of 25OHD in older people in Europe. CONCLUSIONS: Our findings of the higher 25OHD concentrations in supplement users (omega-3 fish oil, fish liver oil, vitamin D) add to current recommendations to reduce vitamin D deficiency. We were unable to fully assess the role of dietary vitamin D as we lacked information on vitamin D-fortified foods.

[38] *Liu J, Huang H, Shi S et al.* **Atorvastatin upregulates apolipoprotein M expression via attenuating LXRalpha expression in hyperlipidemic apoE-deficient mice**. Experimental and therapeutic medicine 2018; 16:3785-3792.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30344653
ABSTRACT
Apolipoprotein M (apoM) is a recently identified human apolipoprotein that is associated with the formation of high-density lipoprotein (HDL). Studies have demonstrated that statins may affect the expression of apoM; however, the regulatory effects of statins on apoM are controversial. Furthermore, the underlying mechanisms by which statins regulate apoM remain unclear. In the present study, in vivo and in vitro models were used to investigate whether the anti-atherosclerotic effects of statins are associated with its apoM-regulating effects and the underlying mechanism. Hyperlipidemia was induced by in apolipoprotein E-deficient mice by providing a high-fat diet. Atorvastatin was administered to hyperlipidemic mice and HepG2 cells to investigate its effect on apoM expression. The liver X receptor alpha (LXRalpha) agonist T0901317 was also administered together with atorvastatin to hyperlipidemic mice and HepG2 cells. The results revealed that atorvastatin increased apoM expression, which was accompanied with decreased expression of LXRalpha in the liver of hyperlipidemic apolipoprotein E-deficient mice and HepG2 cells. Additionally, apoM upregulation was inhibited following treatment with T0901317. In summary, atorvastatin exhibited anti-atherosclerotic effects by upregulating apoM expression in hyperlipidemic mice, which may be mediated by the inhibition of LXRalpha.

[39] *Petrov IS, Postadzhiyan AS, Tokmakova MP et al.* **Management of High and Very High-Risk Subjects with Familial Hypercholesterolemia: Results from an Observational Study in Bulgaria**. Folia medica 2018; 60:389-396.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30355848
ABSTRACT
BACKGROUND: Familial hypercholesterolaemia (FH) is a genetic disorder causing accelerated atherosclerosis and premature cardiovascular disease (CVD). This retrospective observational study examined the clinical characteristics and management of FH subjects in Bulgaria over a

12-month period. MATERIALS AND METHODS: Twelve cardiology sites participated in this study from May 2015 to May 2016. Eligible subjects had at least two routine low-density lipo-protein cholesterol (LDL C) measurements and a prescription for lipid-lowering therapy (LLT) at the start of the observation period. Mean values for gender, age and cardiovascular (CV) event history at baseline and LDL-C over time were estimated. RESULTS: Of the 220 eligible subjects, 196 fulfilled the criteria for FH diagnosis: 27 definite, 94 probable and 75 possible. Mean age at enrolment was 54.4 years and 64.1% of subjects were male. Mean CV risk classification at baseline was 26.8% high-risk (HR) and 73.2% very high-risk (VHR). Mean LDL-C was 5.6 mmol/L at enrolment and 4.1 mmol/L at last observation visit (12 months). The ESC/EAS Guideline LDL-C targets (applicable at the time of the study) were achieved by 14.5% of HR and 5.0% of VHR subjects. Most subjects (n=219) received statins. One subject was statin intolerant (ezetimibe therapy). Intensive statin treatment (atorvastatin 40-80 mg/daily and rosuvastatin 20-40 mg/daily) was used in 38.6% of individuals during the observation period and 10% of subjects received combination therapy (statin plus ezetimibe or other LLT). CONCLUSIONS: Most subjects with FH do not reach the ESC/EAS defined LDL-C targets. Early identification and physician education may improve FH management.

[40] *Bessac A, Cani PD, Meunier E et al.* **Inflammation and Gut-Brain Axis During Type 2 Diabetes: Focus on the Crosstalk Between Intestinal Immune Cells and Enteric Nervous System**. Frontiers in neuroscience 2018; 12:725.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30364179
ABSTRACT
The gut-brain axis is now considered as a major actor in the control of glycemia. Recent discoveries show that the enteric nervous system (ENS) informs the hypothalamus of the nutritional state in order to control glucose entry in tissues. During type 2 diabetes (T2D), this way of communication is completely disturbed leading to the establishment of hyperglycemia and insulin-resistance. Indeed, the ENS neurons are largely targeted by nutrients (e.g., lipids, peptides) but also by inflammatory factors from different origin (i.e., host cells and gut microbiota). Inflammation, and more particularly in the intestine, contributes to the development of numerous pathologies such as intestinal bowel diseases, Parkinson diseases and T2D. Therefore, targeting the couple ENS/inflammation could represent an attractive therapeutic solution to treat metabolic diseases. In this review, we focus on the role of the crosstalk between intestinal immune cells and ENS neurons in the control of glycemia. In addition, given the growing evidence showing the key role of the gut microbiota in physiology, we will also briefly discuss its potential contribution and role on the immune and neuronal systems.

[41] *Tabukashvili R, Kapetivadze V, Tchaava K et al.* **[THE COMBINED THERAPY IN HYPERTENSIVE PATIENTS WITH DYSLIPIDEMIA]**. Georgian medical news 2018:87-91.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30358547
ABSTRACT
Purpose - studying of clinical efficiensy of the combined therapy (Amlodipin with Valsartan and fibrates) in hypertensive patients with dyslipidemia. Were studied 58 patients (40-65 years old) with hypertension (the level of arterial pressure was >/=140/90 and </=180/110mm.Hg.RR).

The patients have been divided into 3 groups: Group 1(n=18, middle age 55,8+/-5,9) were given Amlodipin 10 mg., Fenofibrates 200mg. (Lipantil); Group 2 (n=20, middle age 58,0+/-4,9) were given Exforge (Amlodipin 5mg./Valsartan 160mg.) and Lipantil 200mg.; Group3 (n=20, middle age 57,0+/-6,9) were given Exforge. Research duration- 4 months. Was done collection of anamnesis, calculation of BMI, Heart rate, Blood pressure. Before and after observation were investigated: lipid range, Total Cholesterol, Triglycerides, High Density Lipoproteins, Low Density Lipoproteins by using W.Friedwald's formula. After 4 month in group 3 was found significantly reduce of Blood Pressure, systolic- 26,6%, (small er, Cyrillic<0,001), and diastolic - 18,0%; Significantly improve Lipid range. Were decreased the levels of Total Cholesterol -14,5%, Triglycerides-15,9%, Low Density Lipoproteins -20,2%. The combined therapy by Exforge and fibrates provides effective decrease in levels of blood pressure and improvement in lipid range in hypertensive patients with dyslipidemia.

[42] *Boulmpou A, Kartas A, Farmakis I et al.* **Motivational Interviewing to Support LDL-C Therapeutic Goals and Lipid-Lowering Therapy compliance in patients with Acute Coronary Syndromes (IDEAL-LDL) Study: Rationale and design**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30352291
ABSTRACT
BACKGROUND: Achieving low-density lipoprotein cholesterol (LDL-C) target levels after an acute coronary syndrome (ACS) is of paramount importance, often burdened by undertreatment and medication or lifestyle non-adherence issues. OBJECTIVE: We examined the effect of a patient-centered, physician-led motivational intervention following ACS on relevant secondary prevention aspects. METHODS: Design: The IDEAL-LDL is a single-center, randomized controlled clinical trial, conducted among patients hospitalized due to an ACS. Following discharge, all patients undergo a baseline assessment of lipid profile. Patients in the intervention group receive an in-person educational session and an informative leaflet, and also undergo two phone-based, motivational interviewing sessions at 1 and 6 months. These interventions emphasize on LDL-C goals, adherence to lipid-lowering medication, and healthy dietary-lifestyle habits, and are not provided to patients in the control group, who receive usual care. At 12-months after each patient's discharge, an in-person interview and lipid profile reassessment are performed. The primary outcomes are the assessment of LDL-C goal achievement (<70 mg/dL or >50% reduction from baseline levels) from baseline to 1 year as well as changes in medication adherence. Secondary outcomes relate to the incidence of the composite outcome of cardiovascular death, nonfatal myocardial infarction/stroke, need for myocardial revascularization and recurrent hospitalization during the follow-up period. DISCUSSION: This paper describes the protocol, design and rationale for key methodology for an ongoing clinical trial featuring a simple, feasible intervention. Similar adherence efficacy trials have not led to sufficient improvements, and there remains a gap regarding how adherence interventions should be implemented into clinical care.

[43] *Klose G, Nitschmann S*. **[Bezafibrate for primary biliary cholangitis : Bezafibrate in combination with ursodeoxycholic acid in primary biliary cholangitis (BEZURSO) trial]**. Internist (Berl) 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30357433
ABSTRACT

[44] *Fayad ZA, Swirski FK, Calcagno C et al.* **Monocyte and Macrophage Dynamics in the Cardiovascular System: JACC Macrophage in CVD Series (Part 3)**. Journal of the American College of Cardiology 2018; 72:2198-2212.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30360828
ABSTRACT
It has long been recognized that the bone marrow is the primary site of origin for circulating monocytes that may later become macrophages in atherosclerotic lesions. However, only in recent times has the complex relationship among the bone marrow, monocytes/macrophages, and atherosclerotic plaques begun to be understood. Moreover, the systemic nature of these interactions, which also involves additional compartments such as extramedullary hematopoietic sites (i.e., spleen), is only just becoming apparent. In parallel, progressive advances in imaging and cell labeling techniques have opened new opportunities for in vivo imaging of monocyte/macrophage trafficking in atherosclerotic lesions and at the systemic level. In this Part 3 of a 4-part review series covering the macrophage in cardiovascular disease, the authors intersect systemic biology with advanced imaging techniques to explore monocyte and macrophage dynamics in the cardiovascular system, with an emphasis on how events at the systemic level might affect local atherosclerotic plaque biology.

[45] *Lu JX, Guo C, Ou WS et al.* **Citronellal prevents endothelial dysfunction and atherosclerosis in rats**. Journal of cellular biochemistry 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30367511
ABSTRACT
BACKGROUND: Atherosclerosis is a chronical inflammatory disease in arterial walls, which is involved in oxidative stress and endothelial dysfunction. Aromatherapy is one of the complementary therapies that use essential oils as the major therapeutic agents to treat several diseases. Citronellal (CT) is a monoterpene predominantly formed by the secondary metabolism of plants, producing antithrombotic, antiplatelet, and antihypertensive activities. AIM: The aim of the present study is to explore whether aromatherapy with CT improves endothelial function to prevent the formation of atherosclerotic plaque in vivo. METHODS: An AS model in carotid artery was induced by balloon injury and vitamin D3 injection in rats fed with a high-fat diet. The size of the carotid atherosclerotic plaque was determined by ultrasound, oil red, and hematoxylin-eosin staining. Endothelial function was assessed by measuring acetylcholine-induced vessel relaxation in an organ chamber. RESULTS: Administrations of CT (50, 100, and 150 mg/kg) as well as lovastatin dramatically reduced the size of carotid atherosclerotic plaque in rats in a dose-dependent manner, compared with atherosclerotic rats fed with a high-fat diet plus balloon injury and vitamin D3. Mechanically, CT improved endothelial dysfunction, increased cell migration, and suppressed oxidative stress and inflammation in vascular endothelium in rats feeding on the high-fat diet plus balloon injury. Further, CT downregulated the protein levels of sodium-hydrogen exchanger 1 in rats with atherosclerosis. CONCLUSION: CT improves endothelial dysfunction and prevents the

growth of atherosclerosis in rats by reducing oxidative stress. Clinically, CT is potentially considered as a medicine to treat patients with atherosclerosis.

[46] *Chyzhyk V, Kozmic S, Brown AS et al.* **Extreme hypertriglyceridemia: Genetic diversity, pancreatitis, pregnancy, and prevalence**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30352774
ABSTRACT
BACKGROUND: Triglyceride (TG) concentrations >2000 mg/dL are extremely elevated and increase the risk of pancreatitis. OBJECTIVES: We characterized five cases and two kindreds and ascertained prevalence in a reference laboratory population. METHODS: Plasma lipids and DNA sequences of LPL, GPIHBP1, APOA5, APOC2, and LMF1 were determined in cases and two kindreds. Hypertriglyceridemia prevalence was assessed in 440,240 subjects. RESULTS: Case 1 (female, age 28 years) had TG concentrations >2000 mg/dL and pancreatitis since infancy. She responded to diet and medium-chain triglycerides, but not medications. During two pregnancies, she required plasma exchange for TG control. She was a compound heterozygote for a p.G236Gfs*15 deletion and a p.G215E missense mutation at LPL, as was one sister with hypertriglyceridemia and pancreatitis during pregnancy. Her father was heterozygous for the deletion and had hypertriglyceridemia and recurrent pancreatitis. Other family members had either the missense mutation or the deletion, and had hypertriglyceridemia but no pancreatitis. In kindred 2, three preschool children had severe hypertriglyceridemia and were homozygous for a GPIHBP1 p.T108R missense mutation. Case 5 (male, age 43 years) presented with pancreatitis and TG levels >5000 mg/dL and had heterozygous GPIHBP1 p.G175R and APOC2 intron 2-4G>C mutations. On diet, fenofibrate, fish oil, and atorvastatin in his TG concentration was 2526 mg/dL, but normalized to <100 mg/dL with added pioglitazone. In our population study, 60 subjects (0.014%) of 440,240 had TG concentrations >2000 mg/dL, and 66.7% were diabetic and had elevated insulin levels. CONCLUSIONS: Extreme hypertriglyceridemia is rare (0.014%); and during pregnancy, it may require plasma exchange.

[47] *Tscharre M, Herman R, Rohla M et al.* **Prognostic impact of familial hypercholesterolemia on long-term outcomes in patients undergoing percutaneous coronary intervention**. Journal of clinical lipidology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30344049
ABSTRACT
BACKGROUND: Patients with familial hypercholesterolemia (FH) are at increased risk for premature and subsequent cardiovascular disease. Data on long-term major adverse cardiovascular events (MACE) in patients with FH after percutaneous coronary intervention (PCI) in the era of high-intensity statins are scarce. OBJECTIVE: We assessed the prognostic impact of clinically diagnosed FH on long-term MACE, a composite of all-cause death, myocardial infarction, and ischemic stroke in patients admitted for stable coronary artery disease (SCAD) or acute coronary syndromes (ACSs) undergoing PCI. METHODS: FH was diagnosed according to the Dutch Lipid Clinic Network diagnosis criteria: "Unlikely FH" diagnosis was defined as 0 to 2 points, "possible FH" as 3 to 5 points, and "probable/definite FH" diagnosis as 6 or higher. RESULTS: From a total of 1550 eligible patients (47.4% were admitted for SCAD and 52.6% for ACS), 77 (5.0%) were classified as probable/definite FH, 332 (21.4%) as

possible FH, and 1141 (73.6%) as unlikely FH. Mean follow-up was 6.0 +/- 2.4 years. After adjustment for possible confounders, patients classified with probable or definite FH (hazard ratio [HR] 1.922 [95% confidence interval (CI) 1.220-2.999]; P = .004), but not patients with possible FH (HR 1.105 [95% CI 0.843-1.447]; P = .470) faced a significant, approximately 2-fold increased risk of MACE compared with patients with unlikely FH. CONCLUSION: After adjustment for confounders, patients with probable or definite FH faced an approximate 2-fold increased risk for long-term MACE compared with patients without FH despite the widespread use of high-intensity statins. The new option of proprotein convertase subtilisin/kexin type 9 gene inhibitors in addition to other current optimal lipid-lowering strategies might help to further improve clinical outcome in patients with probable/definite FH.

[48] *Cai XQ, Tian F, Han TW et al.* **Subclinical hypothyroidism is associated with lipid-rich plaques in patients with coronary artery disease as assessed by optical coherence tomography**. Journal of geriatric cardiology : JGC 2018; 15:534-539.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30344533
ABSTRACT
Background: Subclinical hypothyroidism (SCH) has recently been acknowledged as an unconventional risk factor for coronary artery disease (CAD) and characterized by poor prognosis, which may be due to atherosclerotic plaque characteristics. We conducted this study to observe coronary plaque characteristics in coronary artery disease patients with concomitant SCH. Methods: Patients with coronary artery disease were enrolled in the study and divided into an SCH group (patients, n = 26; plaques, n = 35) and a non-SCH group (patients, n = 52; plaques, n = 66). They were divided 1: 2 according to propensity-matched analysis including age, diabetes mellitus, gender, CAD severity and culprit vessel. Optical coherence tomography (OCT) imaging was performed on all patients, and images were analyzed by two independent investigators. Lipid-rich plaques (LRP), the precursor of vulnerable plaques, were defined as having more than one quadrant occupied with lipid pool. Maximum lipid arcs were simultaneously recorded. Fibrotic plaques and calcific plaques were also identified. The presence of coronary dissection, plaque erosion, thrombus, macrophage, calcific nodule, thin-cap fibroatheroma and micro channel were all noted. Results: The ratio of LRP in SCH group was significantly higher than that in non-SCH group (54% vs. 30.3%, P = 0.037). That was the case as well for the maximum lipid arcs value (181.5 degrees +/- 61.6 degrees vs. 142.1 degrees +/- 35.9 degrees , P = 0.046). While thin-cap fibroatheroma (TCFA) was detected, no difference was identified between the two groups in either TCFA ratio (20% vs. 16.7%, P = 0.579) or fibrous cap thickness (57.5 +/- 14.0 vs. 63.5 +/- 10.7 microm, P = 0.319). Other OCT characteristics such as dissection, plaque erosion, thrombus, macrophage shadow and calcific nodule were also similar. Conclusion: Higher ratio of LRP with greater lipid arc in SCH patients may be related to the plaque instability and poor prognosis in CAD patients with SCH.

[49] *Pei WN, Hu HJ, Liu F et al.* **C-reactive protein aggravates myocardial ischemia/reperfusion injury through activation of extracellular-signal-regulated kinase 1/2**. Journal of geriatric cardiology : JGC 2018; 15:492-503.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30364730
ABSTRACT

Background: Ischemia/reperfusion injury (IRI) is an inflammatory response that occurs when tissue is reperfused following a prolonged period of ischemia. Several studies have indicated that C-reactive protein (CRP) might play an important role in inducing IRI. However, the effects of CRP on myocardial IRI and the underlying mechanisms have not been fully elucidated. This study aimed to investigate the association between CRP and myocardial IRI and the underlying mechanisms. Methods: We simulated ischemia/reperfusion using oxygen-glucose deprivation/ reoxygenation (OGD/R) in neonatal Sprague-Dawley rat cardiomyocytes; reperfusion injury was induced by three hours of hypoxia with glucose and serum deprivation followed by one hour of reperfusion. Cell viability was tested with MTS assays, and cardiomyocyte damage was evaluated by lactate dehydrogenase (LDH) leakage. Mitochondrial membrane potential was measured using tetramethylrhodamine ethyl ester (TMRE) and mitochondrial permeability transition pore (mPTP) opening was measured using calcein/AM; both TMRE and caocein/AM were visualized with laser scanning confocal microscopy. In addition, we studied the signaling pathways underlying CRP-mediated ischemia/reperfusion injury via Western blot analysis. Results: Compared with the simple OGD/R group, after intervention with 10 microg/mL CRP, cell viability decreased markedly (82.36 % +/- 6.18% vs. 64.84% +/- 4.06%, P = 0.0007), and the LDH leakage significantly increased (145.3 U/L +/- 16.06 U/L vs. 208.2 U/L +/- 19.23 U/L, P = 0.0122). CRP also activated mPTP opening and reduced mitochondrial membrane potential during myocardial ischemia/reperfusion. Pretreatment with 1 microM atorvastatin (Ator) before CRP intervention protected cardiomyocytes from IRI. Mitochondrial KATP channel opener diazoxide and mPTP inhibitor cyclosporin A also offset the effects of CRP in this process. The level of phosphorylated extracellular-signal-regulated kinase (ERK) 1/2 was significantly higher after pre-treatment with CRP compared with the OGD/R group (170.4% +/- 3.00% vs. 93.53% +/- 1.94%, P < 0.0001). Western blot analysis revealed that Akt expression was markedly activated (184.2% +/- 6.96% vs. 122.7% +/- 5.30%, P = 0.0003) and ERK 1/2 phosphorylation significantly reduced after co-treatment with Ator and CRP compared with the level after CRP pretreatment alone. Conclusions: Our results suggested that CRP directly aggravates myocardial IRI in myocardial cells and that this effect is primarily mediated by inhibiting mitochondrial ATP-sensitive potassium (mitoKATP) channels and promoting mPTP opening. Ator counteracts these effects and can reduce CRP-induced IRI. One of the mechanisms of CRP-induced IRI may be related to the sustained activation of the ERK signaling pathway.

[50] *Parvar SL, Fitridge R, Dawson J, Nicholls SJ*. **Medical and lifestyle management of peripheral arterial disease**. Journal of vascular surgery 2018; 68:1595-1606.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30360849

ABSTRACT

OBJECTIVE: Peripheral arterial disease (PAD) is a global health issue associated with impaired functional capacity and elevated risk of major adverse cardiovascular events (MACEs). With changing risk factor profiles and an aging population, the burden of disease is expected to increase. This review considers evidence for the noninvasive management of PAD and makes clinical recommendations accordingly. METHODS: A comprehensive literature review was performed to examine the evidence for smoking cessation, exercise therapy, antiplatelet therapy, anticoagulant therapy, antihypertensive therapy, lipid-lowering therapy, and glycemic

control in diabetes for patients with PAD. RESULTS: Nicotine replacement, bupropion, and varenicline are safe and more effective than placebo in achieving smoking abstinence. Wherever it is practical and available, supervised exercise therapy is ideal treatment for intermittent claudication. Alternatively, step-monitored exercise can increase walking performance and the participant's compliance with less staff supervision. Clopidogrel is preferable to aspirin alone for all patients. However, small studies support the use of dual antiplatelet therapy after revascularization to improve limb outcomes. More recently, the addition of low-dose rivaroxaban to aspirin alone was proven to be more effective in reducing MACEs without a significant increase in major bleeding. However, the exact role of direct oral anticoagulant therapy in the management of PAD is still being understood. Evidence is emerging for more intensive blood pressure and lipid-lowering therapy than traditional targets. Whereas research in PAD is limited, there is clinical scope for an individualized approach to these risk factors. The management of diabetes remains challenging as glycemic control has not been demonstrated to improve macrovascular outcomes. Any potential impact of glycemic control on microvascular disease needs to be weighed against the risks of hypoglycemia. Sodium-glucose cotransporter 2 inhibitors appear to reduce MACEs, although caution is advised, given the increased incidence of lower limb amputation in clinical trials of canagliflozin. CONCLUSIONS: Medical and lifestyle management of PAD should aim to improve functional outcomes and to reduce MACEs. Smoking cessation counseling or pharmacotherapy is recommended, although new strategies are needed. Whereas supervised exercise therapy is ideal, there can be barriers to clinical implementation. Other initiatives are being used as an alternative to walking-based supervised exercise therapy. More studies are required to investigate the role of intensive glycemic, blood pressure, and dyslipidemia control in patients with PAD. Overall, a multifactorial approach is recommended to alter the natural history of this condition.

[51] *Slomski A*. **Fish Oil in Pregnancy Stimulates Growth in Children**. Jama 2018; 320:1631.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30357292
ABSTRACT

[52] *Pei E, Liu Y, Jiang W et al.* **Sleeve gastrectomy attenuates high fat diet-induced non-alcoholic fatty liver disease**. Lipids in health and disease 2018; 17:243.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30355361
ABSTRACT
BACKGROUND: A high-fat diet (HFD) is known to lead to obesity, and contributes to the progression of non-alcoholic fatty liver disease. The objective of this study was to evaluate the effects of sleeve gastrectomy (SG) on the progression of HFD-induced hepatic steatosis. METHODS: Fifteen 4-week-old, male Wistar rats were randomly assigned into three groups: NC, HFD + SHAM and HFD + SG. Their body weight, glucose-lipid metabolism, inflammation indices, hepatic steatosis and fibroblast growth factor 21 (FGF21) levels were measured. RESULTS: Postoperatively, body weights in the HFD + SHAM and HFD + SG group rats decreased during the first week. Thereafter, HFD + SG rats regained their body weight. Differences in insulin, homeostasis model assessment of insulin resistance, triglyceride, free fatty acid, tumor necrosis factor-alpha and monocyte chemotactic protein-1 levels were statistically significant across the

three groups (all P < 0.05). Interestingly, FGF21 levels in the HFD + SG group were markedly lower than in the HFD + SHAM group (P = 0.015), however, there were no differences in the NC group. Hematoxylin and eosin staining demonstrated that more vacuoles were present in the HFD + SHAM liver when compared to the HFD + SG liver. Oil-red O staining showed less red dots in the HFD + SG liver. CONCLUSIONS: Despite eating, surgical re-routing of the gut may prevent weight accumulation, regulate glucose-lipid metabolism and insulin sensitivity, control a chronic inflammatory state, change the secretion pattern of FGF21 and alleviate the severity of fatty liver.

[53] *Kleinauskiene R, Jonkaitiene R*. **Degenerative Aortic Stenosis, Dyslipidemia and Possibilities of Medical Treatment**. Medicina (Kaunas, Lithuania) 2018; 54.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30344255
ABSTRACT
Degenerative aortic stenosis (DAS) is the most frequently diagnosed heart valve disease in Europe and North America. DAS is a chronic progressive disease which resembles development of atherosclerosis. Endothelial dysfunction, lipid infiltration, calcification and ossification are evidenced in both diseases. The same risk factors such as older age, male sex, smoking, and elevated levels of lipids are identified. The effect of smoking, visceral obesity, metabolic syndrome, hypercholesterolemia, low-density lipoprotein, high-density lipoprotein, lipoprotein(a), adiponectin and apolipoprotein(a) on development of DAS are being studied. The search for genetic ties between disorders of lipid metabolism and DAS has been started. DAS is characterized by a long symptom-free period which can last for several decades. Aortic valve replacement surgery is necessary when the symptoms occur. The lipid-lowering therapy effect on stopping or at least slowing down the progression of DAS was studied. However, the results of the conducted clinical trials are controversial. In addition, calcium homeostasis, bone metabolism and calcinosis-reducing medication are being studied. Although prospective randomized clinical trials have not demonstrated any positive effect of statins used for slowing progression of the disease, statins are still recommended for patients with dyslipidemia. Recent study has suggested that a specific modification of treatment, based on severity of disease, may have a beneficial effect in patients with aortic sclerosis and mild DAS. New clinical studies analyzing new treatment possibilities which could correct the natural course of the disease and reduce the need for aortic valve replacement by surgery or transcatheter treatment interventions are needed.

[54] *Selak V, Jackson R, Poppe K et al.* **Are the benefits of aspirin likely to exceed the risk of major bleeds among people in whom aspirin is recommended for the primary prevention of cardiovascular disease?** The New Zealand medical journal 2018; 131:19-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30359352
ABSTRACT
AIM: The 2018 New Zealand Consensus Statement on cardiovascular disease (CVD) risk assessment and management recommends the use of aspirin in people aged less than 70 years with a five-year CVD risk >15% but without prior CVD. We determined whether the estimated number of CVD events avoided by taking aspirin is likely to exceed the number of additional major bleeds caused by aspirin in this patient population. METHOD: Major bleeding rates were

obtained from the PREDICT primary care study, a large New Zealand cohort of people eligible for CVD risk assessment, after excluding those with no other indications for (eg, established CVD) or contraindications/cautions (eg, prior major bleed) to aspirin use. We modelled the benefits (CVD events avoided) and harms (additional major bleeds) of aspirin for primary prevention of CVD over five years using hypothetical populations aged 40 to 79 years, stratified by sex, age-group and estimated five-year CVD risk. Two clinical scenarios were modelled, according to whether or not optimisation of lipid- and blood pressure-lowering therapy was required prior to aspirin initiation. RESULTS: In both clinical scenarios the number of CVD events prevented by aspirin over five years was estimated to be, on average, more than the number of bleeds caused by aspirin among people aged less than 70 years with estimated five-year CVD risk of >15%. However, the magnitude of the net benefit of aspirin was modest among people aged 60-69 years, particularly if lipid- and blood pressure-lowering therapy had not already been optimised. CONCLUSION: The benefits of aspirin are likely to exceed the risk of major bleeds among people in whom aspirin is recommended for the primary prevention of CVD. A more cautious approach to the use of aspirin is appropriate for people aged 60-69 years who are likely to have a smaller net benefit from aspirin, particularly those in whom lipid- and blood pressure-lowering therapy has not already been optimised or who have other bleeding risk factors, such as diabetes or smoking. More specific recommendations will be possible when bleeding risk equations are developed to complement the recently developed New Zealand CVD risk equations.

[55] *Stoekenbroek RM, Lambert G, Cariou B, Hovingh GK*. **Inhibiting PCSK9 - biology beyond LDL control**. Nature reviews. Endocrinology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30367179
ABSTRACT
Clinical trials have unequivocally shown that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) efficaciously and safely prevents cardiovascular events by lowering levels of LDL cholesterol. PCSK9 in the circulation is derived mainly from the liver, but the protein is also expressed in the pancreas, the kidney, the intestine and the central nervous system. Although PCSK9 modulates cholesterol metabolism by regulating LDL receptor expression in the liver, in vitro and in vivo studies have suggested that PCSK9 is involved in various other physiological processes. Although therapeutic PCSK9 inhibition could theoretically have undesired effects by interfering with these non-cholesterol-related processes, studies of individuals with genetically determined reduced PCSK9 function and clinical trials of PCSK9 inhibitors have not revealed clinically meaningful adverse consequences of almost completely eradicating PCSK9 from the circulation. The clinical implications of PCSK9 functions beyond lipid metabolism in terms of wanted or unwanted effects of therapeutic PCSK9 inhibition therefore appear to be limited. The objective of this Review is to describe the physiological role of PCSK9 beyond the LDL receptor to provide a rational basis for monitoring the effects of PCSK9 inhibition as these drugs gain traction in the clinic.

[56] *Ferro CJ, Mark PB, Kanbay M et al.* **Lipid management in patients with chronic kidney disease**. Nature reviews. Nephrology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30361677

ABSTRACT
An increased risk of cardiovascular disease, independent of conventional risk factors, is present even at minor levels of renal impairment and is highest in patients with end-stage renal disease (ESRD) requiring dialysis. Renal dysfunction changes the level, composition and quality of blood lipids in favour of a more atherogenic profile. Patients with advanced chronic kidney disease (CKD) or ESRD have a characteristic lipid pattern of hypertriglyceridaemia and low HDL cholesterol levels but normal LDL cholesterol levels. In the general population, a clear relationship exists between LDL cholesterol and major atherosclerotic events. However, in patients with ESRD, LDL cholesterol shows a negative association with these outcomes at below average LDL cholesterol levels and a flat or weakly positive association with mortality at higher LDL cholesterol levels. Overall, the available data suggest that lowering of LDL cholesterol is beneficial for prevention of major atherosclerotic events in patients with CKD and in kidney transplant recipients but is not beneficial in patients requiring dialysis. The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in CKD provides simple recommendations for the management of dyslipidaemia in patients with CKD and ESRD. However, emerging data and novel lipid-lowering therapies warrant some reappraisal of these recommendations.

[57] *Li K, Sinclair AJ, Zhao F, Li D*. **Uncommon Fatty Acids and Cardiometabolic Health**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30347833
ABSTRACT
Cardiovascular disease (CVD) is a major cause of mortality. The effects of several unsaturated fatty acids on cardiometabolic health, such as eicosapentaenoic acid (EPA) docosahexaenoic acid (DHA), alpha linolenic acid (ALA), linoleic acid (LA), and oleic acid (OA) have received much attention in past years. In addition, results from recent studies revealed that several other uncommon fatty acids (fatty acids present at a low content or else not contained in usual foods), such as furan fatty acids, n-3 docosapentaenoic acid (DPA), and conjugated fatty acids, also have favorable effects on cardiometabolic health. In the present report, we searched the literature in PubMed, Embase, and the Cochrane Library to review the research progress on anti-CVD effect of these uncommon fatty acids. DPA has a favorable effect on cardiometabolic health in a different way to other long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs), such as EPA and DHA. Furan fatty acids and conjugated linolenic acid (CLNA) may be potential bioactive fatty acids beneficial for cardiometabolic health, but evidence from intervention studies in humans is still limited, and well-designed clinical trials are required. The favorable effects of conjugated linoleic acid (CLA) on cardiometabolic health observed in animal or in vitro cannot be replicated in humans. However, most intervention studies in humans concerning CLA have only evaluated its effect on cardiometabolic risk factors but not its direct effect on risk of CVD, and randomized controlled trials (RCTs) will be required to clarify this point. However, several difficulties and limitations exist for conducting RCTs to evaluate the effect of these fatty acids on cardiometabolic health, especially the high costs for purifying the fatty acids from natural sources. This review provides a basis for better nutritional prevention and therapy of CVD.

Literature update week 43 (2018)

[58] *Murakami K, Livingstone MBE, Fujiwara A, Sasaki S*. **Breakfast in Japan: Findings from the 2012 National Health and Nutrition Survey**. Nutrients 2018; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30347762
ABSTRACT
We assessed breakfast in Japan using data from the 2012 National Health and Nutrition Survey. Dietary data were obtained from 1444 children (aged 6(-)11 years), 1134 adolescents (aged 12(-)17 years), 6531 younger adults (aged 18(-)49 years), and 13,343 older adults (aged >/= 50 years), using a one-day weighed dietary record. Overall, 97% of participants reported consuming breakfast. Compared with breakfast skippers, breakfast consumers had a higher daily diet quality score assessed by the Nutrient-Rich Food Index 9.3 (NRF9.3). For those who consumed breakfast, breakfast accounted for 20(-)25% of daily energy intake. In comparison with the contribution to energy, breakfast accounted for higher proportions of carbohydrate and riboflavin, and lower proportions of MUFA, n-3 PUFA, thiamin, and niacin, as well as vitamins B-6 and C. The overall diet quality (NRF9.3 score) was positively associated with breakfast intake of protein, n-6 PUFA, n-3 PUFA, carbohydrate, dietary fiber, and almost all micronutrients examined, and inversely with that of added sugar. For foods, the NRF9.3 score was positively associated with breakfast intake of rice, potatoes, pulses, vegetables, fruits, and eggs and inversely with that of bread, sugar, and soft drinks. The findings will be useful in developing dietary recommendations for a balanced breakfast among Japanese.

[59] *Chukkapalli SS, Ambadapadi S, Varkoly K et al.* **Impaired innate immune signaling due to combined Toll-like receptor 2 and 4 deficiency affects both periodontitis and atherosclerosis in response to polybacterial infection**. Pathogens and disease 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30351354
ABSTRACT
Plasma membrane-associated Toll-like receptor (TLR2 and TLR4) signaling contributes to oral microbe infection-induced periodontitis and atherosclerosis. We recently reported that either TLR2 or TLR4 receptor deficiency alters recognition of a consortium of oral pathogens, modifying host responses in periodontitis and atherosclerosis. We evaluated the effects of combined TLR2-/-TLR4-/- double knockout mice on innate immune signaling and induction of periodontitis and atherosclerosis after polybacterial infection with Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, and Fusobacterium nucleatum in a mouse model. Multispecies infections established gingival colonization in all TLR2-/-TLR4-/- mice and induced production of bacterial-specific IgG antibodies. In combined TLR2-/-TLR4-/- deficiency there was, however, reduced alveolar bone resorption and mild gingival inflammation with minimal migration of junctional epithelium and infiltration of inflammatory cells. This indicates a central role for TLR2 and TLR4 in periodontitis. Atherosclerotic plaque progression was markedly reduced in infected TLR2-/-TLR4-/- mice or in heterozygotes indicating a profound effect on plaque growth. However, bacterial genomic DNA was detected in multiple organs in TLR2-/-TLR4-/- mice indicating an intravascular dissemination from gingival tissue to heart, aorta, kidney, and lungs. TRL2 and TLR4 were dispensable for systemic spread after polybacterial infections but TLR2 and 4 deficiency markedly reduces atherosclerosis induced by oral bacteria.

Literature update week 43 (2018)

[60] *Xiang Q, Zhang X, Ma L et al.* **The association between the SLCO1B1, apolipoprotein E, and CYP2C9 genes and lipid response to fluvastatin: a meta-analysis**. Pharmacogenetics and genomics 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30363031
ABSTRACT
OBJECTIVE: The aim of this study was to determine the impact of the SLCO1B1, apolipoprotein E (ApoE), and CYP2C9 genotypes on the lipid-lowering efficacy of fluvastatin. METHODS: We performed electronic searches on the PubMed, Embase, and Cochrane Library databases to identify studies published through October 2017. Studies that reported the effect estimates with 95% confidence intervals (CIs) of total cholesterol (TC), triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein were included so that the different genotype categories could be compared. Weighted mean difference (WMD) was used to summarize the effect estimates. RESULTS: Six studies, involving a total of 1171 individuals, were included in the final analysis. We noted that the patient carrier SLCO1B1 521TT was associated with greater change in TC (WMD: -2.98; 95% CI: -5.12 to -0.84; P=0.006) and LDL (WMD: -5.58; 95% CI: -10.64 to -0.52; P=0.031) compared with 521TC or CC. Furthermore, the patient carrier ApoE*2/*3 showed more change in high-density lipoprotein compared with ApoE*3/*3 (WMD: 18.76; 95% CI: 8.97-28.55; P<0.001) and ApoE*3/*4 or *4/*4 (WMD: 22.51; 95% CI: 0.98-44.04; P=0.040). Finally, the CYP2C9 genotypes showed no correlation with the effects of fluvastatin on TC, triglyceride, and LDL. CONCLUSION: The findings of this study suggested that the SLCO1B1 and ApoE polymorphisms could influence the lipid-lowering effect of fluvastatin, whereas the CYP2C9 genotypes were not associated with the therapeutic effects of fluvastatin.

[61] *Pawar AM, LaPlante KL, Timbrook TT, Caffrey AR*. **Improved survival with continuation of statins in bacteremic patients**. SAGE open medicine 2018; 6:2050312118801707.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30364748
ABSTRACT
Objectives: Varying statin exposures in bacteremic patients have different impacts on mortality. Among patients with adherent statin use, we sought to evaluate the impact of statin continuation on inpatient mortality in bacteremic patients. Methods: A retrospective cohort study was conducted using Optum Clinformatics(TM) with matched Premier Hospital data (October 2009-March 2013). Patients with a primary diagnosis of bacteremia and 6 months of continuous enrollment prior to the admission, receiving antibiotics at least 2 days of antibiotics during the first 3 days of admission, were selected for inclusion. Furthermore, patients demonstrating adherent statin use based on 90 days of continuous therapy prior to admission were included. We then compared those continuing statin therapy for at least the first 5 days after admission and those not continuing during the admission. Results: Simvastatin (53.2%) and atorvastatin (33.8%) were the most commonly used statins among the 633 patients who met our inclusion and exclusion criteria. Propensity score adjusted Cox proportional hazards regression models demonstrated significantly lower inpatient mortality among those continuing statin therapy compared with those not continuing (n = 232 vs 401, adjusted hazard ratio 0.25, 95% confidence interval 0.08-0.79). Conclusion: Among patients adherent to their statin therapy prior to a bacteremia hospitalization, continued statin use after admission increased survival by 75% compared with those not continuing.

[62] *Yan MM, Wu SS, Ying YQ et al.* **Safety assessment of concurrent statin treatment and evaluation of drug interactions in China**. SAGE open medicine 2018; 6:2050312118798278.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30345053

ABSTRACT

Objectives: Acute muscle injury and potentially fatal rhabdomyolysis may occur with the use of statins and certain enzyme inhibitors, but data on this topic from China are quite limited. This study aimed to measure the concomitant exposure of patients to different statins and their enzyme inhibitors or interacting medications in 76 hospitals in six Chinese cities. Methods: Prescription database was retrieved from Hospital Prescription Analysis Cooperation Project from January 2015 to December 2015, covering 76 tertiary facilities in six cities in China. Every evidence-based enzyme inhibitor was included, and labeled enzyme inhibitors and other relevant information were identified and obtained using the Drug Safety Update from the UK Medicines and Healthcare Products Regulatory Agency. The proportions of different statin types among all patients and those co-medicated with their inhibitors were examined. Results: A total of 296,765 patients exposed to statins were included in this study. 80% of patients (n = 144,863, 80.5%) were concomitantly prescribed a CYP3A4-metabolized statin with an interacting drug during the study period. Among those prescribed a non-CYP3A4-metabolized statin, 40.0% of patients were concomitantly given an interacting drug, and approximately 20% of patients were concomitantly given a labeled inhibitor, predominantly calcium channel blockers, other statins, and fibrates. Rates of co-prescription were higher in patients aged over 65 years and in patients taking high-dose statins. Conclusion: Statins were frequently co-prescribed with metabolic inhibitors in China, where drug safety strategy on highlighting warnings and contraindications of statins are still lacking. For high-dose statins patients who are over 65 years and co-administered with any metabolic inhibitors, prescribers and pharmacists should be more concerned in order to prevent adverse drug reactions.