Literature update week 24 (2018)

[1] *Hadzi-Petrushev N, Dimovska K, Jankulovski N et al.* **Supplementation with Alpha-Tocopherol and Ascorbic Acid to Nonalcoholic Fatty Liver Disease's Statin Therapy in Men**. Advances in pharmacological sciences 2018; 2018:4673061.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29887885
ABSTRACT
Oxidative stress and inflammation contribute to the pathogenesis and progression of nonalcoholic fatty liver disease (NAFLD), and the control of lipid status by statins may help to stop the progression of NAFLD. We hypothesized that the addition of antioxidant vitamins C and E to atorvastatin therapy is associated with improved serum enzyme antioxidant status. NAFLD-related serum parameters and the activity of antioxidant enzymes, before and after 3 months of treatment, were determined in patients receiving atorvastatin alone or atorvastatin plus antioxidants. Compared to healthy controls, the patients, before receiving therapy, had increased catalase and glutathione reductase, with no significant difference in glutathione peroxidase activity. After the treatment, the levels of all three antioxidant markers were reduced to the same degree in both groups of patients, indicating therapy-induced lower level of reactive oxygen species production and/or improved nonenzymatic antioxidant mechanisms. Both therapies led to the normalization of the serum lipid profile and aminotransferase levels in the patients, but the reduction in CRP, although significant, did not reduce levels to those of the controls. The obtained results favor the notion that therapy with atorvastatin alone is equally efficient during the early stages of NAFLD, regardless of the addition of antioxidant vitamins. This trial is registered with TCTR20180425001.

[2] *Lowenstern A, Li S, Navar AM et al.* **Does clinician-reported lipid guideline adoption translate to guideline-adherent care? An evaluation of the Patient and Provider Assessment of Lipid Management (PALM) registry**. American heart journal 2018; 200:118-124.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29898839
ABSTRACT
BACKGROUND: The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guideline recommends statin treatment based on patients' predicted atherosclerotic cardiovascular disease (ASCVD) risk. Whether clinician-reported guideline adoption translates to implementation into practice is unknown. OBJECTIVES: We aimed to compare clinician lipid management in hypothetical scenarios versus observed practice. METHODS: The PALM Registry asked 774 clinicians how they would treat 4 hypothetical scenarios of primary prevention patients with: (1) diabetes; (2) high 10-year ASCVD risk (>/=7.5%) with high low-density lipoprotein cholesterol (LDL-C; >/=130 mg/dL); (3) low 10-year ASCVD risk (<7.5%) with high LDL-C (130-189mg/dL); or (4) primary and secondary prevention patients with persistently elevated LDL-C (>/=130 mg/dL) despite high-intensity statin use. We assessed agreement between clinician survey responses and observed practice. RESULTS: In primary prevention scenarios, 85% of clinicians reported they would prescribe a statin to a diabetic patient and 93% to a high-risk/high LDL-C patient (both indicated by guidelines), while 40% would prescribe statins to a low-risk/high LDL-C patient. In clinical practice, statin prescription rates were 68% for diabetic patients, 40% for high-risk/high LDL-C patients, and 50% for low-risk/high LDL-C patients. Agreement between hypothetical and observed practice was 64%, 39%, and 52% for patients with diabetes, high-risk/high LDL-C, and low-risk/high LDL-

C, respectively. Among patients with persistently high LDL-C despite high-intensity statin treatment, 55% of providers reported they would add a non-statin lipid-lowering medication, while only 22% of patients were so treated. CONCLUSIONS: While the majority of clinicians report adoption of the 2013 ACC/AHA guideline recommendations, observed lipid management decisions in practice are frequently discordant.

[3] *Jones HM, Fang Z, Sun W et al.* **Erratum: Atorvastatin exhibits anti-tumorigenic and anti-metastatic effects in ovarian cancer in vitro**. American journal of cancer research 2018; 8:915.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29888764
ABSTRACT
[This corrects the article on p. 2478 in vol. 7, PMID: 29312801.].

[4] *Long J, Zhang CJ, Zhu N et al.* **Lipid metabolism and carcinogenesis, cancer development**. American journal of cancer research 2018; 8:778-791.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29888102
ABSTRACT
The disorder of lipid metabolism is pathologically linked to hyperlipidemia, lipid storage disease, obesity and other related diseases. Intriguingly, recent studies have revealed that lipid metabolism disorders play an important role in carcinogenesis and development as well, since they cause abnormal expression of various genes, proteins, and dysregulation of cytokines and signaling pathways. More importantly, lipid-lowering drugs and anti-lipid per-oxidation treatment have been showing their advantages in clinic, in comparison with other anti-cancer drugs with high toxicity. Thus, further elucidation of molecular mechanism between lipid metabolism and cancer is essential in developing novel diagnostic biomarkers and therapeutic targets of human cancers.

[5] *Lai CQ, Smith CE, Parnell LD et al.* **Epigenomics and metabolomics reveal the mechanism of the APOA2-saturated fat intake interaction affecting obesity**. The American journal of clinical nutrition 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29901700
ABSTRACT
Background: The putative functional variant -265T>C (rs5082) within the APOA2 promoter has shown consistent interactions with saturated fatty acid (SFA) intake to influence the risk of obesity. Objective: The aim of this study was to implement an integrative approach to characterize the molecular basis of this interaction. Design: We conducted an epigenome-wide scan on 80 participants carrying either the rs5082 CC or TT genotypes and consuming either a low-SFA (<22 g/d) or high-SFA diet (>/=22 g/d), matched for age, sex, BMI, and diabetes status in the Boston Puerto Rican Health Study (BPRHS). We then validated the findings in selected participants in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study (n = 379) and the Framingham Heart Study (FHS) (n = 243). Transcription and metabolomics analyses were conducted to determine the relation between epigenetic status, APOA2 mRNA expression, and blood metabolites. Results: In the BPRHS, we identified methylation site cg04436964 as exhibiting significant differences between CC and TT participants consuming a high-SFA diet, but not among those consuming low-SFA. Similar results were observed in the

GOLDN Study and the FHS. Additionally, in the FHS, cg04436964 methylation was negatively correlated with APOA2 expression in the blood of participants consuming a high-SFA diet. Furthermore, when consuming a high-SFA diet, CC carriers had lower APOA2 expression than those with the TT genotype. Lastly, metabolomic analysis identified 4 pathways as overrepresented by metabolite differences between CC and TT genotypes with high-SFA intake, including tryptophan and branched-chain amino acid (BCAA) pathways. Interestingly, these pathways were linked to rs5082-specific cg04436964 methylation differences in high-SFA consumers. Conclusions: The epigenetic status of the APOA2 regulatory region is associated with SFA intake and APOA2 -265T>C genotype, promoting an APOA2 expression difference between APOA2 genotypes on a high-SFA diet, and modulating BCAA and tryptophan metabolic pathways. These findings identify potential mechanisms by which this highly reproducible gene-diet interaction influences obesity risk, and contribute new insights to ongoing investigations of the relation between SFA and human health. This study was registered at clinicaltrials.gov as NCT03452787.

[6] *Muller HH*. **Effect of mipomersen on LDL-cholesterol in patients with severe LDL-hypercholesterolaemia and atherosclerosis treated by lipoprotein apheresis: Corrections of the report on the randomized MICA-study**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891439
ABSTRACT

[7] *Waldmann E, Vogt A, Crispin A et al.* **Reply to: "Effect of mipomersen on LDL-cholesterol in patients with severe LDL-hypercholesterolaemia and atherosclerosis treated by lipoprotein apheresis: Corrections of the report on the randomized MICA-study"**. Atherosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29903466
ABSTRACT

[8] *Giangreco F, Hofinger S, Bakalis E, Zerbetto F*. **Impact of the green tea ingredient epigallocatechin gallate and a short pentapeptide (Ile-Ile-ala-Glu-Lys) on the structural organization of mixed micelles and the related uptake of cholesterol**. Biochimica et biophysica acta 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29886279
ABSTRACT
BACKGROUND: High levels of blood cholesterol are conventionally linked to an increased risk of developing cardiovascular disease (Grundy, 1986). Here we examine the molecular mode of action of natural products with known cholesterol-lowering activity, such as for example the green tea ingredient epigallocatechin gallate and a short pentapeptide, Ile-Ile-Ala-Glu-Lys. METHODS: Molecular Dynamics simulations are used to gain insight into the formation process of mixed micelles and, correspondingly, how active agents epigallocatechin gallate and Ile-Ile-Ala-Glu-Lys could possibly interfere with it. RESULTS: Self-assembly of physiological micelles occurs on the order of 35-50ns; most of the structural properties of mixed micelles are unaffected by epigallocatechin gallate or Ile-Ile-Ala-Glu-Lys which integrate into the micellar surface; the diffusive motion of constituting lipids palmitoyl-oleoyl-phosphatidylcholine and cholesterol is significantly down-regulated by both epigallocatechin gallate and Ile-Ile-Ala-Glu-

Lys; CONCLUSIONS: The molecular mode of action of natural compounds epigallocatechin gallate and Ile-Ile-Ala-Glu-Lys is a significant down-regulation of the diffusive motion of micellar lipids. GENERAL SIGNIFICANCE: Natural compounds like the green tea ingredient epigallocatechin gallate and a short pentapeptide, Ile-Ile-Ala-Glu-Lys, lead to a significant down-regulation of the diffusive motion of micellar lipids thereby modulating cholesterol absorption into physiological micelles.

[9] *Soko ND, Masimirembwa C, Dandara C*. **A cost effective RFLP method to genotype Solute carrier organic anion 1B1 (SLCO1B1) c.1929A>C (p.Leu643Phe, rs34671512); a variant with potential effect on rosuvastatin pharmacokinetics**. BMC research notes 2018; 11:384.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29898760
ABSTRACT
OBJECTIVE: This study describes a restriction fragment polymorphism protocol for rapidly screening the polymorphism SLCO1B1 c.1929A>C in genomic DNA samples. The polymorphism SLCO1B1 c.1929A>C has been associated with increased activity resulting in increased hepatic uptake of drugs. Currently SLCO1B1 c.1929A>C is genotyped using direct sequencing techniques and 5' nuclease based assays which can be cost prohibiting in resource limited settings. The aim of this study therefore was to design and validate a cost effective RFLP for genotyping the SLCO1B1 c.1929A>C polymorphism. This study was designed to investigate the effect of the polymorphism SLCO1B1 c.1929A>C on interindividual variability in rosuvastatin pharmacokinetics in healthy volunteers of African descent. RESULTS: We describe a restriction fragment length polymorphism method to genotype SLCO1B1 c.1929A>C polymorphism using the restriction enzyme Ase1. A student's t test with Welch correction was used to establish association between the SLCO1B1 c.1929A>C variant and rosuvastatin exposure. The frequency of the SLCO1B1 c.1929C allele amongst Zimbabweans was 6%. The SLCO1B1 c.1929C allele was associated with a 75% reduction ($P < 0.001$) in rosuvastatin exposure when compared to individuals carrying the wild type SLCO1B1 c.1929A allele. Polymorphism c.1929A>C may therefore play a significant role in rosuvastatin response. The RFLP method is quick and cost effective.

[10] *Laxy M, Wilson ECF, Boothby CE, Griffin SJ*. **How good are GPs at adhering to a pragmatic trial protocol in primary care? Results from the ADDITION-Cambridge cluster-randomised pragmatic trial**. BMJ open 2018; 8:e015295.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29903781
ABSTRACT
OBJECTIVE: To assess the fidelity of general practitioners' (GPs) adherence to a long-term pragmatic trial protocol. DESIGN: Retrospective analyses of electronic primary care records of participants in the pragmatic cluster-randomised ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care)-Cambridge trial, comparing intensive multifactorial treatment (IT) versus routine care (RC). Data were collected from the date of diagnosis until December 2010. SETTING: Primary care surgeries in the East of England. STUDY SAMPLE/PARTICIPANTS: A subsample (n=189, RC arm: n=99, IT arm: n=90) of patients from the ADDITION-Cambridge cohort (867 patients), consisting of patients 40-69 years old with screen-detected diabetes mellitus. INTERVENTIONS: In the RC arm treatment

was delivered according to concurrent treatment guidelines. Surgeries in the IT arm received funding for additional contacts between GPs/nurses and patients, and GPs were advised to follow more intensive treatment algorithms for the management of glucose, lipids and blood pressure and aspirin therapy than in the RC arm. OUTCOME MEASURES: The number of annual contacts between patients and GPs/nurses, the proportion of patients receiving prescriptions for cardiometabolic medication in years 1-5 after diabetes diagnosis and the adherence to prescription algorithms. RESULTS: The difference in the number of annual GP contacts (beta=0.65) and nurse contacts (beta=-0.15) between the study arms was small and insignificant. Patients in the IT arm were more likely to receive glucose-lowering (OR=3.27), ACE-inhibiting (OR=2.03) and lipid-lowering drugs (OR=2.42, all p values <0.01) than patients in the RC arm. The prescription adherence varied between medication classes, but improved in both trial arms over the 5-year follow-up. CONCLUSIONS: The adherence of GPs to different aspects of the trial protocol was mixed. Background changes in healthcare policy need to be considered as they have the potential to dilute differences in treatment intensity and hence incremental effects. TRIAL REGISTRATION NUMBER: ISRCTN86769081.

[11] *Santos C, Dourado DM, Silva B et al.* **Effect of Ischemic Postconditioning and Atorvastatin in the Prevention of Remote Lung Reperfusion Injury**. Brazilian journal of cardiovascular surgery 2018; 33:115-121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29898139
ABSTRACT
OBJECTIVE: The aim of the present study was to evaluate the ability of ischemic postconditioning, atorvastatin and both associated to prevent or minimize reperfusion injury in the lung of rats subjected to ischemia and reperfusion by abdominal aortic clamping. METHODS: We used 41 Wistar norvegic rats, which were distributed into 5 groups: ischemia and reperfusion (I/R), ischemic postcondictioning (IPC), postconditioning + atorvastatin (IPC+A), atorvastatin (A) and SHAM. It was performed a medium laparotomy, dissection and isolation of the infra-renal abdominal aorta; except for the SHAM group, all the others were submitted to the aortic clamping for 70 minutes (ischemia) and posterior clamp removal (reperfusion, 70 minutes). In the IPC and IPC+A groups, postconditioning was performed between the ischemia and reperfusion phases by four cycles of reperfusion and ischemia lasting 30 seconds each. In the IPC+A and A groups, preceding the surgical procedure, administration of 3.4 mg/day of atorvastatin was performed for seven days by gavage. After the surgical procedure, the right caudal lobe was removed from the lung for histological study, using tissue injury score ranging from grade 1 (normal tissue) to grade 4 (intense lesion). RESULTS: The mean lung injury was 3.6 in the I/R group, 1.6 in the IPC group, 1.2 in the IPC+A group, 1.2 in the A group, and 1 in the SHAM group (P<0.01). CONCLUSION: Ischemic postconditioning and atorvastatin were able to minimize lung reperfusion injury, alone or in combination.

[12] *Shigiyama F, Kumashiro N, Fuchigami A, Hirose T*. **Rationale and design of study of dapagliflozin versus sitagliptin treatment efficacy on prevention of cardiovascular risk factors in type 2 diabetes patients: the DIVERSITY-CVR study**. Cardiovascular diabetology 2018; 17:86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29895330
ABSTRACT

BACKGROUND: Recent studies reported that sodium glucose cotransporter 2 (SGLT2) inhibitors reduced the cardiovascular morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) compared to placebo in contrast to no reduction with dipeptidyl peptidase 4 (DPP4) inhibitors. However, there are no comparative studies on the effects of SGLT2 inhibitors and DPP4 inhibitors on HbA1c, body weight and hypoglycemia as risk factors of cardiovascular diseases. The aim of the present ongoing study is to compare the effects of dapagliflozin, a SGLT2 inhibitor, with those of sitagliptin, a DPP4 inhibitor, on cardiovascular risk factors in T2DM patients with inadequate glycemic control. METHODS: The study of dapagliflozin versus sitagliptin treatment efficacy on prevention of cardiovascular risk factors in T2DM patients (DIVERSITY-CVR study) is a prospective, randomized, open-label, blinded-endpoint, parallel-group, comparative study. A total of 340 T2DM patients treated with metformin alone or with no glucose-lowering agents (hemoglobin A1c >/= 7.0 and < 10.0%) will be randomized into the dapagliflozin group (5-10 mg/day, n = 170) and the sitagliptin group (50-100 mg/day, n = 170), and treated for 24 weeks. The primary endpoint is the rate of achieving a composite endpoint of the following three items at 24th week; (1) HbA1c < 7.0%; (2) body weight loss of >/= 3.0% from baseline; (3) avoidance of hypoglycemia. Hypoglycemia will be monitored using the flash glucose monitoring system. The secondary outcomes include each component of the primary endpoint, plus indices of lipid metabolism, and evaluations related to safety. CONCLUSIONS: There is lack of solid information on differences in the therapeutic effects of SGLT2 inhibitors and DPP4 inhibitors on multiple risk factors for cardiovascular diseases. It is anticipated that the results of the DIVERSITY-CVR study provides useful clinical data on the management of patients with T2DM, including reducing the risk of CVD. The results of this study will become available in 2019. Trial registration University Hospital Medical Information Network Clinical Trial Registry (UMIN000028014). Registered 30 June 2017.

[13] *Ma CY, Xu ZY, Wang SP et al.* **Change of Inflammatory Factors in Patients with Acute Coronary Syndrome**. Chinese medical journal 2018; 131:1444-1449.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29893361

ABSTRACT

Background: Acute coronary syndrome (ACS) is closely related to unstable plaques and secondary thrombosis. The inflammatory cells in plaques and their inflammatory products may be the cause for plaque instability and ruptures. The study aimed to disclose the changes of inflammatory factors including serum intracellular adhesion molecule-1 (ICAM-1), chitinase-3-like protein 1 (YKL-40), and lipoprotein-associated phospholipase A2 (Lp-PLA2) in patients with ACS and its clinical significance. Methods: A total of 120 patients with coronary heart disease (CHD) were categorized into 2 groups: 69 with ACS and 51 with stable angina pectoris (SAP); 20 patients with chest pain and normal angiography served as a control group. The 120 patients with CHD were categorized into single-vessel disease group, double-vessel disease group, and three-vessel disease group based on the number of coronary artery stenosis. The severity of coronary artery stenosis was quantified based on coronary angiography using Gensini score. They were further divided into mild CHD group with its Gensini score <26 (n = 36), moderate CHD group with its Gensini score being 26-54 (n = 48) and severe CHD group with its Gensini score >54 (n = 36). Serum levels of ICAM-1, YKL-40, and Lp-PLA2 of different groups were determined by enzyme-linked immunosorbent assay. Correlation between ICAM-1, YKL-40, Lp-

PLA2, and Gensini score was analyzed. Results: The levels of serum inflammatory factors ICAM-1, YKL-40, and Lp-PLA2 were significantly higher in the ACS group than those in control group and SAP group (all P < 0.05); and compared with control group, no significant difference was observed in terms of the serum ICAM-1, YKL-40, and Lp-PLA2 levels in the SAP group (P > 0.05).The levels of serum ICAM-1, YKL-40, and Lp-PLA2 were not significantly different among control group, single-vessel disease group, double-vessel disease group, and three-vessel disease group (all P > 0.05). The levels of serum ICAM-1, YKL-40, and Lp-PLA2 were not significantly different among control group, mild CHD group (Gensini score <26), moderate CHD group (Gensini score 26-54), and severe CHD group (Gensini score >54) (all P > 0.05). Nonparametric Spearman correlation analysis showed that the levels of serum ICAM-1, YKL-40, and Lp-PLA2 were not correlated with the Gensini score in CHD patients (r = 0.093, r = -0.149, and r = -0.085, all P > 0.05; respectively). Conclusions: The serum levels of ICAM-1, YKL-40, and Lp-PLA2 were correlated with different clinical types of CHD, but not well correlated the severity and extent of artery stenosis, suggesting that ICAM-1, YKL-40, and Lp-PLA2 might be involved in occurrence of instability of atherosclerotic plaque, and might reflect the severity of CHD mostly through reflecting the plaque stability.

[14] *Bohula EA, Wiviott SD, Giugliano RP et al.* **Response by Bohula et al to Letters Regarding Article, "Prevention of Stroke With the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 137:2662-2663.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891625
ABSTRACT

[15] *Cordero A, Bertomeu-Gonzalez V, Rodriguez-Manero M*. **Letter by Cordero et al Regarding Article, "Prevention of Stroke With the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 137:2658-2659.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891623
ABSTRACT

[16] *Del Pinto R, Ferri C, Borghi C*. **Letter by Del Pinto et al Regarding Article, "Prevention of Stroke With the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 137:2654-2655.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891621
ABSTRACT

[17] *Koh KK*. **Letter by Koh Regarding Article, "Prevention of Stroke With the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 137:2660-2661.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891624
ABSTRACT

[18] *Thomopoulos C, Michalopoulou H*. **Letter by Thomopoulos and Michalopoulou Regarding Article, "Prevention of Stroke With the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"**. Circulation 2018; 137:2656-2657.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891622
ABSTRACT

[19] *Kamari VE, Hileman CO, Gholam PM et al.* **Statin Therapy Does Not Reduce Liver Fat Scores in Patients Receiving Antiretroviral Therapy for HIV Infection**. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29908359
ABSTRACT
BACKGROUND & AIMS: Therapies are needed to limit progression of fatty liver diseases in patients with HIV infection. We analyzed data from a prospective study of the effects of rosuvastatin (a statin) on hepatic steatosis in HIV-positive adults. METHODS: We performed secondary analysis of data from a double-blind trial of adult patients with HIV infection (78% male; 68% African American; mean age, 46 years; body mass index, 29 kg/m(2); HIV1 RNA<1000 copies/mL; LDL-cholesterol <130 mg/dL) receiving antiretroviral therapy. The patients were randomly assigned to groups given 10 mg daily rosuvastatin (n=72) or placebo (n=75). Demographic and clinical data were collected, and blood samples were analyzed. Changes in liver fat score (LFS, a composite score calculated from metabolic and liver function parameters) and markers of systemic inflammation and immune activation were assessed through 96 weeks of drug or placebo administration. We performed multivariable linear and logistic regressions to study relationships among variables. RESULTS: The placebo and rosuvastatin groups each had significant increases in LFS, compared to baseline, at 96 weeks (P=.01 and P<.01; P=.49 for difference increase between groups). Baseline LFS was independently associated with blood level of C-X-C motif chemokine ligand 10 (CXCL10) (P=.04) and soluble CD163 molecule (P=.01). After we adjusted for baseline characteristics, an increase in LFS over time was significantly associated with blood level of CXCL10 (P=.04), insulin resistance (P<.01), and viral load (P=.02), but not rosuvastatin use (P=.06). CONCLUSION: In a secondary analysis of data from a trial of patients receiving treatment for HIV infection, hepatic steatosis increased over time, regardless of statin treatment, and was independently associated with markers of immune activation. Patients who received rosuvastatin appeared to have a nonsignificant increase hepatic steatosis over 96 weeks. Despite their ability to reduce risk of cardiovascular disease, statins do not appear to reduce hepatic steatosis. Clinicaltrials.gov no: NCT01218802.

[20] *Osowska S, Kunecki M, Sobocki J et al.* **Effect of changing the lipid component of home parenteral nutrition in adults**. Clinical nutrition (Edinburgh, Scotland) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29907355
ABSTRACT
BACKGROUND: The effect of different lipid emulsions (LEs) within the parenteral nutrition (PN) regimen of adult home PN (HPN) patients is not clear. This study investigated the effect of

changing adult HPN patients from a soybean oil based LE (Intralipid) to either a fish oil containing LE (providing n-3 fatty acids) (SMOFLipid) or an olive oil based LE (ClinOleic). METHODS: Thirty two adults receiving long-term HPN with Intralipid as the LE were transferred to receive either SMOFLipid (n = 13) or ClinOleic (n = 19) for 60 days. Liver function markers, cholesterol, triglycerides, a full profile of fatty acids, and several cytokines were measured at study entry and after 60 days. RESULTS: SMOFLipid did not affect liver function markers, blood lipids or plasma cytokines. ClinOleic lowered both gamma-glutamyltranspeptidase (P = 0.044) and interleukin-8 (P = 0.030) concentrations. Both LEs induced marked changes in the fatty acid profile of plasma. SMOFLipid resulted in significant decreases in the proportions of linoleic acid, several other n-6 fatty acids and the essential fatty acid (EFA) deficiency indicator mead acid and significant increases in the proportions of the n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. ClinOleic resulted in significant decreases in the proportions of some saturated fatty acids, linoleic acid, several n-6 fatty acids, all n-3 fatty acids and mead acid and a significant increase in the proportion of oleic acid. The ratio of mead to arachidonic acid in plasma was not altered by either SMOFLipid or ClinOleic. No patient had a mead acid to arachidonic acid ratio of >0.2, the cut-off used to indicate EFA deficiency. CONCLUSION: Both SMOFLipid and ClinOleic significantly alter the fatty acid profile of plasma in adult HPN patients previously using Intralipid. Neither LE induces EFA deficiency in these patients. SMOFLipid did not alter liver function markers or inflammation. In contrast, ClinOleic decreased some, though not all, markers of liver function and inflammation. SMOFLipid and ClinOleic may both be considered for use in adult HPN patients.

[21] *Reiss AB, Shah N, Muhieddine D et al.* **PCSK9 in cholesterol metabolism: from bench to bedside**. Clinical science (London, England : 1979) 2018; 132:1135-1153.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29895529

ABSTRACT

Dyslipidemia, and specifically elevated low-density lipoprotein (LDL) cholesterol, is one of the most important cardiovascular risk factors. Statins are considered first line therapy for the primary and secondary prevention of cardiovascular disease. However, statins may not be adequate treatment for elevated circulating LDL levels and are ineffective in certain familial hypercholesterolemias. The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9), a regulatory protein that affects LDL receptors, offers a new alternative for these patients. Moreover, gain-of-function PCSK9 mutations were discovered to be the root cause of familial autosomal dominant hypercholesterolemia. Inhibition of PSCK9 reduces plasma LDL levels, even in patients for whom statins are ineffective or not tolerated. Alirocumab and evolocumab, human monoclonal antibodies that inhibit PCSK9, have been approved to lower LDL levels. While there are drawbacks to these treatments, including adverse events, administration by subcutaneous injection, and high cost, these drugs are indicated for the treatment of atherosclerotic cardiovascular disease and familial hypercholesterolemia as adjunct to diet and maximally tolerated statin therapy. PCSK9 inhibitors may work synergistically with statins to lower LDL. Novel approaches to PCSK9 inhibition are currently in development with the aim of providing safe and effective treatment options to decrease cardiovascular event burden, ideally at lower cost and with oral bioavailability.

Literature update week 24 (2018)

[22] *Packard CJ*. **Determinants of Achieved LDL Cholesterol and "Non-HDL" Cholesterol in the Management of Dyslipidemias**. Current cardiology reports 2018; 20:60.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29904807
ABSTRACT
PURPOSE OF REVIEW: The advent of combination therapy to provide LDL lowering beyond that achieved with statins necessitates the development of greater understanding of how drugs work together, what changes occur in key lipoprotein fractions, and what residual risk remains. RECENT FINDINGS: Clinical trials of agents that, when added to statins, generate profound LDL lowering have been successful in reducing further the risk of cardiovascular disease. LDL cholesterol can be now decreased to unprecedented levels, so the focus of attention then shifts to other apolipoprotein B-containing, atherogenic lipoprotein classes such as lipoprotein(a) and remnants of the metabolism of triglyceride-rich particles. "Non-HDL cholesterol" is used increasingly (especially if measured in the non-fasting state) as a more comprehensive index of risk. Metabolic studies reveal how current drugs act in combination to achieve profound lipid lowering. However, care is needed in interpreting achieved LDLc and non-HDLc levels in the emerging treatment paradigm.

[23] *Gitt AK, Lautsch D, Ferrieres J et al.* **Contemporary data on treatment practices for low-density lipoprotein cholesterol in 6794 patients with stable coronary heart disease across the world**. Data in brief 2018; 18:1937-1940.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29904698
ABSTRACT
DYSIS II CHD was a longitudinal, observational study in 6794 patients from 18 countries. They were attending an outpatient physician appointment for coronary heart disease (CHD). 6370 patients (93.8%) were on active lipid lowering therapy (LLT). The mean atorvastatin dose equivalent was 25mg per day and 10.5% received ezetimibe in combination with a statin. The mean low-density lipoprotein cholesterol (LDL-C) level was 88mg/dL, with 29.4% of patients displaying a level below the 70mg/dL target for very high-risk subjects. Conclusion: While more than 90% of patients with CHD were on lipid lowering drugs, only three out of ten patients achieved their LDL-C target value.

[24] *Yuan C, Hu J, Parathath S et al.* **Human Aldose Reductase Expression Prevents Atherosclerosis Regression in Diabetic Mice**. Diabetes 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29891593
ABSTRACT
Guidelines to reduce cardiovascular risk in diabetes include aggressive LDL lowering, but benefits are attenuated compared to those in patients without diabetes. Consistent with this, we have reported in mice that hyperglycemia impaired atherosclerosis regression. Aldose reductase (AR) is thought to contribute to clinical complications of diabetes by directing glucose into pathways producing inflammatory metabolites. Mice have low levels of AR, thus, raising them to human levels would be a more clinically relevant model to study changes in diabetes under atherosclerosis regression conditions. Donor aortae from western diet-fed Ldlr(-/-) mice were transplanted into normolipidemic wild-type, Ins2Akita (Akita(+/-), insulin-deficient), human AR (hAR) transgenic, or Akita(+/-) /hAR mice. Akita(+/-) mice had impaired plaque

regression as measured by changes in plaque size and the contents of CD68+ cells (macrophages), lipids, and collagen. Supporting synergy between hyperglycemia and hAR were the even more pronounced changes in these parameters in Akita(+/-) /hAR mice, which had atherosclerosis progression in spite of normolipidemia. Plaque CD68+ cells from the Akita(+/-) /hAR mice had increased oxidant stress and expression of inflammation-associated genes, but decreased expression of anti-inflammatory genes. In summary, hAR expression amplifies impaired atherosclerosis regression in diabetic mice, likely by interfering with the expected reduction in plaque macrophage inflammation.

[25] *Ferrieres J, Lautsch D, Gitt AK et al.* **Body Mass Index impacts the choice of lipid lowering treatment with no correlation to blood cholesterol - findings from 52,916 patients in the Dyslipidemia International Study (DYSIS)**. Diabetes Obes Metab 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29888459
ABSTRACT
A high body mass index (BMI) is associated with increased cardiovascular risk. We sought to identify whether BMI influences the choice of lipid lowering treatment in a large, real world cohort of 52,916 patients treated with statins. The Dyslipidemia International Study (DYSIS) is a cross-sectional, observational, multicenter study in statin-treated patients>/=45 years of age from 30 countries. 1.1% were underweight (BMI<18.5 kg/m(2)), 33.1% had normal weight (BMI 18.5 to 24.9 kg/m(2)), 41.5% were overweight (BMI 25 to 29.9 kg/m(2)), 17.1% had class I obesity (BMI 30.0 to 34.9 kg/m(2)), 5.0% had class II obesity (BMI 35 to 39.9 kg/m(2)), and 2.1% had class III obesity (>/=40 kg/m(2)). BMI correlated with high-density lipoprotein cholesterol (HDL-C) and triglycerides (Spearman's rho: -0.147 and 0.170, respectively; p < 0.0001 for both); however, there was no correlation with low-density lipoprotein cholesterol (LDL-C; rho: 0.003; p=0.51). Statin intensity increased with increasing BMI (rho: 0.13; p<0.001), an association that held after adjustment for comorbidities (OR: 2.4; 95% CI: 2.0-3.0) on BMI >/=30 kg/m(2) for atorvastatin equivalent >/=40mg/day.

[26] *Beaumont M, Neyrinck AM, Olivares M et al.* **The gut microbiota metabolite indole alleviates liver inflammation in mice**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201800544.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29906245
ABSTRACT
The gut microbiota regulates key hepatic functions, notably through the production of bacterial metabolites that are transported via the portal circulation. We evaluated the effects of metabolites produced by the gut microbiota from aromatic amino acids (phenylacetate, benzoate, p-cresol, and indole) on liver inflammation induced by bacterial endotoxin. Precision-cut liver slices prepared from control mice, Kupffer cell (KC)-depleted mice, and obese mice (ob/ ob) were treated with or without LPS and bacterial metabolites. We observed beneficial effects of indole that dose-dependently reduced the LPS-induced up-regulation of proinflammatory mediators at both mRNA and protein levels in precision-cut liver slices prepared from control or ob/ ob mice. KC depletion partly prevented the antiinflammatory effects of indole, notably through a reduction of nucleotide-binding domain and leucine-rich

repeat containing (NLR) family pyrin domain-containing 3 (NLRP3) pathway activation. In vivo, the oral administration of indole before an LPS injection reduced the expression of key proteins of the NF-kappaB pathway and downstream proinflammatory gene up-regulation. Indole also prevented LPS-induced alterations of cholesterol metabolism through a transcriptional regulation associated with increased 4beta-hydroxycholesterol hepatic levels. In summary, indole appears as a bacterial metabolite produced from tryptophan that is able to counteract the detrimental effects of LPS in the liver. Indole could be a new target to develop innovative strategies to decrease hepatic inflammation.-Beaumont, M., Neyrinck, A. M., Olivares, M., Rodriguez, J., de Rocca Serra, A., Roumain, M., Bindels, L. B., Cani, P. D., Evenepoel, P., Muccioli, G. G., Demoulin, J.-B., Delzenne, N. M. The gut microbiota metabolite indole alleviates liver inflammation in mice.

[27] *Musso G, Cassader M, Paschetta E, Gambino R*. **Bioactive lipid species and metabolic pathways in progression and resolution of Non-Alcoholic Steatohepatitis**. Gastroenterology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29906416
ABSTRACT
The prevalence of non-alcoholic steatohepatitis (NASH) is increasing worldwide, yet there are no effective treatments. A decade has passed since initial lipidomic analyses of liver tissues from patients with non-alcoholic fatty liver disease. We have learned that liver cells from patients with NASH have an abnormal lipid composition, and the accumulation of lipids leads to organelle dysfunction, cell injury and death, and chronic inflammation, called liptoxicity. We review the lipid species and metabolic pathways that contribute to pathogenesis of NASH, as well as potential therapeutic targets, including enzymes involved in fatty acid and triglyceride synthesis, bioactive sphingolipids and polyunsaturated-derived eicosanoids and specialized proresolving lipid mediators. We discuss the concept that NASH is a disease that can resolve, and the roles of lipid molecules in resolution of inflammation and regression of fibrosis.

[28] *Romano G, Reggi S, Kutryb-Zajac B et al.* **APOA-1Milano muteins, orally delivered via genetically modified rice, show anti-atherogenic and anti-inflammatory properties in vitro and in Apoe(-/-) atherosclerotic mice**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29907443
ABSTRACT
BACKGROUND: Atherosclerosis is a slowly progressing, chronic multifactorial disease characterized by the accumulation of lipids, inflammatory cells, and fibrous tissue that drives to the formation of asymmetric focal thickenings in the tunica intima of large and mid-sized arteries. Despite the high therapeutic potential of ApoA-1 proteins, the purification and delivery into the disordered organisms of these drugs is still limited by low efficiency in these processes. METHODS AND RESULTS: We report here a novel production and delivery system of anti-atherogenic APOA-1Milano muteins (APOA-1M) by means of genetically modified rice plants. APOA-1M, delivered as protein extracts from transgenic rice seeds, significantly reduced macrophage activation and foam cell formation in vitro in oxLDL-loaded THP-1 model. The APOA-1M delivery method and therapeutic efficacy was tested in healthy mice and in Apoe(-/-) mice fed with high cholesterol diet (Western Diet, WD). APOA-1M rice milk significantly

reduced atherosclerotic plaque size and lipids composition in aortic sinus and aortic arch of WD-fed Apoe(-/-) mice as compared to wild type rice milk-treated, WD-fed Apoe(-/-) mice. APOA-1M rice milk also significantly reduced macrophage number in liver of WD-fed Apoe(-/-) mice as compared to WT rice milk treated mice. TRANSLATIONAL IMPACT: The delivery of therapeutic APOA-1M full length proteins via oral administration of rice seeds protein extracts (the 'rice milk') to the disordered organism, without any need of purification, might overcome the main APOA1-based therapies' limitations and improve the use of this molecules as therapeutic agents for cardiovascular patients.

[29] *Simon TG, Corey KE, Cannon CP et al.* **The nonalcoholic fatty liver disease (NAFLD) fibrosis score, cardiovascular risk stratification and a strategy for secondary prevention with ezetimibe**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29903515
ABSTRACT
OBJECTIVE: The nonalcoholic fatty liver disease fibrosis score (NFS) is comprised of unique metabolic risk indicators that may accurately predict residual cardiovascular (CV) risk in patients with established coronary disease and metabolic dysfunction. METHODS: We applied the NFS prospectively to 14,819 post-ACS patients randomized to ezetimibe/simvastatin (E/S) or placebo/simvastatin (P/S), in the IMPROVE-IT trial, using validated NFS cutoffs. The primary endpoint included CV death, myocardial infarction, unstable angina, revascularization or stroke. Outcomes were compared between NFS categories and treatment arms using frequency of events, KM rates and adjusted Cox proportional hazard models. The ability of the NFS to predict recurrent CV events was independently validated in 5395 placebo-treated patients enrolled in the SOLID-TIMI 52 trial. RESULTS: Among 14,819 patients enrolled in IMPROVE-IT, 14.2% (N=2106) were high-risk (NFS>0.67). The high-risk group had a 30% increased risk of recurrent major CV events, compared to the low-risk NFS group (HR 1.30 [1.19-1.43]; p<0.001). Among high-risk patients, ezetimibe/simvastatin conferred a 3.7% absolute reduction in risk of recurrent CV events, compared to placebo/simvastatin (HR 0.85 [0.74-0.98]), translating to a number-needed-to-treat of 27. Similar benefit was not found in the low-risk group (HR ezetimibe/simvastatin vs. placebo/simvastatin, 1.01 [0.91-1.12]; p-interaction=0.053). The relationship between NFS category and recurrent CV events was independently validated in patients enrolled in SOLID-TIMI 52 (HR for NFS>0.67 vs. NFS<-1.455=1.55 [1.32-1.81]; p<0.001). CONCLUSION: Stratification of cardiovascular risk by NFS identifies an independent population of patients who are at highest risk of recurrent events, and most likely to benefit from dual lipid-lowering therapy. Clinical trials.gov: NCT00202878.

[30] *Verbree-Willemsen L, Zhang YN, Gijsberts CM et al.* **LDL extracellular vesicle coagulation protein levels change after initiation of statin therapy. Findings from the METEOR trial**. International journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29898827
ABSTRACT
BACKGROUND: Statins are thought to have pleiotropic properties, including anticoagulant effects, in addition to reducing lipoprotein (LDL) levels. Plasma extracellular vesicles (EVs) are small bilayer membrane vesicles involved in various biological processes including coagulation.

Since subsets of EVs in the LDL plasma fraction (LDL-EVs) correlate with thrombin activity, we hypothesized that changes in LDL-EVs after statin therapy may differ from that of serum levels of coagulation proteins, providing insight into the effects of statins on coagulation. METHODS: The study was conducted in 666 subjects with available serum from the METEOR trial, a trial of the effect of rosuvastatin versus placebo in patients with subclinical atherosclerosis. Changes in protein levels of von Willebrand Factor (VWF), SerpinC1 and plasminogen were measured in serum and in LDL-EVs, and were compared between the rosuvastatin and placebo groups. RESULTS: LDL-EV levels of plasminogen and VWF increased with rosuvastatin treatment compared to placebo (mean change of 126+/-8 versus 17+/-12mug/mL for plasminogen ($p<0.001$) and 310+/-60 versus 64+/-55mug/mL for VWF ($p=0.015$)). There was no difference between groups for change in LDL-EV-SerpinC1. In contrast, serum plasminogen levels increased to a lesser extent with rosuvastatin compared to placebo (23+/-29 versus 67+/-17mug/mL, $p=0.024$) and serum VWF levels showed no significant difference between both groups. CONCLUSIONS: Rosuvastatin increases LDL-EV coagulation proteins plasminogen and VWF in patients with subclinical atherosclerosis, an effect that is different from the effect of rosuvastatin on the same proteins in serum. This identifies LDL-EVs as a newly detected possible intermediate between statin therapy and coagulation.

[31] *Vishnu A, Choo J, Kadota A et al.* **Comparison of carotid plaque burden among healthy middle-aged men living in the US, Japan, and South Korea**. International journal of cardiology 2018; 266:245-249.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29887456
ABSTRACT
BACKGROUND: Carotid plaque has emerged as a marker of coronary heart disease (CHD) risk. Comparison of carotid plaque burden between different race/ethnic groups may provide a relative estimate of their future CHD risk. METHODS: We conducted a population-based study among apparently healthy middle-aged men aged 40-49years (ERA JUMP study (n=924)) and recruited 310 Whites in Pittsburgh, US, 313 Japanese in Otsu, Japan, and 301 Koreans in Ansan, South Korea. The number of carotid plaque and CHD risk factors was assessed using a standardized protocol across all centers. The burden of carotid plaque was compared between race/ethnic groups after adjustment for age and BMI, and after multivariable adjustment for other CHD risk factors using marginalized zero-inflated Poisson regression models. Cross-sectional associations of risk factors with plaque were examined. RESULTS: Whites (22.8%) had more than four-fold higher prevalence ($p<0.01$) of carotid plaque than Japanese men (4.8%) while the prevalence among Koreans was 10.6%. These differences remained significant after adjustment for age, BMI as well as other risk factors - incidence density ratio (95% confidence interval) for plaque was 0.13 (0.07, 0.24) for Japanese and 0.32 (0.18, 0.58) for Koreans as compared to Whites. Age, hypertension and diabetes were the only risk factors significantly associated with presence of carotid plaque in the overall population. CONCLUSION: Whites have significantly higher carotid plaque burden than men in Japan and Korea. Lower carotid plaque burden among Japanese and Koreans is independent of traditional CVD risk factors.

[32] *Watts GF, Norman R*. **Squaring up the health economics of PCSK9 monoclonal antibodies 'down under'**. International journal of cardiology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29887280
ABSTRACT

[33] *Wei WY, Zhang N, Tang QZ*. **The potential role of PPARgamma in obesity-induced adipose tissue inflammation**. International journal of cardiology 2018; 266:220.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29887452
ABSTRACT

[34] *Yan BP, Chiang FT, Ambegaonkar B et al.* **Low-density lipoprotein cholesterol target achievement in patients surviving an acute coronary syndrome in Hong Kong and Taiwan - findings from the Dyslipidemia International Study II**. International journal of cardiology 2018; 265:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29885676
ABSTRACT
BACKGROUND: Individuals are at increased risk for cardiovascular events following an acute coronary syndrome (ACS). Effective management of hyperlipidemia, an associated risk factor, is essential for improving outcomes. We aimed to quantify the extent of hyperlipidemia and its treatment in ACS survivors in Hong Kong and Taiwan. METHODS: The multinational, observational Dyslipidemia International Study (DYSIS) II included patients hospitalized for an ACS. Lipid levels and use of lipid-lowering therapy (LLT) were evaluated at baseline and 4months post-discharge. The proportions of patients attaining the recommended LDL-C target for individuals at very high cardiovascular risk (<70mg/dL) was assessed and potential predictors of this outcome evaluated. RESULTS: In total, 270 patients were enrolled, 125 (46.3%) of which were being treated with LLT prior to hospitalization. Of these, 28.8% had an LDL-C level<70mg/dL, compared to only 6.9% of those not being treated. Statin monotherapy was the most commonly employed LLT, with a mean atorvastatin-equivalent dosage of 14mg/day. By 4-month follow-up, target attainment had risen to 45.1% for patients treated with LLT at baseline, and 43.3% for those who had not been treated. LLT was being used by 88.4% of patients at follow-up, with a mean atorvastatin dosage of 18mg/day. Use of statins in combination with ezetimibe/other non-statin was scarce. No predictors of LDL-C target attainment were identified. CONCLUSIONS: In patients hospitalized with an ACS, rates of LDL-C target achievement were poor. While LLT was widely employed, statin intensity was low and combination therapy underused, indicating scope for improvement.

[35] *Muniandy M, Velagapudi V, Hakkarainen A et al.* **Plasma metabolites reveal distinct profiles associating with different metabolic risk factors in monozygotic twin pairs**. International journal of obesity (2005) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29907843
ABSTRACT
BACKGROUND: Obesity is related to a myriad of cardiometabolic outcomes, each of which may have a specific metabolomic signature and a genetic basis. We identified plasma metabolites associating with different cardiometabolic risk factors (adiposity, cholesterol, insulin resistance, and inflammation) in monozygotic (MZ) twins. Additionally, we assessed if metabolite profiling can identify subgroups differing by cardiometabolic risk factors. METHODS: We quantified 111

plasma metabolites (Acquity UPLC-triple quadrupole mass spectrometry), and measured blood lipids, HOMA index, CRP, and adiposity (BMI, %bodyfat by DEXA, fat distribution by MRI) in 40 MZ twin pairs (mean BMI 27.9 kg/m(2), age 30.7). We determined associations among individuals (via linear regression) between metabolites and clinical phenotypes, and assessed, with within-twin pair analysis, if these associations were free from genetic confounding. We also performed cluster analysis to identify distinct subgroups based on subjects' metabolite profiles. RESULTS: We identified 42 metabolite-phenotype associations (FDR < 0.05), 19 remained significant after controlling for shared factors within the twin pairs. Aspartate, propionylcarnitine, tyrosine hexanoylcarnitine, and deoxycytidine associated positively with two or more adiposity measures. HDL cholesterol (HDL-C) associated negatively and BMI positively with the most numbers of metabolites; 12 were unique for HDL-C and 3 for BMI. Metabolites associating with HDL-C had the strongest effect size. Metabolite profiling revealed two distinct subgroups of individuals, differing by 32 metabolites ($p < 0.05$), and by total and LDL cholesterol (LDL-C). Forty-two metabolites predicted subgroup membership in correlation with total cholesterol and 45 metabolites predicted subgroup membership in correlation with LDL-C. CONCLUSIONS: Different fat depots share metabolites associating with general adiposity. BMI and HDL-C associated with the most pronounced and specific metabolomic signature. Metabolomics profiling can be used to identify distinct subgroups of individuals that differ by cholesterol measures. Most of the observed metabolite-phenotype associations are free of confounding by genetics and environmental factors shared by the co-twins.

[36] *Nohara A, Ohmura H, Okazaki H et al.* **Statement for Appropriate Clinical Use of PCSK9 Inhibitors**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29899173
ABSTRACT

[37] *Okami Y, Ueshima H, Nakamura Y et al.* **The Relationship of Dietary Cholesterol with Serum Low-Density Lipoprotein Cholesterol and Confounding by Reverse Causality: The INTERLIPID Study**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29887537
ABSTRACT
AIM: The positive relationship between dietary cholesterol and serum cholesterol has been questioned by a set of recent cohort studies. This study aimed to investigate how employment status and education years relate to the association between dietary cholesterol and serum low-density lipoprotein cholesterol (LDL-C) in a Japanese population. METHODS: A population-based, random sample, cross-sectional study (INTERLIPID) was performed. Among 1,145 Japanese individuals aged 40-59 years, 106 were excluded because of special diets, use of lipid-lowering drugs, hormone replacement, and missing data, leaving 1,039 individuals (533 men and 506 women). Dietary cholesterol was assessed from four 24-h dietary recalls, and LDL-C was measured enzymatically with an auto-analyzer. A standard questionnaire inquired about employment status and education years. RESULTS: In men, a 1 standard deviation (SD) higher dietary cholesterol was associated with 3.16 mg/dL lower serum LDL-C (P=0.009; unadjusted model). After adjustment for covariates, higher serum LDL-C was estimated per 1 SD higher intake of dietary cholesterol in nonemployed men [self-employed, homemakers, farmers,

fishermen, and retired employees; beta=9.08, 95% confidence interval (CI)=0.90-17.27] and less educated men (beta=4.46, 95% CI=0.97-9.90), whereas an inverse association was observed in employed men (beta=3.02, 95% CI=5.49-0.54) and more educated men (beta=3.66, 95% CI=6.25-1.07). CONCLUSIONS: In men who were nonemployed and less educated, a higher intake of dietary cholesterol was associated with elevated concentrations of serum LDL-C, whereas an inverse association was observed in men who were employed and more educated.

[38] *Harb AA, Bustanji YK, Abdalla SS*. **Hypocholesterolemic effect of beta-caryophyllene in rats fed cholesterol and fat enriched diet**. Journal of clinical biochemistry and nutrition 2018; 62:230-237.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29892161
ABSTRACT
Hypercholesterolemia is a major risk factor for cardiovascular diseases. This study investigated the cholesterol-lowering potential of beta-caryophyllene in a rat model. Hypercholesterolemia was induced by feeding male Wistar rats a high cholesterol and fat diet for 2 weeks. This was followed by oral administration of beta-caryophyllene to hypercholesterolemic rats at 30, 100 and 300 mg/kg b.w. for 4 weeks. A dose of 30 mg/kg of beta-caryophyllene significantly lowered serum total cholesterol, low density lipoprotein and the atherogenic index and significantly increased high density lipoprotein level. Moreover, it ameliorated liver injury as evidenced by decreasing hepatomegaly, macrovesicular steatosis and the activity of hepatic marker enzymes alanine aminotransferase and aspartate aminotransferase. Furthermore, it increased the activity of the antioxidant enzyme superoxide dismutase. This dose of beta-caryophyllene significantly inhibited the activity of hepatic hydroxy-methylglutaryl coenzyme A reductase. Higher doses (100 and 300 mg/kg) of beta-caryophyllene, however, did not induce significant beneficial effects on the studied parameters. These observations demonstrate that beta-caryophyllene has a cholesterol-lowering effect on hypercholesterolemic rats, thus offering protection against hypercholesterolemia-induced diseases such as atherosclerosis and fatty liver.

[39] *Kaysen G, Ye X, Raimann JG et al.* **Lipid levels are inversely associated with infectious and all-cause mortality: International MONDO study results**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29895699
ABSTRACT
Cardiovascular events (CV) are increased 36 fold in patients with end stage renal disease. However, randomized controlled trials to lower LDL-C and TC have not shown significant mortality improvements. An inverse association of serum total cholesterol (TC) and LDL cholesterol (LDL-C) with all-cause and cardiovascular (CV) mortality has been observed in patients on chronic dialysis. Lipoproteins also may protect against infectious diseases. We used data from 37,250 patients in the international Monitoring Dialysis Outcomes (MONDO) database to evaluate the association between lipids and infection-related or CV mortality. The study began on the first day of lipid measurement and continued for up to 4 years. We applied Cox proportional models with time-varying covariates to study associations of LDL-C, HDL cholesterol (HDL-C), and TGs with all-cause, CV, infectious, and other causes of death. Overall, 6,147 patients died (19.2% from CV, 13.2% from infection, 67.6% from other causes). After

multivariable adjustment, higher LDL-C, HDL-C, and TGs were independently associated with lower all-cause death risk. Neither LDL-C nor TGs were associated with CV death and HDL-C was associated with lower CV risk. Higher LDL-C and HDL-C were associated with a lower risk of death from infection or other non CV causes. LDL-C was associated with reduced all-cause and infectious, but not CV mortality, which resulted in the inverse association with all-cause mortality.

[40] *Tsivgoulis G, Safouris A, Kim DE, Alexandrov AV*. **Recent Advances in Primary and Secondary Prevention of Atherosclerotic Stroke**. J Stroke 2018; 20:145-166.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29886715
ABSTRACT
Atherosclerosis is a major cause of ischemic stroke that can be effectively prevented with appropriate lifestyle modifications and control of cardiovascular risk factors. Medical advances in recent years along with aggressive cardiovascular risk factor modifications have resulted in decreased recurrence rates of atherosclerotic stroke. Non-statin lipid-lowering molecules have recently shown clinical benefit and are recommended for very high-risk patients to reduce their risk of stroke. Aggressive hypertension treatment is crucial to reduce atherosclerotic stroke risk. Advances in antithrombotic treatments include combinations of antiplatelets and new antiplatelet agents in the acute phase post-stroke, which carries a high risk of recurrence. Intensive medical treatment has also limited the indications for carotid interventions, especially for asymptomatic disease. Intracranial atherosclerotic disease may provoke stroke through various mechanisms; it is increasingly recognized as a cause of ischemic stroke with advanced imaging and is best managed with lifestyle modifications and medical therapy. The diagnostic search for the vulnerable culprit atherosclerotic plaque is an area of intense research, from the level of the intracranial arteries to that of the aortic arch. Ultrasonography and novel magnetic resonance imaging techniques (high-resolution vessel-wall imaging) may assist in the identification of vulnerable atherosclerotic plaques as the underlying cause in cryptogenic or misdiagnosed non-atherosclerotic ischemic stroke. Vertebrobasilar atherosclerotic disease is less common than carotid artery disease; thus, high-quality data on effective prevention strategies are scarcer. However, aggressive medical treatment is also the gold standard to reduce cerebrovascular disease located in posterior circulation.

[41] *Martin SS, Giugliano RP, Murphy SA et al.* **Comparison of Low-density Lipoprotein Cholesterol Assessment by Martin/Hopkins Estimation, Friedewald Estimation, and Preparative Ultracentrifugation: Insights From the FOURIER Trial**. JAMA cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29898218
ABSTRACT
Importance: Recent studies have shown that Friedewald underestimates low-density lipoprotein cholesterol (LDL-C) at lower levels, which could result in undertreatment of high-risk patients. A novel method (Martin/Hopkins) using a patient-specific conversion factor provides more accurate LDL-C levels. However, this method has not been tested in proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor-treated patients. Objective: To investigate accuracy of 2 different methods for estimating LDL-C levels (Martin/Hopkins and Friedewald) compared with gold standard preparative ultracentrifugation (PUC) in patients with low LDL-C

levels in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk (FOURIER) trial. Design, Setting, and Participants: The FOURIER trial was a randomized clinical trial of evolocumab vs placebo added to statin therapy in 27564 patients with stable atherosclerotic cardiovascular disease. The patients' LDL-C levels were assessed at baseline, 4 weeks, 12 weeks, 24 weeks, and every 24 weeks thereafter, and measured directly by PUC when the level was less than 40 mg/dL per the Friedewald method (calculated as non-HDL-C level - triglycerides/5). In the Martin/Hopkins method, patient-specific ratios of triglycerides to very low-density lipoprotein cholesterol (VLDL-C) ratios were determined and used to estimate VLDL-C, which was subtracted from the non-HDL-C level to obtain the LDL-C level. Main Outcomes and Measures: Low-density lipoprotein cholesterol calculated by the Friedewald and Martin/Hopkins methods, with PUC as the reference method. Results: For this analysis, the mean (SD) age was 62.7 (9.0) years; 2885 of the 12 742 patients were women (22.6%). A total of 56624 observations from 12742 patients had Friedewald, Martin/Hopkins, and PUC LDL-C measurements. The median difference from PUC LDL-C levels for Martin/Hopkins LDL-C levels was -2 mg/dL (interquartile range [IQR], -4 to 1 mg/dL) and for Friedewald LDL-C levels was -4 mg/dL (IQR, -8 to -1 mg/dL; P < .001). Overall, 22.9% of Martin/Hopkins LDL-C values were more than 5 mg/dL different than PUC values, and 2.6% were more than 10 mg/dL different than PUC levels. These were significantly less than respective proportions with Friedewald estimation (40.1% and 13.3%; P < .001), mainly because of underestimation by the Friedewald method. The correlation with PUC LDL-C was significantly higher for Martin/Hopkins vs Friedewald (rho, 0.918 [95% CI 0.916-0.919] vs rho, 0.867 [0.865-0.869], P < .001). Conclusions and Relevance: In patients achieving low LDL-C with PCSK9 inhibition, the Martin/Hopkins method for LDL-C estimation more closely approximates gold standard PUC than Friedewald estimation does. The Martin/Hopkins method may prevent undertreatment because of LDL-C underestimation by the Friedewald method. Trial Registration: ClinicalTrials.gov Identifier: NCT01764633.

[42] *Vershinina EO, Repin AN, Timofeev MS, Udut VV*. **[Prevention of periprocedural kidney ingury by loading doses of statins in elective percutaneous small es, Cyrillicoronary interventions]**. Kardiologiia 2018:20-29.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29894673
ABSTRACT
PURPOSE OF THE STUDY: To compare the effect of loading doses of atorvastatin and rosuvastatin on the value of the acute kidney injury and acute inflammatory response to elective percutaneous coronary interventions. MATERIALS AND METHODS: An open prospective comparative study included 68 patients referred for elective percutaneous coronary intervention (PCI). At baseline, all patients had been taking statins for a long time as a standard lipid-lowering therapy. The first group included 33 patients who received a loading dose of 80 mg of atorvastatin (As) 12 hours before the intervention with saving this dose for 2-6 days. The second group included 35 patients treated with rosuvastatin (Rs) 40 mg / day in the same manner. The levels of creatinine and cystatin C in the blood were determined at baseline and 12, 24, 48 and 72 hours after the intervention. HsCRP level was determined at baseline and 72 hours after PCI. RESULTS: AKI was diagnosed in 5 patients (7.94 %): 4 patients (12.1 %) in group As and 1 patient (3.3 %) in group Rs (p = 0.36). The increase of serum creatinine level in the

group As patients was 43.4 % higher than one in the Rs group patients (p = 0.024). The decrease of glomerular filtration rate (GFR) in group As was 15.5 % higher than one in group Rs (p = 0.09). Initially, the level of cystatin C in the groups did not differ (698.9 (560.2-869.6) ng / ml in group As vs 759.5 (673.8-899.9) ng/ml in group Rs, p = 0.75). Significant intergroup differences were found in the level of serum cystatin C 12 hours after PCI (718.3 (555.6-839.6) ng/ml in group As vs 470.6 (378.2-689.4) ng/ml in the Rs group, p = 0.007) that persisted 24 hours after the intervention (732.1 (632.3-887) ng/ml vs 526.4 (357.4-802.7) ng/ml, respectively, p = 0.02). From the second day after PCI, intergroup differences in serum cystatin C disappeared. The level of hsCRP significantly increased 72 hours after the intervention in group As (1.65 (0.9-4) mg/l at baseline vs 4.55 (1.6-8.7) mg/l 72 hours after PCI, p = 0.01). The level of hsCRP did not change significantly at the same time in the Rs group (2.8 (0.8-6.8) mg/l at baseline vs 2.75 (1.5-6.5) mg/l 72 hours after PCI, p = 0.16). CONCLUSION: The loading dose of rosuvastatin better prevents periprocedural kidney injury in PCI and more significantly reduces the overall inflammatory response to intervention compared to the loading dose of atorvastatin.

[43] *Zabawa C, Cottenet J, Zeller M et al.* **Thirty-day rehospitalizations among elderly patients with acute myocardial infarction: Impact of postdischarge ambulatory care**. Medicine (Baltimore) 2018; 97:e11085.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29901621
ABSTRACT
Rehospitalization after acute myocardial infarction (AMI) is common in elderly patients. It increases morbimortality and health care expenditures. The association between ambulatory care after discharge for AMI and rehospitalization has never been studied in France. We analyzed the impact of ambulatory care on rehospitalization of elderly patients (>/=65 years) within 30 days after hospital discharge.We conducted a nationwide population-based study of elderly patients hospitalized with a main diagnosis of AMI in France between 2011 and 2013. We excluded patients hospitalized for AMI in the previous year and those who died during the index hospitalization or within 30 days after discharge. The primary outcome was the first all-cause 30-day rehospitalization in an acute care hospital. Individual and neighborhood-level variables were compared among rehospitalized and nonrehospitalized patients. Determinants of 30-day rehospitalization were identified using logistic regression models.Among the 624 eligible patients, 137 (22.0%) were rehospitalized within 30 days after discharge. In multivariate analyses, chronic kidney failure (odds ratio [OR] 1.88; 95% confidence interval [CI], 1.01-3.53) was an independent predictor of 30-day rehospitalization. We found no association among deprivation and spatial accessibility measures and 30-day rehospitalization. The purchase of lipid-lowering drugs prescription within 7 days after discharge was associated with a reduced risk of 30-day rehospitalization (OR 0.53; 95% CI, 0.36-0.79).This study highlights the role of coordination among hospital and primary care physicians in post-AMI discharge and follow-up among elderly patients. Specifically, targeted interventions to reduce 30-day rehospitalizations should focus on patients with comorbidities and use of prescription drugs after hospital discharge.

[44] **High-Dose Atorvastatin after Stroke or Transient Ischemic Attack**. The New England journal of medicine 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29898369
ABSTRACT

[45] *Logan SM, Storey KB*. **Pro-inflammatory AGE-RAGE signaling is activated during arousal from hibernation in ground squirrel adipose**. PeerJ 2018; 6:e4911.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29888131
ABSTRACT
Background: Inflammation is generally suppressed during hibernation, but select tissues (e.g. lung) have been shown to activate both antioxidant and pro-inflammatory pathways, particularly during arousal from torpor when breathing rates increase and oxidative metabolism fueling the rewarming process produces more reactive oxygen species. Brown and white adipose tissues are now understood to be major hubs for the regulation of immune and inflammatory responses, yet how these potentially damaging processes are regulated by fat tissues during hibernation has hardly been studied. The advanced glycation end-product receptor (RAGE) can induce pro-inflammatory responses when bound by AGEs (which are glycated and oxidized proteins, lipids, or nucleic acids) or damage associated molecular pattern molecules (DAMPs, which are released from dying cells). Methods: Since gene expression and protein synthesis are largely suppressed during torpor, increases in AGE-RAGE pathway proteins relative to a euthermic control could suggest some role for these pro-inflammatory mediators during hibernation. This study determined how the pro-inflammatory AGE-RAGE signaling pathway is regulated at six major time points of the torpor-arousal cycle in brown and white adipose from a model hibernator, Ictidomys tridecemlineatus. Immunoblotting, RT-qPCR, and a competitive ELISA were used to assess the relative gene expression and protein levels of key regulators of the AGE-RAGE pathway during a hibernation bout. Results: The results of this study revealed that RAGE is upregulated as animals arouse from torpor in both types of fat, but AGE and DAMP levels either remain unchanged or decrease. Downstream of the AGE-RAGE cascade, nfat5 was more highly expressed during arousal in brown adipose. Discussion: An increase in RAGE protein levels and elevated mRNA levels of the downstream transcription factor nfat5 during arousal suggest the pro-inflammatory response is upregulated in adipose tissue of the hibernating ground squirrel. It is unlikely that this cascade is activated by AGEs or DAMPs. This research sheds light on how a fat-but-fit organism with highly regulated metabolism may control the pro-inflammatory AGE-RAGE pathway, a signaling cascade that is often dysregulated in other obese organisms.

[46] *Kim MC, Yun SC, Lee SO et al.* **Statins increase the risk of herpes zoster: A propensity score-matched analysis**. PloS one 2018; 13:e0198263.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29902266
ABSTRACT
OBJECTIVES: Statins, which are lipid-lowering agents, have anti-inflammatory and immunomodulatory properties that may affect the occurrence of various infectious diseases. We assessed whether statins increase the risk of herpes zoster (HZ) with propensity score-matching. METHODS: The study was based on the National Health Insurance database and its subset database of the "medical check-up" population of South Korea. These cohorts consist of about one million and 570,000 people, respectively, representative of the entire population of

South Korea. We identified 103,930 statin users and 430,685 non-statin users. After propensity score-matching, 25,726 statin users and the same number of non-statin users were finally analyzed. The development of HZ was monitored in these matched pairs over the 11 years from 2003 to 2013. RESULTS: Statin users had a significantly higher risk of HZ than non-statin users: hazard ratio (HR) 1.25 (95% CI, 1.15 to 1.37) (p < .0001). The risk of HZ associated with statins was especially high in the elderly: HR 1.39 (95% CI, 1.12 to 1.73) in the over 70-year-olds (p = 0.003) and HR 1.18 (95% CI, 1.00 to 1.39) in the 60-to-69-year-olds (p = 0.056). Furthermore, there was a significant p for trend in terms of cumulative dose effect between the risk of HZ and the duration of statin use (p < .0001). CONCLUSIONS: These epidemiologic findings provide strong evidence for an association between HZ and statin use, and suggest that unnecessary statins should be avoided.

[47] *Yamanaka JS, Ribeiro KEC, Yanagihara GR et al.* **Effects of simvastatin associated with exercise on the mechanical resistance of muscle and bone in rats**. Revista brasileira de ortopedia 2018; 53:287-292.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29892578
ABSTRACT
Objective: The aim of the present study was to evaluate the influence of simvastatin on mechanical properties of muscle and bone in hypercholesterolemic rats submitted to physical exercise. Methods: Ten male Wistar rats were submitted to a high-fat diet rich in cholesterol for 90 days. The animals were then divided into two groups: animals treated with physical exercise (EG) and animals treated with physical exercise and simvastatin (ESG). Protocols for physical exercise in water and simvastatin administration were performed for eight weeks. After this period, the animals were euthanized; the left tibia and right gastrocnemius muscle were dissected for mechanical analysis, and the right tibia for densitometry. The data were analyzed using Student's t-test, considering a level of significance of 5%. Results: The comparison of maximum load and stiffness revealed no significant differences between the groups for both the tibia (p = 0.851 and p = 0.259) and the gastrocnemius (p = 0.911 and p = 0.083). The tibia BMD also showed no significant difference between the groups (p = 0.803). Conclusion: Simvastatin had no negative effects on mechanical properties in tibia and gastrocnemius of hypercholesterolemic rats submitted to physical exercise.

[48] *Hagita S, Rogers MA, Pham T et al.* **Transcriptional control of intestinal cholesterol absorption, adipose energy expenditure and lipid handling by Sortilin**. Scientific reports 2018; 8:9006.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29899496
ABSTRACT
The sorting receptor Sortilin functions in the regulation of glucose and lipid metabolism. Dysfunctional lipid uptake, storage, and metabolism contribute to several major human diseases including atherosclerosis and obesity. Sortilin associates with cardiovascular disease; however, the role of Sortilin in adipose tissue and lipid metabolism remains unclear. Here we show that in the low-density lipoprotein receptor-deficient (Ldlr(-/-)) atherosclerosis model, Sortilin deficiency (Sort1(-/-)) in female mice suppresses Niemann-Pick type C1-Like 1 (Npc1l1) mRNA levels, reduces body and white adipose tissue weight, and improves brown adipose

tissue function partially via transcriptional downregulation of Kruppel-like factor 4 and Liver X receptor. Female Ldlr(-/-)Sort1(-/-) mice on a high-fat/cholesterol diet had elevated plasma Fibroblast growth factor 21 and Adiponectin, an adipokine that when reduced is associated with obesity and cardiovascular disease-related factors. Additionally, Sort1 deficiency suppressed cholesterol absorption in both female mice ex vivo intestinal tissue and human colon Caco-2 cells in a similar manner to treatment with the NPC1L1 inhibitor ezetimibe. Together our findings support a novel role of Sortilin in energy regulation and lipid homeostasis in female mice, which may be a potential therapeutic target for obesity and cardiovascular disease.

[49] *Li S, Zhang HW, Guo YL et al.* **Familial hypercholesterolemia in very young myocardial infarction**. Scientific reports 2018; 8:8861.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29892007
ABSTRACT
Familial hypercholesterolemia (FH) is one of the most common causes of premature myocardial infarction (MI). However, The patterns of FH remained unrecognized in clinical care, especially in very young patients (VYPs, </=35 years) with MI. The present study enrolled a total of 1,093 VYPs (</=35 years) presenting a first MI. Clinical diagnosis of FH was made using Dutch Lipid Clinic Network criteria. Coronary severity was assessed by Gensini score (GS). Patients were followed for a median of 40-months with cardiac death, stroke, MI, post-discharge revascularization or unstable angina as primary endpoints. The detected rates of definite/probable FH were 6.5%. The prevalence reached up to 10.3% in patients </=25 years. The FH had similar levels of comorbidities but was younger, more likely to be very high risk (VHR) and had higher GS ($p < 0.05$) than unlikely FH. Notably, the FH on prior lipid-lowering medication presented a lower GS compared to those untreated. Differences in event rates were similar in FH as unlikely FH (11.8% vs. 8.1%, adjusted hazard ratio 1.35 [0.64-2.86], $p = 0.434$) but patients on treatment improved outcome (6.5% vs. 10.5%, adjusted hazard ratio 0.35[0.13-0.95], $p = 0.039$). The early identification and treatment might be critical to reduce cardiovascular risk in VYPs with MI.

[50] *Fang D, Liang LL, Qiu WJ et al.* **[Clinical, molecular genetic analysis, and treatment of 3 children with sitosterolemia]**. Zhonghua er ke za zhi = Chinese journal of pediatrics 2018; 56:435-439.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29886606
ABSTRACT
Objective: To investigate clinical, molecular genetic characteristics, and treatment outcomes of 3 children with sitosterolemia. Methods: Three cases of children presented with multiple xanthomas during June 2016 to June 2017 were included. The clinical manifestations, laboratory examinations and follow-up data were retrospectively analyzed. DNA was extracted from peripheral blood and analyzed with whole exome sequencing(WES). All the detected variants were confirmed by Sanger sequencing. Plasma plant sterol concentrations were measured by gas chromatography-mass spectrometry. Results: Three cases of children including 1 boy and 2 girls presented with multiple linear and intertriginous xanthomas around skin of the joint areas at the age from 15 months to 6 years and 2 months. Total cholesterol of

the 3 cases was elevated to 14.45, 15.47 and 15.85 mmol/L (3.36-6.46), and low density lipoprotein cholesterol was 9.02, 13.54 and 12.47 mmol/L (< 3.36) respectively. Genetic analysis with WES revealed that 2 cases carried compound heterozygous variants in ABCG5 gene, 1 case carried compound heterozygous variants in ABCG8 gene. Two reported variants (p. N437K, p.R446X) and one novel variant (p.Q251X) of ABCG5 were identified in case 2 and 3. Two novel ABCG8 variants (p.R263Q, c.1528_1530delATC) were found in case 1. All these children had extremely high plasma plant sterol levels, thus the diagnosis of sitosterolemia was confirming. The campesterol level was 111.35, 102.86 and 58.91 mumol/L(0.01-10.00), the stigmasterol was 14.97, 29.43 and 17.79 mumol/L (0.10-8.50) and the sitosterol was 231.20, 177.66 and 114.20 mumol/L (1.00-15.00) respectively. The total serum cholesterol levels of three children decreased to nomal after the patients were placed on the low plant sterol/low cholesterol diet. The xanthomas regressed gradually, and almost disappeared after 8 months of treatment in case 1 and 3. Conclusions: Children with sitosterolemia presented with skin xanthomas around the joint areas. The level of total cholesterol, low density lipoprotein cholesterol and plant sterols increased obviously. One novel variant (p.Q251X) of ABCG5 and 2 novel variants (p.R263Q, c.1528_1530delATC) of ABCG8 were identified. Children with sitosterolemia responded well to a low plant sterols/low cholesterol diet.