Literature update week 12 (2020)

[1] *Kim MJ, Lee KJ*. **Analysis of the dietary factors associated with suspected pediatric nonalcoholic fatty liver disease and potential liver fibrosis: Korean National Health and Nutrition Examination Survey 2014-2017**. BMC pediatrics 2020; 20:121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32171275

ABSTRACT
BACKGROUND: The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased as the obese pediatric population has increased. NAFLD causes progressive liver injury and the only effective treatment is lifestyle modifications. However, few studies have examined the dietary risk factors for pediatric NAFLD or liver fibrosis. Here, we evaluated the dietary factors associated with suspected NAFLD and potential liver fibrosis in Korean children. METHODS: Data collected from 1674 children and adolescents aged 10-18 years during the 2014-2017 Korean National Health and Nutrition Examination Surveys analyzed. The 24-h recall method measured the food consumed 1 day before the survey. The "suspected NAFLD" group included excessive body mass index (BMI) subjects >/= 85th percentile) with alanine aminotransferase (ALT) levels exceeding the upper normal limit (24.1 U/L for boys and 17.7 U/L for girls); the "healthy control" group included subjects with a BMI and ALT level below these thresholds. Sodium intake was assessed by the urinary sodium-to-urinary specific gravity unit ratio (U-Na-to-SGU ratio). A pediatric NAFLD index (PNFI) higher than 3 indicated potential liver fibrosis. RESULTS: The overall prevalence of suspected NAFLD and potential liver fibrosis was 8.2 and 4.5%, respectively. The suspected NAFLD group had a larger proportion of males and subject with a greater height, BMI standard deviation score (BMI-SDS), systolic and diastolic blood pressure SDS, waist circumference, hemoglobin A1c, and levels of total cholesterol, triglycerides, aspartate aminotransferase (AST) and ALT than the control group. The suspected NAFLD group presented significantly higher U-Na-to-SGU ratios and cholesterol intake. The PNFI > 3 subgroup included a significantly larger proportion of males and subjects with higher BMI-SDS, AST and ALT values, and intake of water, carbohydrate, protein, calcium, phosphorus, iron and vitamin B2. After adjusting for confounders, male, BMI-SDS, AST, and protein and carbohydrate intake were independent risk factors for potential liver fibrosis. Niacin intake was an independent protective factor for potential liver fibrosis. CONCLUSIONS: Children with suspected NAFLD had higher urinary sodium level and cholesterol intake than healthy controls. Protein and carbohydrate intake were independent risk factors for potential liver fibrosis; niacin was an independent protective factor.

[2] *Fang CEH, Crowe C, Murphy A et al.* **Cross-sectional study of the association between skin tags and vascular risk factors in a bariatric clinic-based cohort of Irish adults with morbid obesity**. BMC research notes 2020; 13:156.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32178726

ABSTRACT
OBJECTIVE: Skin tags are associated with an insulin resistant phenotype but studies in White Europeans with morbid obesity are lacking. We sought to determine whether the presence of cervical or axillary skin tags was associated with increased cardiovascular risk in Irish adults with morbid obesity. We conducted a cross-sectional study of patients attending our Irish regional bariatric centre with a BMI >/= 40 kg m(-2) (or >/= 35 kg m(-2) with co-morbidities). We compared anthropometric and metabolic characteristics in those with versus without skin tags. RESULTS: Of 164 patients, 100 (31 male, 37 with type 2 diabetes, 36 on lipid lowering therapy, 41 on

antihypertensive therapy) participated. Mean age was 53.7 +/- 11.3 (range 31.1-80) years. Cervical or axillary tags were present in 85 patients. Those with tags had higher systolic blood pressure 138.0 +/- 16.0 versus 125.1 +/- 8.3 mmHg, p = 0.003) and HbA1c (46.5 +/- 13.2 versus 36.8 +/- 3.5 mmol/mol, p = 0.017). Tags were present in 94.6% of patients with diabetes, compared to 79.4% of those without diabetes (p = 0.039). Antihypertensive therapy was used by 45.8% of patients with skin tags compared to 13.3% without tags (p = 0.018). In bariatric clinic attenders skin tags were associated with higher SBP and HbA1c and a higher prevalence of diabetes and hypertension, consistent with increased vascular risk, but lipid profiles were similar.

[3] *Lamb KL, Lynn A, Russell J, Barker ME*. **Effect of tart cherry juice on risk of gout attacks: protocol for a randomised controlled trial**. BMJ open 2020; 10:e035108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32179562
ABSTRACT
INTRODUCTION: Gout is a painful form of inflammatory arthritis associated with several comorbidities, particularly cardiovascular disease. Cherries, which are rich in anti-inflammatory and antioxidative bioactive compounds, are proposed to be efficacious in preventing and treating gout, but recommendations to patients are conflicting. Cherry consumption has been demonstrated to lower serum urate levels and inflammation in several small studies. One observational case cross-over study reported that cherry consumption was associated with reduced risk of recurrent gout attacks. This preliminary evidence requires substantiation. The proposed randomised clinical trial aims to test the effect of consumption of tart cherry juice on risk of gout attacks. METHODS AND ANALYSIS: This 12-month, parallel, double-blind, randomised, placebo-controlled trial will recruit 120 individuals (aged 18-80 years) with a clinical diagnosis of gout who have self-reported a gout flare in the previous year. Participants will be randomly assigned to an intervention group, which will receive Montmorency tart cherry juice daily for a 12-month period, or a corresponding placebo group, which will receive a cherry-flavoured placebo drink. The primary study outcome is change in frequency of self-reported gout attacks. Secondary outcome measures include attack intensity, serum urate concentration, fractional excretion of uric acid, biomarkers of inflammation, blood lipids and other markers of cardiovascular risk. Other secondary outcome measures will be changes in physical activity and functional status. Statistical analysis will be conducted on an intention-to-treat basis. ETHICS AND DISSEMINATION: This study has been granted ethical approval by the National Research Ethics Service, Yorkshire and The Humber-Leeds West Research Ethics Committee (ref: 18/SW/0262). Results of the trial will be submitted for publication in a peer-reviewed journal. TRIAL REGISTRATION NUMBER: NCT03621215.

[4] *Taheri H, Filion KB, Windle SB et al.* **Cholesteryl Ester Transfer Protein Inhibitors and Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Cardiology 2020; 145:236-250.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32172237
ABSTRACT
BACKGROUND: Cholesteryl ester transfer protein (CETP) inhibitors increase serum high-density lipoprotein cholesterol (HDL-c) concentration; however, their impact on cardiovascular outcomes is not clear. This systematic review examines the effect of CETP inhibitors on serum lipid profiles, cardiovascular events, and all-cause mortality. METHODS: We searched MEDLINE, Embase, and the

Cochrane Library of Clinical Trials for placebo-controlled randomized controlled trials (RCTs) that examined the effect of a CETP inhibitor (dalcetrapib, anacetrapib, evacetrapib, or TA-8995) on all-cause mortality, major adverse cardiovascular events (MACE), or the components of MACE at >/=6 months. Data were pooled using random-effects models. RESULTS: A total of 11 RCTs (n = 62,431) were included in our systematic review; 4 examined dalcetrapib (n = 16,612), 6 anacetrapib (n = 33,682), and 1 evacetrapib (n = 12,092). Compared to dalcetrapib, ana-cetrapib and evacetrapib were more efficacious at raising HDL-c levels (approximately 100-130 vs. approximately 30%). Anacetrapib and evacetrapib also decreased low-density lipoprotein cholesterol (LDL-c) by approximately 30% while dalcetrapib did not affect the LDL-c level. Overall, CETP inhibitors were not associated with the incidence of MACE (pooled relative risk [RR]: 0.97; 95% confidence interval [CI]: 0.91-1.04). CETP inhibitors may decrease the risks of nonfatal myocardial infarction (MI) (RR: 0.93; 95% CI: 0.87-1.00) and cardiovascular death (RR: 0.92; 95% CI: 0.83-1.01), though these trends did not reach statistical significance. CONCLUSIONS: CETP inhibitors are not associated with an increased risk of MACE or all-cause mortality. There is a trend towards small reductions in nonfatal MI and cardiovascular death, though the clinical im-portance of such reductions is likely modest.

[5] *Lu T, Grewal T*. **Ezetimibe: An Unusual Suspect in Angioedema**. Case reports in medicine 2020; 2020:9309382.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32180811
ABSTRACT
We describe a case of new onset angioedema likely due to Ezetimibe therapy in an elderly patient with a prior history of drug-induced bradykinin reactions who had been on the medication for multiple years. This is the second reported incidence of Ezetimibe-associated angioedema in literature. A 90-year-old African American female presented with angioedema of the face and oral mucosa with associated difficulty speaking developing hours after taking Ezetimibe 10 mg PO. She denied adding any new or unusual foods to her diet. A thorough clinical history determined Ezetimibe was the likely culprit. Ezetimibe was immediately discontinued. The swelling subsided after administration of methylprednisolone 125 mg, epinephrine 1 mg/mL, injection 0.3 mL, diphenhydramine 25 mg, and famotidine 20 mg BID within 48 hours. The patient's C1 esterase inhibitor level was measured to be within normal limits. Food panel allergy testing showed very low or undetectable IgE levels in all categories. Based on the limited reports in literature and our current case, we conclude that there is a likely association of angioedema with Ezetimibe. The mechanism, however, is unknown since it is not related to bradykinin or mast cell-mediated activation. Clinicians should advise patients taking Ezetimibe to report any swelling of the lips, face, and tongue and to immediately discontinue its use if these signs are present.

[6] *Uceda DE, Zhu XY, Woollard JR et al.* **Accumulation of Pericardial Fat Is Associated With Alterations in Heart Rate Variability Patterns in Hypercholesterolemic Pigs**. Circulation. Arrhythmia and electrophysiology 2020; 13:e007614.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32189516
ABSTRACT
BACKGROUND: Heart rate variability (HRV) and pulse rate variability are indices of autonomic cardiac modulation. Increased pericardial fat is associated with worse cardiovascular outcomes. We

hypothesized that progressive increases in pericardial fat volume and inflammation prospectively dampen HRV in hypercholesterolemic pigs. METHODS: WT (wild type) or PCSK9 (proprotein convertase subtilisin-like/kexin type-9) gain-of-function Ossabaw mini-pigs were studied in vivo before and after 3 and 6 months of a normal diet (WT-normal diet, n=4; PCSK9-normal diet, n=6) or high-fat diet (HFD; WT-HFD, n=3; PCSK9-HFD, n=6). The arterial pulse waveform was obtained from an arterial telemetry transmitter to analyze HRV indices, including SD (SD of all pulse-to-pulse intervals over a single 5-minute period), root mean square of successive differences, proportion >50 ms of normal-to-normal R-R intervals, and the calculated ratio of low-to-high frequency distributions (low-frequency power/high-frequency power). Pericardial fat volumes were evaluated using multidetector computed tomography and its inflammation by gene expression of TNF (tumor necrosis factor)-alpha. Plasma lipid panel and norepinephrine level were also measured. RESULTS: At diet completion, hypercholesterolemic PCSK9-HFD had significantly ($P<0.05$ versus baseline) depressed HRV (SD of all pulse-to-pulse intervals over a single 5-minute period, root mean square of successive differences, proportion >50 ms, high-frequency power, low-frequency power), and both HFD groups had higher sympathovagal balance (SD of all pulse-to-pulse intervals over a single 5-minute period/root mean square of successive differences, low-frequency power/high-frequency power) compared with normal diet. Pericardial fat volumes and LDL (low-density lipoprotein) cholesterol concentrations correlated inversely with HRV and directly with sympathovagal balance, while sympathovagal balance correlated directly with plasma norepinephrine. Pericardial fat TNF-alpha expression was upregulated in PCSK9-HFD, colocalized with nerve fibers, and correlated inversely with root mean square of successive differences and proportion >50 ms. CONCLUSIONS: Progressive pericardial fat expansion and inflammation are associated with a fall in HRV in Ossabaw mini-pigs, implying aggravated autonomic imbalance. Hence, pericardial fat accumulation is associated with alterations in HRV and the autonomic nervous system. Visual Overview: A visual overview is available for this article.

[7] *Langer A, Tan M, Goodman SG et al.* **GOAL Canada: Physician Education and Support Can Improve Patient Management**. CJC Open 2020; 2:49-54.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32190825

ABSTRACT

Background: Despite the widespread use of statins, approximately 40% to 50% of Canadian patients with known cardiovascular disease do not achieve the low-density lipoprotein cholesterol (LDL-C) goal. Guidelines Oriented Approach to Lipid lowering (GOAL) is an investigator-initiated study aiming to ascertain the use of second- and third-line therapy and its impact on LDL-C goal achievement in a real-world setting. Methods: GOAL enrolled patients with clinical vascular disease or familial hypercholesterolemia and LDL-C > 2.0 mmol/L despite maximally tolerated statin therapy. During follow-up, physicians managed patients as clinically indicated but with online reminders of guideline recommendations. Results: Of 2009 patients enrolled (median age 63 years, 42% were female), baseline total cholesterol was 5.5 +/- 1.4 mmol/L, LDL-C was 3.3 +/- 1.3 mmol/L, non-high-density lipoprotein cholesterol was 4.1 +/- 1.4 mmol/L, high-density lipoprotein cholesterol was 1.3 +/- 0.4 mmol/L, and triglycerides were 2.0 +/- 1.5 mmol/L. Lipid-lowering therapy used at baseline was statin therapy in 76% (with 24% statin intolerant) and ezetimibe in 25%. During follow-up, the proportion of patients achieving an LDL-C level of < 2.0 mmol/L increased significantly to 50.8% as a result of additional lipid-lowering therapy. Patients achieving

the recommended LDL-C level were more likely to not be statin intolerant (83.8% vs 70.7%, P < 0.0001) and to be taking a high-efficacy type and dose of statin (52.4% vs 35.9%, P < 0.0001). The 3 top reasons for not using the recommended therapy with ezetimibe were patient refusal in 33%, not needed in 22%, and intolerance in 20%, whereas for PCSK9i the reasons were cost in 26%, not needed in 27%, or patient refusal in 25%. Conclusion: The results indicate the feasibility of optimizing management, resulting in achievement of the guideline-recommended LDL-C level. This has the potential to translate into reductions in cardiovascular morbidity and mortality of Canadian patients.

[8] *van Rooij JLM, Takx RAP, Velthuis BK et al.* **Coiling of the Internal Carotid Artery is Associated with Hypertension in Patients Suspected of Stroke**. Clin Neuroradiol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32189014
ABSTRACT
PURPOSE: The etiology of coiling (i.e. severe elongation) of the extracranial part of the internal carotid artery (ICA) is poorly understood with the proposed etiology being congenital, atherosclerotic or hypertension. The objective was to investigate the association of coiling with hypertension, carotid artery atherosclerosis and other cardiovascular risk factors. METHODS: A case control study was performed in patients suspected of stroke, with (cases) or without (controls) coiling of the ICA determined on compute tomography angiography (CTA). Baseline characteristics included age, gender, hypertension, diabetes, smoking and hypercholesterolemia. Coiling of the ICA and atherosclerotic plaque at the carotid bifurcation were assessed on CTA. Logistic regression analyses were conducted. RESULTS: Coiling was identified in 108 patients with a median age of 71 years. Cases were compared with 256 controls with a median age of 69 years. Hypertension was present in 63% of the patients with coiling compared to 51% in the control group. Univariable analysis showed that hypertension was significantly associated with coiling, with an odds ratio of 1.65 (95% confidence interval (CI) 1.04-2.61, p= 0.034). Multivariable analysis corrected for age and sex resulted in an odds ratio of 1.71 (95% CI 1.05-2.80, p= 0.032), while correcting for atherosclerotic plaque at the bifurcation yielded an odds ratio of 1.63 (95% CI 1.00-2.66, p= 0.049). Age and atherosclerotic plaque were not significantly associated with coiling. CONCLUSION: The main finding of this study was the significant association of hypertension with coiling of the ICA and the absence of an association with age, plaques and atherosclerotic risk factors other than hypertension.

[9] *Siasos G*. **The Role of Endothelium in Cardiovascular Diseases: New Insights**. Curr Med Chem 2020; 27:1019-1020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32194019
ABSTRACT

[10] *Zhong Y, Ding Y, Li L et al.* **Effects and Mechanism of Chlorogenic Acid on Weight Loss**. Current pharmaceutical biotechnology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32188382
ABSTRACT
OBJECTIVE: Chlorogenic acid has a wide range of health effects and has been recognized. This study was to explore the effects of chlorogenic acid on fat reduction and their unerlying mechanism.

METHODS: Firstly, we established the Monosodium Glutamate-induced obese mice model, and then were subjected to 4 weeks of chlorogenic acid gavage. Then, we established the oleic acid-induced human fatty liver HepG2 cells model, and then were subjected to 48 h of chlorogenic acid intervention. Finally, we used Oil red O staining, biochemical detection kits, RT-PCR and Western blot to evaluate their effects on fat reduction and related pathway. RESULTS: Chlorogenic acid treatment could reduce the fat accumulation in the liver, and reduced the blood lipid levels. And, chlorogenic acid can reduce the mRNA and proteins levels of PGC-1alpha and UCP-1 in the MSG-induced obese mice and oleic acid-induced human fatty liver HepG2 cells. CONCLUSION: Based on the above results, we deduced chlorogenic acid could improve blood lipid and liver function in obese, the mechanism may be related to PGC-1alpha/UCP-1 pathway. Chlorogenic acid can be developed as lowering blood lipids, obesity treatment drug.

[11] *Yang J, Lin X, Wang LA et al.* **LncRNA MALAT1 Enhances ox-LDL-Induced Autophagy through the SIRT1/MAPK/NF-kappaB Pathway in Macrophages**. Current vascular pharmacology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32183682

ABSTRACT

AIMS: We aimed to detected the biological function of LncRNA MALAT1 in regulating macrophage-related autophagy. BACKGROUND: Atherosclerosis is the mainly cause of cardiovascular and cerebrovascular diseases, which lead to the second cause of death worldwide. In advanced atherosclerotic plaque, macrophage apoptosis coupled with inflammatory cytokines secretion promotes the formation of necrotic cores. OBJECTIVE: To demonstrate the MALAT1-related autophagy and find related signaling pathway. METHOD: We utilized ox-LDL to incubate THP-1-derived macrophages in order to establish the foam cell model in vitro. RT-qPCR and western blot analyses confirmed the increasing expression level of MALAT1 and autophagy-related protein LC-3, Beclin-1. Si-RNAs study showed the significant decrease in autophagy activity and increase in apoptotic rate when knocking down MALAT1. Further study demonstrated that MALAT1 inhibited the expression of MAPK and NF-kappaB (p65) by up-regulating SIRT1. RESULT: Here we demonstrated that the long non-coding RNA MALAT1, which has attracted increasingly attention by its potent function on gene transcription modulation, is also indispensable for maintaining oxidized low density lipoproteins (ox-LDL)-induced autophagy in macrophage. Besides, we also proved that MALAT1 exerted its protective function by activating SIRT1, which subsequently inhibit the MAPK and NF-kappaB signaling pathway. CONCLUSION: LncRNA MALAT1 Enhances Ox-LDL-induced Autophagy via the SIRT1/MAPK/NF-kappaB Pathway in Macrophages.

[12] *Hu M, Huang X, Han X, Ji L*. **Loss of HNF1alpha Function Contributes to Hepatocyte Proliferation and Abnormal Cholesterol Metabolism via Downregulating miR-122: A Novel Mechanism of MODY3**. Diabetes, metabolic syndrome and obesity : targets and therapy 2020; 13:627-639.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32184642

ABSTRACT

Purpose: Mutations in hepatocyte nuclear factor 1alpha (HNF1alpha) are the cause of maturity-onset diabetes of the young type 3 (MODY3) and involved in the development of hepatocellular adenoma and abnormal lipid metabolism. Previously, we have found that the serum microRNA (miR)-122 levels in MODY3 patients were lower than those in type 2 diabetes mellitus and healthy

controls. This study aimed to investigate the mechanism of decreased miR-122 levels in patients with MODY3 and whether low levels of miR-122 mediate tumorigenesis and abnormal lipid metabolism associated with HNF1alpha deficiency in human hepatocytes. Methods: The expression of miR-122 was examined by real-time PCR. Dual-luciferase reporter assay was performed to confirm the transcriptional regulation of miR-122 by HNF1alpha. HepG2 cells were transfected with siRNA or miRNA mimic to downregulate or upregulate the expression of HNF1alpha or miR-122, respectively. CCK-8 and colony formation assay were used to determine cell proliferation. Lipid accumulation was examined by Oil Red O staining and intracellular triglyceride and cholesterol quantification assays. Results: HNF1alpha regulated the expression of miR-122 by directly binding to its promoter. Knockdown of HNF1alpha in HepG2 cells reduced the expression of miR-122, increased proliferation and promoted intracellular cholesterol accumulation. Overexpression of miR-122 partially rescued the phenotypes associated with HNF1alpha deficiency in human hepatocytes. Mechanistically, HNF1alpha modulated cholesterol homeostasis via miR-122-dependent activation of sterol regulatory element-binding protein-2 (SREBP-2) and regulation of proprotein convertase subtilisin/kexin type 9 (PCSK9). Moreover, circulating miR-122 levels were associated with serum cholesterol levels. Conclusion: Loss of HNF1alpha function led to hepatocyte proliferation and abnormal cholesterol metabolism by downregulating miR-122. Our findings revealed a novel mechanism that low levels of miR-122 mediate tumorigenesis and abnormal lipid metabolism associated with MODY3. MiR-122 may be a potential therapeutic target for the treatment of MODY3.

[13] *Lorenzatti AJ, Toth PP*. **New Perspectives on Atherogenic Dyslipidaemia and Cardiovascular Disease**. European cardiology 2020; 15:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32180834
ABSTRACT
Over the past few decades, atherogenic dyslipidaemia has become one of the most common phenotypic presentations of lipid abnormalities, being strongly and unequivocally associated with an increased risk of cardiovascular (CV) disease. Despite the excellent results achieved from statin and non-statin management of LDL cholesterol and CV events prevention, there still remains a significant residual risk, associated with the prevalence of non-LDL cholesterol lipid patterns characterised by elevated triglyceride levels, low HDL cholesterol, a preponderance of small and dense LDL particles, accumulation of remnant lipoproteins and postprandial hyperlipidaemia. These qualitative and quantitative lipid modifications are largely associated with insulin resistance, type 2 diabetes and obesity, the prevalence of which has grown to epidemic proportions throughout the world. In this review, we analyse the pathophysiology of this particular dyslipidaemia, its relationship with the development of atherosclerotic CV disease and, finally, briefly describe the therapeutic approaches, including changes in lifestyle and current pharmacological interventions to manage these lipid alterations aimed at preventing CV events.

[14] *Gonzalez-Colominas E, Batlle M, Monge-Escartin I et al.* **Impact of HCV cure with drug-acting antivirals in the use of concomitant medication and lipid profile: follow-up data 2 years after the sustained virological response**. European journal of gastroenterology & hepatology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32195695
ABSTRACT

Literature update week 12 (2020)

BACKGROUND AND AIM: Patients with chronic hepatitis C (CHC) frequently associated comorbidities and concomitant medication. Sustained virological response (SVR12) has been related to an increase in cholesterol serum levels and in peripheral vascular resistance. Our aim was to evaluate the impact of SVR12 on the use of concomitant medication and serum lipid profile. METHODS: Prospective study including patients treated with direct-acting antivirals who had achieved the SVR12. Clinical data and concomitant drugs were analysed at baseline and at least 1 year after SVR12. Differences from baseline to follow-up in the concomitant medication were evaluated by Stuart-Maxwell test and lipid profile by Wilcoxon signed-rank test. Patients were categorized according to the increase/decrease in the number of drugs included in each class (Anatomical Therapeutic Chemical classification system). RESULTS: Two hundred twenty-six patients with SVR12 were included, 73.5% were receiving concomitant drugs (49.6% with antihypertensive effect, 30.5% antacids, 16.4% anti-diabetic drugs, and 7.1% lipid-lowering agents). One year after SVR12, total cholesterol serum levels increased from 161 to 179 mg/dl ($P < 0.001$) and, after a median time of 25.7 months, the use of lipid-lowering drugs increased from 7.8 to 11.5% ($P = 0.009$). In addition, we observed a trend to use more antihypertensive drugs in older patients ($P = 0.06$), especially in those with cirrhosis. Anxiolytics decreased after SVR12 from 13.7 to 10.6% ($P = 0.035$). CONCLUSION: CHC cure is associated with a significant increase in cholesterol serum levels and the use of lipid-lowering agents, as well as the use of drugs with antihypertensive effect in older patients.

[15] *Kersani D, Mougin J, Lopez M et al.* **Stent coating by electrospinning with chitosan/poly-cyclodextrin based nanofibers loaded with simvastatin for restenosis prevention**. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V 2020; 150:156-167.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32179100

ABSTRACT

The main cause of failure of angioplasty stenting is restenosis due to neointimal hyperplasia, a too high proliferation of smooth muscle cells (SMC). The local and sustained delivery of selective pleiotropic drugs to limit SMC proliferation seems to be the hopeful solution to minimize this post surgery complication. The aim of this study is to develop a stent covered by nanofibers (NFs) produced by electrospinning, loaded with simvastatin (SV), a drug commonly used for restenosis prevention. NFs were prepared from the electrospinning of a solution containing SV and a mixture of chitosan (cationic) and beta-cyclodextrin (CD) polymer (anionic) which form together a polyelectrolyte complex that makes up the NFs matrix. First, the SV/CD interactions were studied by phase solubility diagram, DRX and DSC. The electrospinning process was then optimized to cover a self-expandable NiTiNOL stent and the mechanical resistance of the NFs sheath upon its introduction inside the delivery catheter was considered, using a crimper apparatus. The morphology, coating thicknesses and diameters of nanofibers were studied by scanning electron microscopy. The SV loading rates on the stents were controlled by the electrospinning time, and the presence of SV in the NFs was confirmed by FTIR. NFs stability in PBS pH 7.4 buffer could be improved after thermal post-treatment of NFs and in vitro release of SV in dynamic conditions demonstrated that the release profiles were influenced by the presence of CD polymer in NFs and by the thickness of the NFs sheath. Finally, a covered stent delivering 3 microg/mm(2) of SV within 6 h was obtained, whose efficiency will be investigated in a further in vivo study.

[16] *Gaita D, Gaita L, Mihaescu A*. **Non-HDL cholesterol series: PCSK9 inhibitor new season!** European journal of preventive cardiology 2020:2047487320913375.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32188296
ABSTRACT

[17] *Kotseva K, De Backer G, De Bacquer D et al.* **Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries**. European journal of preventive cardiology 2020:2047487320908698.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32195597
ABSTRACT
BACKGROUND: European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) V in primary care was carried out by the European Society of Cardiology EURObservational Research Programme in 2016-2018. The main objective was to determine whether the 2016 Joint European Societies' guidelines on cardiovascular disease prevention in people at high cardiovascular risk have been implemented in clinical practice. METHODS: The method used was a cross-sectional survey in 78 centres from 16 European countries. Patients without a history of atherosclerotic cardiovascular disease either started on blood pressure and/or lipid and/or glucose lowering treatments were identified and interviewed >/= 6 months after the start of medication. RESULTS: A total of 3562 medical records were reviewed and 2759 patients (57.6% women; mean age 59.0 +/- 11.6 years) interviewed (interview rate 70.0%). The risk factor control was poor with 18.1% of patients being smokers, 43.5% obese (body mass index >/=30 kg/m(2)) and 63.8% centrally obese (waist circumference >/=88 cm for women, >/=102 cm for men). Of patients on blood pressure lowering medication 47.0% reached the target of <140/90 mm Hg (<140/85 mm Hg in people with diabetes). Among treated dyslipidaemic patients only 46.9% attained low density lipoprotein-cholesterol target of <2.6 mmol/l. Among people treated for type 2 diabetes mellitus, 65.2% achieved the HbA1c target of <7.0%. CONCLUSION: The primary care arm of the EUROASPIRE V survey revealed that large proportions of people at high cardiovascular disease risk have unhealthy lifestyles and inadequate control of blood pressure, lipids and diabetes. Thus, the potential to reduce the risk of future cardiovascular disease throughout Europe by improved preventive cardiology programmes is substantial.

[18] *Schindler TH, Varney B, Jain S*. **Molecular imaging of active coronary micro-calcification with (18)F-NaF and PET: emergence of a new biomarker of the vulnerable atherosclerotic plaque?** European journal of preventive cardiology 2020:2047487320912627.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32183559
ABSTRACT

[19] *Escate R, Mata P, Cepeda JM et al.* **miR-505-3p controls chemokine receptor up-regulation in macrophages: role in familial hypercholesterolemia**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018; 32:601-612.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32172543
ABSTRACT

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

[20] *Nelson AJ, Nicholls SJ*. **Translating evidence from clinical trials of omega-3 fatty acids to clinical practice**. Future cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32180456
ABSTRACT
The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial study recently demonstrated that administration of high doses of omega-3 fatty acids confers cardiovascular benefit in high-risk patients with the modest hypertriglyceridemia. This provided optimism for a therapeutic area that has challenged the field of cardiovascular prevention for 2 decades. However, it raises a number of questions including understanding the mechanism underscoring this benefit, how best to use these therapies and whether similar results will be observed with alternative omega-3 fatty acid preparations. Contemporary clinical trials of omega-3 fatty acids and their attempt to prevent cardiovascular events will be reviewed.

[21] *Herrema H, Nieuwdorp M, Groen AK*. **Microbiome and Cardiovascular Disease**. Handbook of experimental pharmacology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32185503
ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is a prime example of a systems disease. In the initial phase, apolipoprotein B-containing cholesterol-rich lipoproteins deposit excess cholesterol in macrophage-like cells that subsequently develop into foam cells. A multitude of systemic as well as environmental factors are involved in further progression of atherosclerotic plaque formation. In recent years, both oral and gut microbiota have been proposed to play an important role in the process at different stages. Particularly bacteria from the oral cavity may easily reach the

circulation and cause low-grade inflammation, a recognized risk factor for ASCVD. Gut-derived microbiota on the other hand can influence host metabolism on various levels. Next to translocation across the intestinal wall, these prokaryotes produce a great number of specific metabolites such as trimethylamine and short-chain fatty acids but can also metabolize endogenously formed bile acids and convert these into metabolites that may influence signal transduction pathways. In this overview, we critically discuss the novel developments in this rapidly emerging research field.

[22] *Siddiqa A, Ahmad J, Ali A, Khan S*. **Deciphering the expression dynamics of ANGPTL8 associated regulatory network in insulin resistance using formal modelling approaches**. IET Syst Biol 2020; 14:47-58.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32196463
ABSTRACT
ANGPTL8 is a recently identified novel hormone which regulates both glucose and lipid metabolism. The increase in ANGPTL8 during compensatory insulin resistance has been recently reported to improve glucose tolerance and a part of cytoprotective metabolic circuit. However, the exact signalling entities and dynamics involved in this process have remained elusive. Therefore, the current study was conducted with a specific aim to model the regulation of ANGPTL8 with emphasis on its role in improving glucose tolerance during insulin resistance. The main contribution of this study is the construction of a discrete model (based on kinetic logic of Rene Thomas) and its equivalent Stochastic Petri Net model of ANGPTL8 associated Biological Regulatory Network (BRN) which can predict its dynamic behaviours. The predicted results of these models are in-line with the previous experimental observations and provide comprehensive insights into the signalling dynamics of ANGPTL8 associated BRN. The authors' results support the hypothesis that ANGPTL8 plays an important role in supplementing the insulin signalling pathway during insulin resistance and its loss can aggravate the pathogenic process by quickly leading towards Diabetes Mellitus. The results of this study have potential therapeutic implications for treatment of Diabetes Mellitus and are suggestive of its potential as a glucose-lowering agent.

[23] *Roy A, Saqib U, Wary K, Baig MS*. **Macrophage neuronal nitric oxide synthase (NOS1) controls the inflammatory response and foam cell formation in atherosclerosis**. Int Immunopharmacol 2020; 83:106382.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32193098
ABSTRACT
Vascular inflammation plays a decisive role in the formation of foam cells and in the pathophysiology of atherosclerosis. However, the underlying mechanisms of these processes are not clearly understood. Macrophages engulf oxidized low-density lipoproteins (OxLDLs) via a scavenger receptor (SR), an event that mediates the elaboration of proinflammatory cytokines to initiate necrotic core formation in atherogenic plaques. In this study, we demonstrate that Nitric oxide synthase 1 (NOS1)-derived nitric oxide (NO) promotes OxLDL uptake and enhances the release of proinflammatory cytokines by macrophages. Conversely, we show that NOS1 inhibition by N(G)-nitro-L-arginine methyl ester (L-NAME) suppresses OxLDL uptake and proinflammatory cytokine expression. Current studies indicate that NOS1 plays a crucial role in vascular inflammation and in the progression of atherosclerosis. Therefore, interference with NOS1

enzymatic activity should serve as an effective strategy to reduce foam cell formation and limit the extent of atherosclerotic plaque expansion.

[24] *Tada H, Okada H, Nomura A et al.* **A Healthy Family of Familial Hypobetalipoproteinemia Caused by a Protein-truncating Variant in the PCSK9 Gene**. Intern Med 2020; 59:783-787.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32173689
ABSTRACT
We present the first case of a Japanese patient with familial hypobetalipoproteinemia (FHBL) caused by a protein-truncating variant in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene. A 34-year-old woman was referred to our hospital due to her low low-density lipoprotein (LDL)-cholesterolemia (34 mg/dL). She did not have any secondary causes of hypobetalipoproteinemia. Her father and her younger sister also exhibited low LDL cholesterol levels. We identified a protein-truncating variant in the PCSK9 gene (c.1090_1091del/p.Pro364ArgfsTer62) among them. None of them exhibited atherosclerotic cardiovascular diseases nor any other complications associated with low LDL cholesterol, including fatty liver, neurocognitive disorders, or cerebral hemorrhaging.

[25] *Shinto L, Lahna D, Murchison CF et al.* **Oxidized Products of Omega-6 and Omega-3 Long Chain Fatty Acids Are Associated with Increased White Matter Hyperintensity and Poorer Executive Function Performance in a Cohort of Cognitively Normal Hypertensive Older Adults**. Journal of Alzheimer's disease : JAD 2020; 74:65-77.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32176647
ABSTRACT
BACKGROUND: Cerebrovascular disease is a common cause of dementia in older adults, and potentially preventable with early intervention. Oxylipins are produced from the oxidation of long-chain polyunsaturated fatty acids (PUFA) possessing potent vascular effects. Oxylipins generated from the cytochrome P450 pathway are enzymatically converted to diols by soluble epoxide hydrolase (sEH); sEH products have been associated with small vessel ischemic disease. Little is known about oxylipins' impact on markers of dementia risk. OBJECTIVE: An exploratory examination of the association between omega-6 and omega-3 derived oxylipins, brain MRI, and cognition. METHODS: Thirty-seven non-demented participants with controlled hypertension (mean age 65.6 years) were enrolled in a dementia prevention study investigating fish oil and lipoic acid on preserving cognitive function. Baseline associations between plasma oxylipins, white matter hyperintensity (WMH), and Trails-B were examined using linear regression. P450-derived diol/epoxide ratio was an indirect measure of sEH activity. RESULTS: Omega-6 derived 9-HODE was associated with increased WMH ($p = 0.017$) and reduced grey matter volume ($p = 0.02$). Omega-6 P450-derived diol/epoxide ratio 9,10-DiHOME/9,10-EpOME was associated with increased WMH ($p = 0.035$) and poorer performance on Trails-B ($p = 0.05$); ratio14,15-DHET/14,15-EET was associated with increased WMH ($p = 0.045$). Omega-3 P450-derived diol/epoxide ratio 19,20-DiHDPE/19,20-EpDPE was associated with increased WMH ($p = 0.04$) and poorer performance on Trails-B ($p = 0.04$). Arachidonic acid was associated with better performance on Trails-B ($p = 0.012$); Omega-3 derived 16,17-EpDPE was associated with decreased WMH ($p = 0.005$). CONCLUSIONS: With the exception of arachidonic acid, it was specific oxylipin products, not their parent PUFAs, that were associated with unfavorable and favorable MRI and cognitive markers of dementia risk.

[26] *Szarek M, Amarenco P, Callahan A et al.* **Atorvastatin Reduces First and Subsequent Vascular Events Across Vascular Territories in the SPARCL Trial**. Journal of the American College of Cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32194196
ABSTRACT
BACKGROUND: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial compared atorvastatin with placebo in 4,731 participants with recent stroke or transient ischemic attack and no known coronary heart disease. Atorvastatin reduced the first occurrence of stroke and the first occurrence of a composite of vascular events. OBJECTIVES: This post hoc analysis assessed the occurrence of all (first and subsequent) vascular events and the effect of atorvastatin to reduce these events by vascular territory (cerebrovascular, coronary, or peripheral) in SPARCL. METHODS: Treatment effects on total adjudicated vascular events, overall and by vascular territory, were summarized by marginal proportional hazards models. Vascular event rates were estimated for each treatment group with cumulative incidence functions. RESULTS: The placebo group had an estimated 41.2 first and 62.7 total vascular events per 100 participants over six years. There were 164 fewer first and 390 fewer total vascular events in the atorvastatin group (total events hazard ratio 0.68, 95% confidence interval 0.60 to 0.77). The total events reduction included 177 fewer cerebrovascular, 170 fewer coronary, and 43 fewer peripheral events. Over six years, an estimated 20 vascular events per 100 participants were avoided with atorvastatin treatment. CONCLUSIONS: In participants with recent stroke or transient ischemic attack, the total number of vascular events prevented with atorvastatin was more than twice the number of first events prevented. Total event reduction provides a comprehensive metric to capture the totality of atorvastatin clinical efficacy in reducing disease burden after stroke or transient ischemic attack.

[27] *Attalah Nee Rezkallah C, Thongkum A, Zhu C, Chen QM*. **Resveratrol for protection against statin toxicity in C2C12 and H9c2 cells**. Journal of biochemical and molecular toxicology 2020:e22484.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32196851
ABSTRACT
Statins are among the most commonly prescribed drugs for the treatment of high blood cholesterol. Myotoxicity of statins in certain individuals is often a severe side effect leading to withdrawal. Using C2C12 and H9c2 cells, both exhibiting characteristics of skeletal muscle cells, we addressed whether resveratrol (RSV) can prevent statin toxicity. Statins decreased cell viability in a dose and time-dependent manner. Among the five statins tested, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin, simvastatin is the most toxic one. Simvastatin at 10 microM caused about 65% loss of metabolic activity as measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays in C2C12 cells or H9c2 cells. Inhibition of metabolic activity correlates with an increase in caspase activity. RSV was found to protect H9c2 cells from simvastatin-induced activation of caspase-3/7. However, such protection was not found in C2C12 cells. This cell type-dependent effect of RSV adds to the complexity in muscle cell toxicity of statins.

[28] *Fernandez-Cidon B, Candas-Estebanez B, Ribalta J et al.* **Precipitated sdLDL: An easy method to estimate LDL particle size**. Journal of clinical laboratory analysis 2020:e23282.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32198796

ABSTRACT

BACKGROUND: LDL-C lowering is the main measure in cardiovascular disease prevention but a residual risk of ischemic events still remains. Alterations of lipoproteins, specially, increase in small dense LDL (sdLDL) particles are related to this risk. OBJECTIVE: To investigate the potential use of sdLDL cholesterol concentration (sdLDL-C) isolated by an easy precipitation method and to assess the impact of a set of clinical and biochemical variables determined by NMR on sdLDL concentration. METHODS: sdLDL-C and NMR lipid profile were performed in 85 men samples. Association among them was evaluated using Pearson coefficients (rxy). A multivariate regression was performed to identify the influence of NMR variables on sdLDL-C. RESULTS: A strong association between sdLDL-C and LDLLDL-P (rxy = 0.687) and with LDL-Z (rxy = -0.603) was found. The multivariate regression explained a 56.8% in sdLDL-C variation (P = 8.77.10-12). BMI, ApoB, triglycerides, FFA, and LDL-Z showed a significant contribution. The most important ones were ApoB and LDL-Z; a 1nm increase (LDL-Z) leads to decrease 126 nmol/L in sdLDL-C. CONCLUSION: The association between sdLDL-C, LDL-Z, and LDL-P is clear. From a large number of variables, especially LDL-Z and apoB influence on sdLDL-C. Results show that the smaller the LDL size, the higher their cholesterol concentration. Therefore, sdLDL-C determination by using this easy method would be useful to risk stratification and to uncover cardiovascular residual risk.

[29] *Bittner VA, Jacobson TA, Ballantyne CM, Guyton JR*. **JCL roundtable: Omega-3 fatty acids and cardiovascular outcomes**. Journal of clinical lipidology 2020; 14:4-15.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32192643

ABSTRACT

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) in 2018 demonstrated the value of an omega-3 fatty acid formulation, icosapent ethyl (eicosapentaenoic acid ethyl ester) for preventive treatment of atherosclerotic cardiovascular disease (ASCVD). This JCL Roundtable discussion brings together three experts to explore the origins and implications of REDUCE-IT and more broadly omega-3 fatty acids for mitigation of ASCVD risk. REDUCE-IT achieved a highly significant 25% reduction of major adverse cardiovascular events. It is the first trial of a triglyceride-lowering drug to gain unequivocal success in high-risk patients treated intensively with statins. It corroborates positive results from an earlier major trial using eicosapentaenoic acid (EPA) ethyl ester, the Japan EPA Lipid Intervention Study (JELIS), which included hypercholesterolemic subjects treated with low-dose statin mostly in primary prevention. Together these studies mark a new avenue for preventive treatment of ASCVD. Omega-3 fatty acids also show some promise, though less decisively, for reducing inflammation and cardiovascular mortality in a broader context.

[30] *Moriarty PM, Thompson PD, Cannon CP et al.* **Efficacy and safety of alirocumab in statin-intolerant patients over 3 years: open-label treatment period of the ODYSSEY ALTERNATIVE trial**. Journal of clinical lipidology 2020; 14:88-97.e82.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32192644

ABSTRACT

BACKGROUND: The 24-week randomized, double-blind ODYSSEY ALTERNATIVE trial (NCT01709513) demonstrated significant low-density lipoprotein cholesterol (LDL-C) reductions with the PCSK9 inhibitor alirocumab vs ezetimibe in statin-intolerant patients, with significantly fewer skeletal

muscle events (SMEs; 32.5%) vs atorvastatin (46.0%; hazard ratio: 0.61, 95% confidence interval: 0.38 to 0.99, P = .042). OBJECTIVE: ALTERNATIVE participants could enter an open-label treatment period (OLTP) for assessment of long-term safety. METHODS: Two hundred and eighty one patients entered the OLTP; 93.7%, 84.0%, and 92.9% of patients who received atorvastatin, ezetimibe, and alirocumab, respectively, during double-blind treatment, including 216 patients (76.9%) who completed double-blind treatment, as well as patients who either prematurely discontinued treatment due to SME (n = 51 [18.1%]) or other reasons (n = 14 [5.0%]) but completed week 24 assessments. All patients in the OLTP received alirocumab (75 or 150 mg every 2 weeks based on investigator decision) for approximately 3 years or until commercial availability, whichever came first. RESULTS: SMEs were reported by 38.4% of patients in the OLTP. Safety results from the OLTP were similar to those of the alirocumab group in the double-blind period, except for a lower rate of discontinuations due to SMEs observed with alirocumab in the OLTP (3.2% vs 15.9% in the double-blind period). At OLTP week 8, mean LDL-C reduction from baseline (=week 0 of double-blind period) was 52.0%, with reductions sustained through to the end-of-treatment visits (55.4% and 53.7% reduction at weeks 100 and 148, respectively). CONCLUSIONS: In this population of statin-intolerant patients, alirocumab was well tolerated and produced durable LDL-C reductions over 3 years.

[31] *Bae J, Hong N, Lee BW et al.* **Comparison of Renal Effects of Ezetimibe-Statin Combination versus Statin Monotherapy: A Propensity-Score-Matched Analysis**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32183405
ABSTRACT
Neither lowering of blood lipid levels nor treatment with statins definitively improves renal outcomes. Ezetimibe, a non-statin antilipidemic agent, is known to not only decrease blood lipid levels but also reduce inflammatory response and activate autophagy. We evaluated the effect of adding ezetimibe to a statin on renal outcome compared with statin monotherapy by analyzing longitudinal data of 4537 patients treated with simvastatin 20 mg plus ezetimibe 10 mg (S + E) or simvastatin 20 mg alone (S) for more than 180 days. A propensity-score-based process was used to match baseline characteristics, medical history, and estimated glomerular filtration rate (eGFR) between S + E and S groups. Changes in serum creatinine and incidence of renal events, defined as doubling of serum creatinine to >/=1.5 mg/dL or occurrence of end-stage renal disease after the first day of treatment initiation, were compared between the groups. Among 3104 well-matched patients with a median follow-up of 4.2 years, the S + E group showed a significantly lower risk of renal events than the S group (hazard ratio 0.58; 95% CI 0.35-0.95, P = 0.032). In addition, the S + E group tended to preserve renal function compared with the S group throughout follow-up, as assessed by serum creatinine changes (P-values for time-group interactions <0.001). These data support the beneficial effects on renal function when combining ezetimibe with a statin.

[32] *Kim MJ, Jung SK*. **Nutraceuticals for prevention of atherosclerosis: Targeting monocyte infiltration to the vascular endothelium**. J Food Biochem 2020:e13200.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32189369
ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death, globally, and is a serious problem in developing countries. Preventing atherosclerosis is key to reducing the risk of developing CVD. Similar to carcinogenesis, atherogenesis can be divided into four stages: initiation, promotion, progression, and acute events. The current study focuses on the promotion stage, which is characterized by circular monocyte penetration into vascular endothelial cells, monocyte differentiation into macrophages, and the formation of foam cells. This early stage of atherogenesis is a major target for nutraceuticals. We discuss nutraceuticals that can potentially inhibit monocyte adhesion to the vascular endothelium, thereby preventing the promotional stage of atherosclerosis. The mechanisms through which these nutraceuticals prevent monocyte adhesion are classified according to the following targets: NF-kappaB, ROS, MAPKs, and AP-1. Additionally, we discuss promising targets for nutraceuticals that can regulate monocyte adhesion to the endothelium. PRACTICAL APPLICATIONS: Introduction of atherogenesis with initiation, promotion, progression, and acute events provide specific information and factors for each step in the development of atherosclerosis. Functional food or pharmaceutical researchers can set target stages and use them to develop materials that control atherosclerosis. In particular, because it focuses on vascular inflammation via interaction between monocytes and vascular endothelial cells, it provides specific information to researchers developing functional foods that regulate this process. Therefore, this manuscript, unlike previous papers, will provide material information and potential mechanisms of action to researchers who want to develop functional foods that control vascular inflammation rather than vascular lipids.

[33] *Lopes TIB, Pereira ES, Freitas DDS et al.* **Spectral profiles of commercial omega-3 supplements: an exploratory analysis by ATR-FTIR and (1)H NMR**. J Food Sci Technol 2020; 57:1251-1257.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32180621

ABSTRACT

Most of the population is dependent on supplemental products to reach the recommended level of omega-3 polyunsaturated fatty acid (omega-3 PUFA) intake. Thus, knowledge about the quality of omega-3 supplements is important for their safe consumption. In this work, attenuated total reflectance-Fourier transform infrared (ATR-FTIR) and nuclear magnetic resonance (NMR) spectroscopy were applied to assess the quality of fourteen commercial omega-3 supplements. Using ATR-FTIR data, we could identify whether omega-3 PUFA was esterified as either triacylglyceride (71%) or ethyl (29%) esters in omega-3 supplements. The type of esterification is rarely included in the product labels, although the consumer should have the right to choose which form of the supplement to consume. On the other hand, (1)H NMR spectra were useful to determine the relative concentration of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, and omega-3 PUFA in these commercial samples. Ethyl esters have higher concentrations of unsaturated fatty acids. The NMR results showed a good agreement between the obtained and declared DHA and EPA amounts on the product labels, except for one sample whose high level of omega-3 PUFA indicated it to be a vegetable oil-enriched supplement. Moreover, omega-3 supplements from Schizochytrium sp. microalgae oil revealed higher levels of DHA and omega-3 PUFA, but lower levels of EPA than fish oil. These findings indicate the need for a constant assessment of the quality of commercial products whose ATR-FTIR spectra could be routinely used for the evaluation of PUFA esterification, and NMR analysis could be used to provide advanced quantitative information on commercial omega-3 supplements.

[34] *Goldberg AC, Hanselman JC, Duell PB*. **Measuring vs Estimating LDL-C Levels in a Clinical Trial of Bempedoic Acid-Reply**. Jama 2020; 323:1095-1096.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32181844
ABSTRACT

[35] *Xu HG, Pan S*. **Measuring vs Estimating LDL-C Levels in a Clinical Trial of Bempedoic Acid**. Jama 2020; 323:1095.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32181841
ABSTRACT

[36] *Josefs T, Barrett TJ, Brown EJ et al.* **Neutrophil extracellular traps promote macrophage inflammation and impair atherosclerosis resolution in diabetic mice**. JCI insight 2020; 5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32191637
ABSTRACT
Neutrophil extracellular traps (NETs) promote inflammation and atherosclerosis progression. NETs are increased in diabetes and impair the resolution of inflammation during wound healing. Atherosclerosis resolution, a process resembling wound healing, is also impaired in diabetes. Thus, we hypothesized that NETs impede atherosclerosis resolution in diabetes by increasing plaque inflammation. Indeed, transcriptomic profiling of plaque macrophages from NET+ and NET- areas in low-density lipoprotein receptor-deficient (Ldlr-/-) mice revealed inflammasome and glycolysis pathway upregulation, indicating a heightened inflammatory phenotype. We found that NETs declined during atherosclerosis resolution, which was induced by reducing hyperlipidemia in nondiabetic mice, but they persisted in diabetes, exacerbating macrophage inflammation and impairing resolution. In diabetic mice, deoxyribonuclease 1 treatment reduced plaque NET content and macrophage inflammation, promoting atherosclerosis resolution after lipid lowering. Given that humans with diabetes also exhibit impaired atherosclerosis resolution with lipid lowering, these data suggest that NETs contribute to the increased cardiovascular disease risk in this population and are a potential therapeutic target.

[37] *Hedayatnia M, Asadi Z, Zare-Feyzabadi R et al.* **Dyslipidemia and cardiovascular disease risk among the MASHAD study population**. Lipids in health and disease 2020; 19:42.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32178672
ABSTRACT
INTRODUCTION: Dyslipidemia may be defined as increased levels of serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), or a decreased serum high-density lipoprotein cholesterol (HDL-C) concentration. Dyslipidemia is an established risk factor for cardiovascular disease (CVD). We aimed to investigate the association of dyslipidemia and CVD events among a population sample from Mashhad, in northeastern Iran. MATERIAL AND METHODS: This prospective cohort study comprised a population of 8698 men and women aged 35-65 years who were recruited from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study. Socioeconomic and demographic status, anthropometric parameters, laboratory evaluations, lifestyle factors, and medical history were gathered through a comprehensive questionnaire and laboratory and clinical assessment for all participants. Cox regression model and

95% confidence interval (CI) were used to evaluate the association of dyslipidemia and its components with CVD incidence. RESULTS: After 6 years of follow-up, 233 cases of CVD (including 119 cases of unstable angina [US], 74 cases of stable angina [SA], and 40 cases of myocardial infarction [MI]) were identified in the study population. Unadjusted baseline serum LDL-C, TC, and TG levels were positively associated with the risk of total CVD events among the entire population (HR: 1.54, 95% CI: 1.19-2; P-value< 0.01; HR: 1.53; 95% CI: 1.18-1.98; P < 0.01; HR: 1.57; 95% CI: 1.27-2.03; P < 0.01, respectively). However, after adjusting for confounding factors (age, body mass index [BMI], family history of CVD, smoking status [non-smoker, ex-smoker and current smoker], lipid lowering drug treatment, anti-hypertensive drug treatment, hypertension, healthy eating index [HEI], total energy intake, and presence of diabetes mellitus), a significant direct association only remained between TC and MI risk in men (HR: 2.71; 95%CI: 1.12-6.57; P-value< 0.05). CONCLUSION: In the present study, TC baseline level was significantly associated with the risk of MI among men.

[38] *Radikova Z, Penesova A, Vlcek M et al.* **Lipoprotein profiling in early multiple sclerosis patients: effect of chronic inflammation?** Lipids in health and disease 2020; 19:49.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32178676
ABSTRACT
BACKGROUND: Inflammatory cytokines contribute to proatherogenic changes in lipid metabolism by reduction of HDL-cholesterol (HDL-C) levels, impairment of its antiinflammatory and antioxidant functions. Therefore, the protective actions of HDL-C can be limited in chronic inflammatory diseases such as multiple sclerosis (MS). The aim of this study was to assess the association between lipoprotein subfractions and inflammatory status in early stages of multiple sclerosis. METHODS: Polyacrylamide gel electrophoresis Lipoprint(c) System was used for lipoprotein profile analysis in 19 newly diagnosed MS patients, and in matched 19 healthy controls. Serum levels of interleukin (IL) 1beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, interferon-gamma and TNF-alpha were measured by multiplex bead assay. RESULTS: Concentrations of the measured cytokines and lipoprotein subclasses were comparable between MS patients and controls. Male, but not female MS patients had significantly higher total HDL-C and small HDL-C subfraction than healthy controls. Large HDL-C negatively correlated with all measured cytokines except IL-17 in MS but not in controls. Intermediate HDL-C subfractions correlated positively with all measured cytokines except G-CSF in MS females but not in MS males or controls. CONCLUSION: Our results of higher HDL-C and mainly its small HDL-C subfraction suggest that male MS patients are at higher risk of atherosclerosis and the subtle dyslipidemia is present in early stages of the disease. The correlations between specific HDL-C subfractions and the inflammatory cytokines demonstrate mutual links between systemic inflammation and lipid metabolism in MS. TRIAL REGISTRATION: ClinicalTrials.gov, Identifier: NCT03052595 Registered on Feb 14, 2017.

[39] *Wang JF, Zhang HM, Li YY et al.* **Correction to: A combination of omega-3 and plant sterols regulate glucose and lipid metabolism in individuals with impaired glucose regulation: a randomized and controlled clinical trial**. Lipids in health and disease 2020; 19:41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32178692
ABSTRACT

Literature update week 12 (2020)

Following publication of the original article [1], the Authors' Contributions statement need to be changed.

[40] *Urbonas G, Venceviciene L, Valius L et al.* **Primary Prevention of Cardiovascular Risk in Lithuania-Results from EUROASPIRE V Survey**. Medicina (Kaunas, Lithuania) 2020; 56.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32197516
ABSTRACT
Background and Objectives: Cardiovascular disease (CVD) prevention guidelines define targets for lifestyle and risk factors for patients at high risk of developing CVD. We assessed the control of these factors, as well as CVD risk perception in patients enrolled into the primary care arm of the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE V) survey in Lithuania. Materials and Methods: Data were collected as the part of the EUROASPIRE V survey, a multicenter, prospective, cross-sectional observational study. Adults without a documented CVD who had been prescribed antihypertensive medicines and/or lipid-lowering medicines and/or treatment for diabetes (diet and/oral antidiabetic medicines and/or insulin) were eligible for the survey. Data were collected through the review of medical records, patients' interview, physical examination and laboratory tests. Results: A total of 201 patients were enrolled. Very few patients reached targets for low-density lipoprotein cholesterol (LDL-C) (4.5%), waist circumference (17.4%) and body mass index (15.4%). Only 31% of very high CVD risk patients and 52% of high-risk patients used statins. Blood pressure target was achieved by 115 (57.2%) patients. Only 21.7% of patients at very high actual CVD risk and 27% patients at high risk correctly estimated their risk. Of patients at moderate actual CVD risk, 37.5% patients accurately self-assessed the risk. About 60%-80% of patients reported efforts to reduce the intake of sugar, salt or alcohol; more than 70% of patients were current nonsmokers. Only a third of patients reported weight reduction efforts (33.3%) or regular physical activity (27.4%). Conclusions: The control of cardiovascular risk factors in a selected group of primary prevention patients was unsatisfactory, especially in terms of LDL-C level and body weight parameters. Many patients did not accurately perceive their own risk of developing CVD.

[41] *Chen S, Yang H, Chen Y et al.* **Association between serum uric acid levels and dyslipidemia in Chinese adults: A cross-sectional study and further meta-analysis**. Medicine (Baltimore) 2020; 99:e19088.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32176036
ABSTRACT
This study aimed to investigate the association of serum uric acid (SUA) levels with dyslipidemia and its components and to further explore the age- and gender-specific association of SUA levels with dyslipidemia in Chinese adults.A cross-sectional study was performed among 8642 adults who underwent health examinations. A meta-analysis covering 17 studies was conducted to confirm the results.The prevalence of hyperuricemia and dyslipidemia was 9.25% and 20.44%, respectively. Participants with hyperuricemia had higher prevalence of dyslipidemia than those without hyperuricemia (34.42% vs 19.01%, $P < .005$). Compared with participants with SUA in the first quintile, the odds ratio (OR) (95% confidence interval) of dyslipidemia in the second, third, fourth, and fifth quintiles of SUA were 1.095 (0.901-1.332), 1.582 (1.315-1.904), 2.095 (1.752-2.505), and 3.212 (2.702-3.818), respectively. Subgroup analysis showed that SUA quintiles were significantly

correlated with the likelihood of dyslipidemia in females aged > 50 years and in males, but not in females aged </=50 years. The meta-analysis also showed that hyperuricemia increased the likelihood of dyslipidemia and the pooled OR for the highest uric acid level vs the lowest uric acid level was 1.84 (1.49-2.28).SUA levels are significantly associated with dyslipidemia, and this association is impacted by age and gender.

[42] *Zhang C, Tang M, Lu X et al.* **Relationship of ankle-brachial index, vibration perception threshold, and current perception threshold to glycemic variability in type 2 diabetes**. Medicine (Baltimore) 2020; 99:e19374.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32195933
ABSTRACT
To explore the relationship of glycemic variability with lower extremity arterial disease (LEAD) and diabetic peripheral neuropathy (DPN).Seventy-eight patients with type 2 diabetes were enrolled. All patients underwent 72-hour dynamic blood glucose monitoring and obtained mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), standard deviation of blood glucose (SD), largest amplitude of glycemic excursion (LAGE), mean blood glucose (MBG), T>/=10.0 (percentage of time for blood glucose levels >/=10.0 mmol/L), T</=3.9 (percentage of time for blood glucose levels </=3.9 mmol/L), and other glycemic variability parameters. In the meanwhile, in order to explore the correlation of glycemic variability parameters with ankle-brachial index (ABI), vibration perception threshold (VPT), and current perception threshold (CPT), all patients underwent quantitative diabetic foot screening, including ABI for quantitative assessment of lower extremity arterial lesions and VPT and CPT for quantitative assessment of peripheral neuropathy.Patients were divided into abnormal CPT group (n = 21) and normal CPT group (n = 57) according to the CPT values. Compared with the normal CPT group, abnormal CPT group showed significantly higher levels of HbA1c, longer duration of diabetes, and higher levels of T</=3.9 (P < .05). However, there was no significant difference of MAGE, SD, LAGE, MODD, and other glycemic variability parameters between abnormal CPT group and normal CPT group (P > .05). Pearson correlation analysis or Spearman correlation analysis showed that ABI negatively correlated with MBG, T>/=10.0, SD, LAGE, and MAGE (P < .05), but no correlation of ABI with T</=3.9 and MODD (P > .05) was shown. VPT showed a positive correlation with T>/=10.0 (P < .05), but no correlation with other glycemic variability parameters (P > .05). There was no correlation between the other CPT values and the glycemic variability parameters (P > .05), except that the left and right 250 Hz CPT values were positively correlated with T</=3.9 (P > .05).The higher the blood glucose levels, the severer the degree of LEAD and DPN lesions; the higher the incidence of hypoglycemia, the severer the degree of DPN lesions; the greater the fluctuation of blood glucose, the severer the degree of LEAD lesions. However, the glycemic variability was not significantly correlated with DPN.

[43] *Zhang T, Jiang Y, Zhang S et al.* **The association between homocysteine and ischemic stroke subtypes in Chinese: A meta-analysis**. Medicine (Baltimore) 2020; 99:e19467.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32195946
ABSTRACT
BACKGROUND: The findings on the association between elevated plasma homocysteine levels and the risk of the trial of org 10172 in acute stroke treatment (TOAST) of ischemic stroke have been inconsistent in Chinese. So far, there is no meta-analysis about the association between Hcy and

the TOAST subtypes of ischemic stroke in Chinese. This study; therefore, aimed to evaluate whether elevated homocysteine levels are associated with the TOAST subtypes of ischemic stroke using a meta-analysis. MATERIALS AND METHODS: A systematic search of electronic databases were conducted for studies reporting homocysteine levels in ischemic stroke and the TOAST of ischemic stroke to April 18, 2018. The data were extracted after the application of inclusion and exclusion criteria. All the data were analyzed using Stata software version 9.0 (Stata Corp LP, College Station, TX). The standardized mean difference (SMD) and 95% confidence interval (CI) were used to compare continuous variables. RESULTS: Thirteen studies comprising 3114 participants (2243 patients and 871controls) met the eligibility criteria and were included in the meta-analysis. The meta-analysis revealed that the ischemic stroke group had significantly higher levels of homocysteine than controls (SMD = 1.15, 95% CI = 0.85-1.45, P < .05). The subgroup analyses suggested that the groups of patients with large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke of other determined etiology and stroke of undetermined etiology had significantly higher levels of homocysteine compared to those in the control group (large-artery atherosclerosis: SMD = 2.12, 95% CI = 1.40-2.84, P < .05; small-vessel occlusion: SMD = 1.10, 95% CI = 0.72-1.48, P < .05; CE: SMD = 1.17, 95% CI = 0.64-1.71, P < .05; stroke of other determined etiology: SMD = 0.88, 95% CI = 0.53-1.24, P < .05; stroke of undetermined etiology: SMD = 1.50, 95% CI = 0.66-2.33, P < .05, respectively). CONCLUSION: This meta-analysis found that ischemic stroke patients and the TOAST of ischemic stroke patients in Chinese had significantly higher homocysteine levels than the controls, suggesting that serum homocysteine levels may be a risk factor for ischemic stroke and the TOAST subtypes of ischemic stroke in Chinese.

[44] *Raal FJ, Kallend D, Ray KK et al.* **Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia**. The New England journal of medicine 2020; 382:1520-1530.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32197277

ABSTRACT

BACKGROUND: Familial hypercholesterolemia is characterized by an elevated level of low-density lipoprotein (LDL) cholesterol and an increased risk of premature atherosclerotic cardiovascular disease. Monoclonal antibodies directed against proprotein convertase subtilisin-kexin type 9 (PCSK9) have been shown to reduce LDL cholesterol levels by more than 50% but require administration every 2 to 4 weeks. In a phase 2 trial, a twice-yearly injection of inclisiran, a small interfering RNA, was shown to inhibit hepatic synthesis of PCSK9 in adults with heterozygous familial hypercholesterolemia. METHODS: In this phase 3, double-blind trial, we randomly assigned, in a 1:1 ratio, 482 adults who had heterozygous familial hypercholesterolemia to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. The two primary end points were the percent change from baseline in the LDL cholesterol level on day 510 and the time-adjusted percent change from baseline in the LDL cholesterol level between day 90 and day 540. RESULTS: The median age of the patients was 56 years, and 47% were men; the mean baseline level of LDL cholesterol was 153 mg per deciliter. At day 510, the percent change in the LDL cholesterol level was a reduction of 39.7% (95% confidence interval [CI], -43.7 to -35.7) in the inclisiran group and an increase of 8.2% (95% CI, 4.3 to 12.2) in the placebo group, for a between-group difference of -47.9 percentage points (95% CI, -53.5 to -42.3; P<0.001). The time-averaged percent change in the LDL cholesterol level between day 90 and day 540 was a reduction of 38.1% (95% CI, -41.1 to -35.1) in the inclisiran group and an increase of

6.2% (95% CI, 3.3 to 9.2) in the placebo group, for a between-group difference of -44.3 percentage points (95% CI, -48.5 to -40.1; P<0.001). There were robust reductions in LDL cholesterol levels in all genotypes of familial hypercholesterolemia. Adverse events and serious adverse events were similar in the two groups. CONCLUSIONS: Among adults with heterozygous familial hypercholesterolemia, those who received inclisiran had significantly lower levels of LDL cholesterol than those who received placebo, with an infrequent dosing regimen and an acceptable safety profile. (Funded by the Medicines Company; ORION-9 ClinicalTrials.gov number, NCT03397121.).

[45] *Gulpen AJW, Claessen RJM, Vanmolkot FHM*. **[PCSK9 inhibitors; who benefits from these new cholesterol-lowering drugs?]**. Ned Tijdschr Geneeskd 2020; 164.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32186821
ABSTRACT
PCSK9 inhibitors are monoclonal antibodies that target the protein PCSK9. These drugs (alirocumab and evolcumab) are a new generation of cholesterol-lowering agents for patients with a very high risk of cardiovascular disease. They lower the LDL cholesterol concentration by approximately 50% in comparison with placebo, thereby lowering the risk of myocardial infarction, stroke and cardiovascular death in high-risk patients. Due to their high cost and the cost-effectiveness, there are strict conditions for reimbursement for these agents in the Netherlands. PCSK9 inhibitors can be given to high-risk patients in whom, despite maximal medicinal therapy with statins and ezetimibe, the target level of LDL cholesterol cannot be reached. This article gives an overview of the efficacy and the safety of PCSK9 inhibitors, and of their use in the Netherlands.

[46] *Yang ZH, Amar M, Sampson M et al.* **Comparison of Omega-3 Eicosapentaenoic Acid Versus Docosahexaenoic Acid-Rich Fish Oil Supplementation on Plasma Lipids and Lipoproteins in Normolipidemic Adults**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32178279
ABSTRACT
BACKGROUND: Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have both shared and different cardiovascular effects, and commonly used fish oil supplements have considerably varied EPA/DHA ratios. AIMS: We compared the effects of fish oil supplements with different EPA/DHA ratios on lipoprotein metabolism. METHODS: In a double-blind, randomized cross-over study, normolipidemic adults (n = 30) consumed 12 g/day of EPA-rich (EPA/DHA: 2.3) or DHA-rich (EPA/DHA: 0.3) fish oil for 8-weeks, separated by an 8-week washout period. RESULTS: Both fish oil supplements similarly lowered plasma TG levels and TG-related NMR parameters versus baseline ($p < 0.05$). There were no changes in plasma cholesterol-related parameters due to either fish oil, although on-treatment levels for LDL particle number were slightly higher for DHA-rich oil compared with EPA-rich oil ($p < 0.05$). Both fish oil supplements similarly altered HDL subclass profile and proteome, and down regulated HDL proteins related to inflammation, with EPA-rich oil to a greater extent. Furthermore, EPA-rich oil increased apoM abundance versus DHA-rich oil ($p < 0.05$). CONCLUSIONS: Overall, fish oil supplements with varied EPA/DHA ratios had similar effects on total lipids/lipoproteins, but differences were observed in lipoprotein subfraction composition and distribution, which could impact on the use of EPA versus DHA for improving cardiovascular health.

[47] *Liu J, Jiang N, Liu T, Luo W*. **Clinical effect of simvastatin combined with exercise training in the treatment of stationary chronic obstructive pulmonary disease complicated with metabolic syndrome**. Pak J Pharm Sci 2020; 33:437-440.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32173640
ABSTRACT
The aim of this study is to observe and analyze the clinical efficacy of simvastatin combined with exercise training in the treatment of stationary chronic obstructive pulmonary disease complicated with metabolic syndrome. In this study, 180 patients who had been treated for stable chronic obstructive pulmonary disease (COPD) complicated with metabolic syndrome in our hospital were enrolled as research objects. The selected patients were randomly divided into research group receiving simvastatin combined with exercise training and control group accepting routine therapy, each containing 90 cases. The therapeutic effects of the two groups were compared. The CAT score, insulin resistance index and 6 min walking distance of the two groups were compared. The results showed that compared with the control group, the improvement effect of the research group was more obvious, and the effect was better than that of the control group, $p<0.05$. The levels of IL-6 (interleukin-6), IL-8 (interleukin-8) and other inflammatory factors were significantly lower in the research group than those in the control group, $p<0.05$. Simvastatin combined with exercise training in the treatment of stationary chronic obstructive pulmonary disease with metabolic syndrome is an effective treatment, which can significantly improve the treatment effect and help patients to achieve a higher quality of life.

[48] *Sifaoui I, Capote Yanes EC, Reyes-Batlle M et al.* **Combined Amoebicidal Effect of Atorvastatin and Commercial Eye Drops against Acanthamoeba castellanii Neff: In Vitro Assay Based on Mixture Design**. Pathogens 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32192043
ABSTRACT
The establishment of an effective therapeutic agent against Acanthamoeba keratitis (AK), remains until present, an issue to be solved due to the existence of a cyst stage in the life cycle of Acanthamoeba. Moreover, the effectiveness of the current standard therapeutic agents varies depending on the tested Acanthamoeba strains and its resistance pattern. In the present study, two 10-point augmented simplex-centroid designs were used to formulate a three-component mixture system using water, atorvastatin, and Diclofenaco-lepori or Optiben. The amoebicidal effects and in vitro-induced toxicity in a eukaryotic cell line were determined for all experiments. The optimal mixture to inhibit the parasite without inducing toxicity was established in the first plan as 30% Optiben, 63.5% atorvastatin, and 3.1% water. As for the second experimental design, the optimal mixture to inhibit Acanthamoeba with lower toxicity effect was composed of 17.6% Diclofenaco-lepori and 82.4% atorvastatin.

[49] *House JS, Motsinger-Reif AA*. **Fibrate pharmacogenomics: expanding past the genome**. Pharmacogenomics 2020; 21:293-306.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32180510
ABSTRACT

Literature update week 12 (2020)

Fibrates are a medication class prescribed for decades as 'broad-spectrum' lipid-modifying agents used to lower blood triglyceride levels and raise high-density lipoprotein cholesterol levels. Such lipid changes are associated with a decrease in cardiovascular disease, and fibrates are commonly used to reduce risk of dangerous cardiovascular outcomes. As with most drugs, it is well established that response to fibrate treatment is variable, and this variation is heritable. This has motivated the investigation of pharmacogenomic determinants of response, and multiple studies have discovered a number of genes associated with fibrate response. Similar to other complex traits, the interrogation of single nucleotide polymorphisms using candidate gene or genome-wide approaches has not revealed a substantial portion of response variation. However, recent innovations in technological platforms and advances in statistical methodologies are revolutionizing the use and integration of other 'omes' in pharmacogenomics studies. Here, we detail successes, challenges, and recent advances in fibrate pharmacogenomics.

[50] *Calderon-Ospina CA, Hernandez-Somerson M, Garcia AM et al.* **A Pharmacogenomic Dissection of a Rosuvastatin-Induced Rhabdomyolysis Case Evokes the Polygenic Nature of Adverse Drug Reactions**. Pharmacogenomics and personalized medicine 2020; 13:59-70.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32184647

ABSTRACT

Rosuvastatin, is a widely-used statin for the treatment of hypercholesterolemia and the prevention of cardiovascular diseases. Although rosuvastatin is well tolerated, about 3/10.000 patients can suffer severe myopathy. Rhabdomyolysis is a severe medical condition that causes injury to the skeletal muscle, electrolyte imbalances, acute renal failure and extreme creatine kinase (CK) elevation. Little is known regarding the molecular involvement of rosuvastatin-induced rhabdomyolysis (RIR). It has been demonstrated that genomic variants associated with decreased enzymatic activity of proteins are important determinants in plasmatic and skeletal muscle distribution of rosuvastatin and its toxicity. Until now, no interactions of ticagrelor, ezetimibe and rosuvastatin have been described with the consideration of pharmacogenomics predisposition. The present report involves a whole-exome sequencing (WES), in a patient affected by rosuvastatin-induced rhabdomyolysis. A pharmacogenomic dissection was performed by analyzing a comprehensive subset of candidate genes (n=160) potentially related to RIR. The genes were selected according to their implication in drug metabolism or inherited myopathies. Using an innovative approach of bioinformatics analysis, considering rare and common variants, we identified 19 genomic variations potentially related to the pharmacokinetic/pharmacodynamic modifications of rosuvastatin, ezetimibe and ticagrelor. The affected genes are involved in Phase I metabolism (CYP2C19, CYP2E1, CYP1A1, CYP2D6 and CYP2C9), Phase II metabolism (UGT2B15 and UGT2B7), influx transportation (SLCO1B3 and SLCO2B1), efflux transportation (ABCG8, ABCB11, ABCC4 and ABCB1), drug targeting (NPC1L1) and inherited myopathy etiology (OBSCN). We report three rare, potentially pathogenic molecular variants in CYP2C19, NPC1L1 and OBSCN genes. Pharmacogenetic analysis indicated that the patient was a carrier of inactivating alleles in several pharmacogenes involved in drug toxicity. The whole-exome sequencing and bioinformatics analysis presented here represents an innovative way to identify genomic variants contributing with RIR s origin and evokes the polygenic nature of adverse drug reactions.

Literature update week 12 (2020)

[51] *Sagar D, Gaddipati R, Ongstad EL et al.* **LOX-1: A potential driver of cardiovascular risk in SLE patients**. PloS one 2020; 15:e0229184.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32182251
ABSTRACT
Traditional cardiovascular disease (CVD) risk factors, such as hypertension, dyslipidemia and diabetes do not explain the increased CVD burden in systemic lupus erythematosus (SLE). The oxidized-LDL receptor, LOX-1, is an inflammation-induced receptor implicated in atherosclerotic plaque formation in acute coronary syndrome, and here we evaluated its role in SLE-associated CVD. SLE patients have increased sLOX-1 levels which were associated with elevated proinflammatory HDL, oxLDL and hsCRP. Interestingly, increased sLOX-1 levels were associated with patients with early disease onset, low disease activity, increased IL-8, and normal complement and hematological measures. LOX-1 was increased on patient-derived monocytes and low-density granulocytes, and activation with oxLDL and immune-complexes increased membrane LOX-1, TACE activity, sLOX-1 release, proinflammatory cytokine production by monocytes, and triggered the formation of neutrophil extracellular traps which can promote vascular injury. In conclusion, perturbations in the lipid content in SLE patients' blood activate LOX-1 and promote inflammatory responses. Increased sLOX-1 levels may be an indicator of high CVD risk, and blockade of LOX-1 may provide a therapeutic opportunity for ameliorating atherosclerosis in SLE patients.

[52] *de Alwis N, Beard S, Mangwiro YT et al.* **Pravastatin as the statin of choice for reducing pre-eclampsia-associated endothelial dysfunction**. Pregnancy hypertension 2020; 20:83-91.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32199147
ABSTRACT
OBJECTIVES: There is avid interest in pravastatin as a therapeutic intervention for pre-eclampsia, however little is known on statin action on endothelial dysfunction. This study aimed to evaluate the ability of pravastatin, simvastatin and rosuvastatin to reduce pre-eclampsia-associated markers of endothelial dysfunction in human endothelial cells. STUDY DESIGN: Primary human umbilical vein endothelial cells (HUVECs) and uterine microvascular cells (UtMVs) were isolated and treated with 0.2, 2, 20 and 200 microM pravastatin, simvastatin and rosuvastatin for 24 h, either with or without pre-treatment with TNF-alpha to induce endothelial dysfunction. MAIN OUTCOME MEASURES: Cell viability (MTS) assays were performed and cells were visually inspected. Expression of endothelial dysfunction markers, endothelin-1 (ET-1) and vascular cell adhesion molecule-1 (VCAM-1) were assessed by qPCR (n=3). Intracellular VCAM-1 protein was examined by Western Blotting (n=5). ET-1 and soluble fms-like tyrosine kinase-1 (sFLT-1) protein secretion was assessed by ELISA in HUVEC conditioned media (n=3). RESULTS: High doses of simvastatin and rosuvastatin significantly compromised HUVEC survival. 200 microM simvastatin significantly reduced UtMV survival. Abnormal cell structure was observed with these doses and thus were excluded from further analysis. The statins did not mitigate TNF-alpha induced ET-1 or VCAM-1 expression in either HUVECs or UtMVs, nor VCAM-1 protein expression in HUVECs. 0.2 microM pravastatin and simvastatin significantly reduced ET-1 and sFLT-1 protein secretion. CONCLUSIONS: Pravastatin significantly reduced secretion of both ET-1 and sFLT-1, key mediators of endothelial dysfunction. Importantly, pravastatin had no toxic effects, in contrast to rosuvastatin and simvastatin. This further supports selection of pravastatin for clinical applications to combat pre-eclampsia.

Literature update week 12 (2020)

[53] *Trebaticka J, Hradecna Z, Surovcova A et al.* **Omega-3 fatty-acids modulate symptoms of depressive disorder, serum levels of omega-3 fatty acids and omega-6/omega-3 ratio in children. A randomized, double-blind and controlled trial**. Psychiatry research 2020; 287:112911.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32179212

ABSTRACT
Omega-3 fatty acids (FA) are a promising adjuvant therapy for depressive disorder (DD) in adults. The objective of this single-centre, randomized, double-blind and controlled study was to compare the efficacy of an omega-3 FA fish oil emulsion with a control oil emulsion alongside the standard treatment for depression in children and adolescents suffering from DD or mixed anxiety depressive disorder (MADD) and to analyse serum fatty acid levels and omega-6/omega-3 FA ratio before and after the intervention. 60 children were randomised 1:1 to the intervention (Om3) or active comparator (Om6) groups. Children's Depression Inventory (CDI) ratings were performed at the baseline, every 2 weeks for a 12-week intervention period. Significant reductions in CDI scores were observed after 6 and 12 weeks of intervention in the Om3 group and in the DD subgroup compared to the Om6 and MADD subgroup. Ratio of omega-6/omega-3 decreased in Om3 but not in Om6 from 24.2/1 to 7.6/1 after 6 weeks, EPA, omega-6/omega-3 ratio, but not DHA, correlated with severity symptoms at the baseline. An omega-3 fatty acid rich fish oil emulsion may be an effective adjuvant supplement during the treatment of depressive disorders in children. Trial registration: ISRCTN 81655012.

[54] *Ale MC, Echeverria G, Jugo A et al.* **[Non-HDL cholesterol levels in Chilean population and their association with diabetes mellitus and cardiovascular disease]**. Revista medica de Chile 2019; 147:1365-1373.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32186596

ABSTRACT
Background Despite aggressive treatment aimed at lowering LDL cholesterol (LDL-C) levels with statins, there is a high residual prevalence of cardiovascular diseases, which may depend on plasma cholesterol transported in other atherogenic lipoproteins. Aims To describe non-HDL cholesterol (non-HDL-C) levels in the Chilean population and their association with diabetes mellitus and cardiovascular disease. To evaluate compliance with non-HDL-C therapeutic goals -according to individual cardiovascular risk- at different levels of triglycerides, in comparison with LDL-C goal achievement. Material and Methods: We analyzed data from 2,792 Chilean subjects aged >/= 15 years who were included in the 2009-2010 National Health Survey and had valid data for blood lipids, diabetes, and cardiovascular disease. Results Forty five percent of subjects had high non-HDL-C levels. The proportion of diabetic and non-diabetic subjects with high non-HDL-C levels was 81 and 42%, respectively ($p < 0.01$). A significant discordance was observed in the achievement of therapeutic objectives when LDL-C or non-HDL-C levels were considered, particularly in presence of triglycerides >/= 150 mg/dl. Namely, 8% of the population showed elevated levels of high non-HDL-C despite adequate LDL-C levels. Conclusions Evaluation and management of elevated non-HDL-C in patients with adequate levels of LDL-C seems worthwhile considering the discordance observed between these blood cholesterol fractions. This strategy may be effective to reduce the residual cardiovascular risk in the Chilean population.

Literature update week 12 (2020)

[55] *Loureiro NSL, Amaral TLM, Amaral CA et al.* **Relationship between anthropometric indicators and risk factors for cardiovascular disease in adults and older adults of Rio Branco, Acre**. Rev Saude Publica 2020; 54:24.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32187312
ABSTRACT
OBJECTIVE: To analyze the association between anthropometric variables and cardiovascular risk factors in adults and older adults of Rio Branco, Acre. METHODS: A population-based cross-sectional study with 641 adults and 957 older adults was conducted. The statistical analyses consisted of the distribution of anthropometric variables according to the cardiovascular risk factors by frequency and dispersion measures. Pearson's correlation coefficient and prevalence ratios (PR) were estimated with their respective 95% confidence intervals (95%CI) using the SPSS (R) version 20.0. RESULTS: Moderate correlations were obtained in adult men for waist-hip ratio and total cholesterol (r = 0.486; p < 0.001) and for waist-hip and triglyceride ratios (r = 0.484; p < 0.001). The highest prevalence of hypertension and diabetes in adults were observed in men; in the older adults, the prevalence of hypertension was above 65% in both sexes. The prevalence of dyslipidemia was above 78% in obese adults and older adults. When analyzing the associations, a higher strength of association was found between arterial hypertension and waist-to-stature ratio (PR = 13.42; 95%CI 12.58-14.31) and body mass index greater than 30 kg/m 2 (PR = 6.61; 95%CI 6.34-6.89) in adult men. In the analysis of diabetes, the waist-hip ratio presented greater robustness in the association for women (PR = 7.53; 95%CI 6.92-8.20) and men (PR = 9.79; 95%CI 9.14-10.49). CONCLUSION: Anthropometric variables are important predictors of cardiovascular risk; however, their assessments should be performed independently, according to sex and age group.

[56] *van der Vorst EPC*. **High-Density Lipoproteins and Apolipoprotein A1**. Subcell Biochem 2020; 94:399-420.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32189309
ABSTRACT
High-density lipoprotein (HDL) and its main protein component apolipoprotein (apo)A-I, play an important role in cholesterol homeostasis. It has been demonstrated that HDLs comprise of a very heterogeneous group of particles, not only regarding size but also composition. HDL's best described function is its role in the reverse cholesterol transport, where lipid-free apoA-I or small HDLs can accept and take up cholesterol from peripheral cells and subsequently transport this to the liver for excretion. However, several other functions have also been described, like anti-oxidant, anti-inflammatory and anti-thrombotic effects. In this article, the general features, synthesis and metabolism of apoA-I and HDLs will be discussed. Additionally, an overview of HDL functions will be given, especially in the context of some major pathologies like cardiovascular disease, cancer and diabetes mellitus. Finally, the therapeutic potential of raising HDL will be discussed, focussing on the difficulties of the past and the promises of the future.