

Literature update week 45 (2019)

[1] Yuan Q, Dong CD, Ge Y et al. **Proteome and phosphoproteome reveal mechanisms of action of atorvastatin against esophageal squamous cell carcinoma.** *Aging* 2019; 11:9530-9543.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31697643>

ABSTRACT

Statins comprise a class of prescription drugs used for reducing cholesterol. Evidence has also showed that statins could reduce cancer incidence. However, the anti-tumor mechanism of statins has not been fully defined. Here, we found that atorvastatin inhibited proliferation of esophageal squamous cell carcinoma (ESCC) cells. The underlying mechanisms were explored by mass spectrometry. The proteome data revealed that atorvastatin inhibited the cAMP and Rap1 signal pathways, except for Ras signal pathway. Interestingly, phosphoproteome profiles suggested that ERK(T185/Y187), CDK1(T14), and BRAC1(S1189) phosphorylation-mediated Th17 cell differentiation, Gap junction and the Platinum drug resistance pathway were down-regulated after atorvastatin treatment. The phosphorylation levels of ERK(T185/Y187), CDK1(T14) and BRAC1(S1189) were confirmed by western blotting in KYSE150 cells. More importantly, atorvastatin suppresses ESCC tumor growth in PDX models. The molecular changes in tumor tissues were confirmed by immunohistochemistry. In conclusion, deep-proteome and phosphoproteome analysis reveal a comprehensive mechanism that contributes to atorvastatin's anti-tumor effect.

[2] AlTurki A, Marafi M, Dawas A et al. **Meta-analysis of Randomized Controlled Trials Assessing the Impact of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies on Mortality and Cardiovascular Outcomes.** *The American journal of cardiology* 2019; 124:1869-1875.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31679643>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition by monoclonal antibodies has been shown to reduce low density lipoprotein (LDL-C) but its effects on cardiovascular (CV) outcomes have not been fully described. The aim of this study is to assess the impact of PCSK9 inhibition on mortality and CV outcomes by pooling data from all available randomized clinical trials (RCT) of PCSK9 inhibitors. We conducted a comprehensive search of electronic databases, up to December 1, 2018, for all RCTs comparing PCSK9 inhibition to placebo or ezetimibe in patients with hypercholesterolemia or coronary artery disease receiving maximally tolerated statin for primary or secondary prevention of mortality and cardiovascular outcomes. We used random-effects meta-analyses to summarize the studies. We retained 23 RCTs having included 88,041 patients in primary and secondary prevention. The follow-up ranged from 6 to 36 months. PCSK9 inhibition was not significantly associated with reductions in total mortality (odds ratio [OR] 0.91, 95% confidence interval [CI] 0.78 to 1.06; p=0.22) and CV mortality (OR 0.95, 95% CI 0.84 to 1.07; p=0.37). In contrast, PCSK9 inhibition was associated with reductions in myocardial infarction (OR 0.80, 95% CI 0.71 to 0.91; p <0.0001), stroke (OR 0.75, 95% CI 0.65 to 0.85; p <0.0001), and coronary revascularization (OR 0.82, 95% CI 0.77 to 0.88; p <0.0001). In conclusion, PCSK9 inhibition was associated with reductions in myocardial infarction, stroke, and coronary revascularization. Future analyses may identify high-risk patients who may benefit more from these agents and longer follow-up of current or new trials may show a mortality benefit.

[3] Gaudet D, Durst R, Lepor N et al. **Usefulness of Gemcabene in Homozygous Familial Hypercholesterolemia (from COBALT-1).** *The American journal of cardiology* 2019; 124:1876-1880.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31685212>

Literature update week 45 (2019)

ABSTRACT

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder characterized by severely elevated plasma low-density lipoprotein-cholesterol (LDL-C), and premature atherosclerotic cardiovascular disease. Depending on residual LDL receptor (LDLR) function, most HoFH patients respond modestly to statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. However, LDL-C typically remains markedly elevated necessitating additional therapies, including apheresis. Gemcabene is a novel lipid-lowering agent with a mechanism of action independent of the LDLR, which has previously demonstrated the ability to reduce levels of LDL-C on top of maximally tolerated statins. The present study (COBALT-1) assessed efficacy, tolerability, and safety of gemcabene as an adjunctive therapy to current lipid-lowering treatment for familial hypercholesterolemia patients. Eight patients with either a clinical or genetic diagnosis of HoFH on stable standard of care, including statins, ezetimibe, and PCSK9 inhibitors, were treated with gemcabene in an open-label study for 12 weeks. DNA analysis for mutations in the LDLR, apolipoprotein B, and PCSK9 genes was performed. Patients received 300 mg gemcabene for the first 4 weeks, 600 mg for the next 4 weeks, and 900 mg for the final 4 weeks. All patients completed the 12-week study. Mean change from baseline in LDL-C was -26% ($p=0.004$) at Week 4 (300 mg), -30% ($p=0.001$) at Week 8 (600 mg), and -29% ($p=0.001$) at Week 12 (900 mg). In conclusion, the COBALT-1 study demonstrates gemcabene has potential to significantly reduce LDL-C levels when used as an adjunctive therapy to current lipid-lowering treatment for familial hypercholesterolemia patients.

[4] Wu NQ, Guo YL, Zhu CG et al. **Rapid Regression of Multiple-Site Xanthomas in an Adult With Homozygous Familial Hypercholesterolemia by Triple Lipid-Lowering Drugs.** American journal of therapeutics 2019; 26:e775-e777.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31703038>

ABSTRACT

[5] Kotani K. **Lipoprotein(a) in the advent of a PCSK9 world.** Annals of clinical biochemistry 2019;4563219884965.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31684740>

ABSTRACT

[6] Gu HQ, Yang X, Rao ZZ et al. **Disparities in outcomes associated with rural-urban insurance status in China among inpatient women with stroke: a registry-based cohort study.** Annals of translational medicine 2019; 7:426.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31700862>

ABSTRACT

Background: Despite a few studies have demonstrated sex differences in stroke care and outcomes, limited research has explored insurance-related disparities in outcomes, particularly among women stroke patients. The aim was to determine whether rural-urban health insurance status affect the stroke treatment, process of care, and 1-year clinical outcomes for inpatient ischemic stroke in women. Methods: Women patients with acute ischemic stroke (AIS) covered by New Rural Cooperative Medical Scheme (NRCMS) and urban resident/employee-based basic medical insurance scheme (URBMI/UEBMI) were abstracted from the China National Stroke Registry II (CNSR II). Shared frailty model in the Cox model or generalized estimating equation with consideration of the hospital's cluster

Literature update week 45 (2019)

effect were used to assess the associations between rural-urban insurance status and quality of care during hospitalization and 1-year stroke outcomes including all-cause death, 1-year recurrence, and 1-year disability. Results: A total of 5,707 women patients enrolled from 219 hospitals in CNSR II were analyzed. Compared with 2,880 women patients covered by URBMI/UEBMI, 2,827 women patients covered by NRCMS were younger (65.7 versus 68.9 years), less likely to have vascular risk factors, awareness and treatment of hypertension and dyslipidemia prior to stroke. Women covered by NRCMS were more likely to receive early antithrombotics, discharge antithrombotics, lipid-lowering drugs, but less likely to receive antihypertensive medication than those covered by URBMI/UEBMI. One-year all-cause mortality and stroke recurrence were both significantly higher in women patients with NRCMS than those with URBMI/UEBMI [adjusted hazard ratio (95% confidence interval): 1.40 (1.06-1.84) and 1.38 (1.04-1.83), separately]. Conclusions: AIS women patients with rural-urban insurance status demonstrated remarkable differences in age, stroke risk factors, awareness and treatment, the process of care, and 1-year stroke recurrence and mortality. Healthcare policymakers need to focus their attention on these disparities and take proper steps to improve primary healthcare service in rural areas.

[7] *Notarnicola M, V DEN, Tutino V et al. Integrated Small Dense Low-density Lipoprotein Profile in Cardiovascular Disease and Cancer: A Longitudinal Study. Anticancer research 2019; 39:6035-6039.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31704829>

ABSTRACT

BACKGROUND/AIM: Low-density lipoproteins (LDL) are a heterogeneous class of particles that differ in size and density from each other. Small dense LDL (sdLDL) particles are considered more atherogenic than larger particles. The aim of the study was to evaluate serum levels of sdLDL in patients who died from cardiovascular diseases (CVD) or cancer in a cohort of patients followed up in the De Bellis Research Hospital for 20 years. PATIENTS AND METHODS: A total of 75 participants who died of cancer and 87 who died of CVD were enrolled and they were matched for age and sex with 135 healthy controls, i.e. without CVD or cancer and are still alive. RESULTS: Patients who died from cancer had the highest value of LDL IV subfraction (0.25+/-1.16), followed by those who died from CVD (0.17+/-0.96). CONCLUSION: The integrated profile of sdLDL between CVD and cancer suggests that therapeutic modulation of sdLDL may be associated with a risk reduction for these diseases.

[8] *Generoso G, Bensenor IM, Santos RD et al. High-density Lipoprotein-cholesterol Subfractions and Coronary Artery Calcium: The ELSA-Brasil Study. Arch Med Res 2019; 50:362-367.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31678894>

ABSTRACT

BACKGROUND: Although elevated high-density lipoprotein cholesterol (HDL-C) is considered protective against atherosclerotic cardiovascular disease, no causal relationship has been demonstrated. HDL-C comprises a group of different subfractions that might have different effects on atherosclerosis. Our objective was to investigate the association between HDL-C subfractions with the coronary artery calcium (CAC) score. METHODS: We included 3,674 (49.8 +/- 8.3 years, 54% women) participants from the ELSA-Brasil study who had no prior history of CVD and were not currently using lipid-lowering medications. We measured the fasting lipoprotein cholesterol fractions (in mmol/l) by a zonal ultracentrifugation method (VAP). We analyzed the independent predictive values of total HDL-C, HDL2-C, and HDL3-C subfractions and in the HDL2-C/HDL3-C ratio using linear regression to predict

Literature update week 45 (2019)

Ln(CAC+1) and logistic regression to predict the presence of CAC. RESULTS: Overall 912 (24.8%) of the participants had CAC>0, and 294 (7.7%) had CAC>100. The mean total HDL-C, HDL2-C, and HDL3-C were: 1.42 +/- 0.37, 0.38 +/- 0.17 and 1.03 +/- 0.21 mmol/l, respectively. Individuals with CAC>0 had lower levels of total HDL-C as well as of each subfraction ($p < 0.001$). When adjusted for age, gender, smoking, hypertension, alcohol use, physical activity, and LDL-C, we observed an inverse association between HDL-C and its subfractions and CAC ($p < 0.05$). However, by adding triglycerides in the adjustment, neither total HDL-C nor its subfractions remained independently associated with the presence or extent of CAC. CONCLUSION: In this cross-sectional analysis, neither the total HDL-C nor its subfractions (HDL2-C and HDL3-C, as well as HDL2-C/HDL3-C ratio) measured by VAP are independently associated with the presence or extent of coronary calcification.

[9] Pearsall R, Shaw RJ, McLean G et al. **Health screening, cardiometabolic disease and adverse health outcomes in individuals with severe mental illness.** *BJPsych open* 2019; 5:e97.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31699180>

ABSTRACT

BACKGROUND: Poor physical health in severe mental illness (SMI) remains a major issue for clinical practice. AIMS: To use electronic health records of routinely collected clinical data to determine levels of screening for cardiometabolic disease and adverse health outcomes in a large sample ($n = 7718$) of patients with SMI, predominantly schizophrenia and bipolar disorder. METHOD: We linked data from the Glasgow Psychosis Clinical Information System (PsyCIS) to morbidity records, routine blood results and prescribing data. RESULTS: There was no record of routine blood monitoring during the preceding 2 years for 16.9% of the cohort. However, monitoring was poorer for male patients, younger patients aged 16-44, those with schizophrenia, and for tests of cholesterol, triglyceride and glycosylated haemoglobin. We estimated that 8.0% of participants had diabetes and that lipids levels, and use of lipid-lowering medication, was generally high. CONCLUSIONS: Electronic record linkage identified poor health screening and adverse health outcomes in this vulnerable patient group. This approach can inform the design of future interventions and health policy.

[10] Ebert H, Lacruz ME, Kluttig A et al. **Advanced glycation end products and their ratio to soluble receptor are associated with limitations in physical functioning only in women: results from the CARLA cohort.** *BMC geriatrics* 2019; 19:299.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31684879>

ABSTRACT

BACKGROUND: Advanced glycation end products (AGEs), modifications of proteins or amino acids, are increasingly produced and accumulated with age-related diseases. Recent studies suggested that the ratio of AGEs and their soluble receptor (sRAGE) is a more accurate biomarker for age-related diseases than each separately. We aim to investigate whether this also applies for physical functioning in a broad age-spectrum. METHODS: AGE and sRAGE levels, and physical functioning (SF-12 questionnaire) of 967 men and 812 women (45-83 years) were measured in the CARLA study. We used ordinal logistic regression to examine associations between AGEs, sRAGE, and AGE/sRAGE ratio with physical functioning in sex- and age-stratified models. RESULTS: Higher levels of AGEs and AGE/sRAGE ratio were associated with lower physical functioning only in women, even after consideration of classical lifestyle and age-related factors (education, BMI, smoking, alcohol consumption, diet, creatinine clearance, diabetes mellitus, lipid lowering and antihypertensive drugs) (odds ratio (OR) =0.86,

Literature update week 45 (2019)

95% confidence interval = 0.74-0.98 and OR = 0.86, 95%CI = 0.75-0.98 for AGEs and AGE/sRAGE ratio respectively). We could not demonstrate a significant difference across age. CONCLUSIONS: We showed a sex-specific association between physical functioning and AGEs and AGE/sRAGE, but no stronger associations of the latter with physical functioning. Further investigation is needed in the pathophysiology of this association.

[11] *Tian J, Tai Y, Shi M et al. Atorvastatin Relieves Cognitive Disorder After Sepsis Through Reverting Inflammatory Cytokines, Oxidative Stress, and Neuronal Apoptosis in Hippocampus. Cellular and molecular neurobiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31696375>

ABSTRACT

This present research work reports the possible effects and the underlying mechanism of atorvastatin on survival rate and cognitive disorders after sepsis. Sepsis is a life-threatening dysfunction that arises when the body's response to infection causes injury to its own tissues and organs. Diffuse sepsis was induced by cecal ligation and puncture surgery (CLP) in ICR mice. 0.2 mg/kg body weight of atorvastatin was administered intraperitoneally at 12 h before surgery. The survival of mice was calculated 24 h, 48 h, 72 h, and 96 h after CLP surgery. Two weeks later, open-field test and Morris water maze test were conducted to evaluate the protective effect of atorvastatin. Inflammatory cytokines in plasma, oxidative stress parameters, number of astrocytes, and neuronal cell deaths in the CA3 region of the hippocampus were examined using enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry. The results indicate that pretreatment with atorvastatin can increase survival percentage and improve cognitive function. Atorvastatin reversed all these alterations in parallel with a decrease in circulating levels of cytokines (IL-1 β , IL-4, IL-6, and TNF- α) in plasma, inhibited the activities of oxidative stress parameters (lower TBARS levels, ratio of GSH/GSSH, and activities of SOD and CAT), enhanced the activity of citrate synthase in brain, and reduced the number of astrocytes and neuronal cell deaths in CA3 region of hippocampus. Overall, our results indicated that atorvastatin exhibited protective effects on survival rate and cognitive disorders after sepsis by inhibiting the release of inflammatory cytokines, oxidative stress, and neuronal apoptosis in brain tissue.

[12] *Mayne ES, Moabi H, Grobbee DE et al. The Utility of the Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) Assay in Detecting Abnormalities in Lipid Metabolism and Cardiovascular Risk in an HIV-Infected South African Cohort. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis* 2019; 25:1076029619883944.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31686546>

ABSTRACT

People with HIV (PWH) have an increased prevalence of cardiovascular disease (CVD) compared to uninfected patients. Lipoprotein-associated phospholipase A2 (Lp-PLA2) catalyzes the synthesis of pro-inflammatory lipids that recruit monocytes. Current guidelines for assessing cardiovascular risk in HIV-infected patients suggest that Lp-PLA2 may be a useful surrogate marker for CVD health in this patient population. Lipoprotein-associated phospholipase A2, lipids, glucose, physical parameters, and carotid intimal-medial thickness (CIMT) were measured in 98 participants (49 HIV-uninfected, 27 antiretroviral therapy [ART]-naive PWH, and 22 ART-treated PWH). HIV viral load (VL) and CD4+ T-cell count were measured in HIV-infected participants. Lipoprotein-associated phospholipase A2 was increased in participants on protease inhibitor (PI) ART (median 50.5 vs 127.0 nmol/mL, P = .05) and correlated with

Literature update week 45 (2019)

age, body mass index, and cholesterol. Lipoprotein-associated phospholipase A2 was not related to Framingham risk score or CIMT but correlated directly with VL ($r = .323$, $P = .025$) and inversely with CD4+ T-cell count ($r = -.727$, $P < .001$). Lipoprotein-associated phospholipase A2 was increased in HIV-infected participants on PIs and correlated strongly with VL and CD4+ T-cell count suggesting that HIV-associated inflammation is linked to increased Lp-PLA2, providing a mechanistic link between HIV and CVD.

[13] Zegarra-Mondragon S, Lopez-Gonzalez R, Martin-Martinez MA et al. **Association of apolipoprotein B/apolipoprotein A1 ratio and cardiovascular events in rheumatoid arthritis: results of the CARMA study.** *Clinical and experimental rheumatology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31694752>

ABSTRACT

OBJECTIVES: To assess the plasma apolipoprotein B/apolipoprotein A1 ratio and its potential association with cardiovascular events (CVE) in patients with rheumatoid arthritis (RA). **METHODS:** A baseline analysis was made of the CARdiovascular in rheuMATology Project (CARMA), a 10-year prospective study evaluating the presence of at least one CVE in 775 Spanish patients with RA. Of them, 29 had already experienced CVE prior to the inclusion in the study. We assessed the association between the elevation of the apoB/apoA1 ratio with the presence of CVE according to a logistic regression model for possible confounding factors. We also analysed the main parameters of activity of RA and parameters related to lipid metabolism. RA patients were classified according to treatment: patients treated with disease-modifying anti-rheumatic drugs without biologics and those undergoing biologic therapy (anti-TNF-alpha, anti-IL-6 receptor, and other biologic agents). **RESULTS:** The apoB/apoA1 ratio of patients who had experienced CVE was higher than that of patients without previous CVE (0.65 vs. 0.60). However, the difference between both subgroups did not reach statistical significance ($p=0.197$). It was also the case after the multivariate analysis [OR: 1.48 (95% CI: 0.15-14.4); $p=0.735$]. RA patients from the group with CVE were more commonly receiving lipid-lowering treatment with statins than those without CVE history (41.4% vs. 20%, $p=0.005$). High HAQ and high atherogenic index were significantly associated with the presence of CVE. There was no statistical association between the type of biologic therapy used in RA and the presence of CVE. **CONCLUSIONS:** No association between ApoB/apoA1 ratio and CVE was found at the baseline visit of patients with RA from the CARMA study.

[14] Liu C, Lu H, Yuan F et al. **A Phase 1, Randomized, Double-Blind, Single-Dose, Placebo-Controlled Safety, Tolerability, And Pharmacokinetic/Pharmacodynamic Study Of Evolocumab In Healthy Chinese Subjects.** *Clinical pharmacology : advances and applications* 2019; 11:145-153.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31695519>

ABSTRACT

Purpose: Evolocumab is a human monoclonal antibody that reduces circulating low-density lipoprotein cholesterol (LDL-C) by inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9). Data on evolocumab pharmacokinetics and pharmacodynamics are derived mostly from Caucasian populations. The objectives of this study were to characterize the single-dose pharmacokinetic and pharmacodynamic parameters, safety, and tolerability of evolocumab in healthy Chinese subjects. **Subjects and methods:** This was a phase 1, randomized, double-blind, placebo-controlled study (CTR20150465). Two parallel cohorts were randomized 5:1 to receive single subcutaneous injections of

Literature update week 45 (2019)

either evolocumab (140 mg or 420 mg) or placebo. Pharmacokinetics, pharmacodynamics, and safety were evaluated through day 85. The primary endpoints were maximum concentration (C_{max}) and area under the drug concentration-time curve from time 0 to time of last quantifiable concentration (AUC_{last}). Results: Thirty-six men (median age 26) were enrolled to receive evolocumab 140 mg (n=15), evolocumab 420 mg (n=15), or placebo (n=6). After 140 mg and 420 mg evolocumab, mean (SD) C_{max} was 13.8 (3.6 μg/mL and 67.6 (15.2) μg/mL, respectively, and mean (SD) AUC_{last} was 166 (55) day.μg/mL and 1110 (274) day.μg/mL, respectively. LDL-C declined reversibly, with reductions of 70% at 140 mg and 71% at 420 mg. Maximum effects on LDL-C and PCSK9 levels were reached by day 15 and 24 hrs, respectively, at 140 mg, and by day 22 and 4 hrs, respectively, at 420 mg. No serious adverse events occurred and the overall incidence of treatment-emergent adverse events was similar for evolocumab and placebo: 26.7% (140 mg) and 33.3% (placebo); 66.7% (420 mg) and 66.7% (placebo). Conclusion: In this population of healthy Chinese subjects, single 140 mg and 420 mg doses of evolocumab exhibited nonlinear kinetics and more than dose-proportional increases in exposure, were associated with up to 71% reduction in LDL-C, and demonstrated a safety profile similar to placebo.

[15] Vuorio A, Kuoppala J, Kovanen PT et al. **Statins for children with familial hypercholesterolemia.** The Cochrane database of systematic reviews 2019; 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31696945>

ABSTRACT

BACKGROUND: Familial hypercholesterolemia is one of the most common inherited metabolic diseases and is an autosomal dominant disorder meaning heterozygotes, or carriers, are affected. Those who are homozygous have severe disease. The average worldwide prevalence of heterozygous familial hypercholesterolemia is at least 1 in 500, although recent genetic epidemiological data from Denmark and next generation sequencing data suggest the frequency may be closer to 1 in 250. Diagnosis of familial hypercholesterolemia in children is based on elevated total cholesterol and low-density lipoprotein cholesterol levels or DNA-based analysis, or both. Coronary atherosclerosis has been detected in men with heterozygous familial hypercholesterolemia as young as 17 years old and in women with heterozygous familial hypercholesterolemia at 25 years old. Since the clinical complications of atherosclerosis occur prematurely, especially in men, lifelong treatment, started in childhood, is needed to reduce the risk of cardiovascular disease. In children with the disease, diet was the cornerstone of treatment but the addition of lipid-lowering medications has resulted in a significant improvement in treatment. Anion exchange resins, such as cholestyramine and colestipol, were found to be effective, but they are poorly tolerated. Since the 1990s studies carried out on children aged 6 to 17 years with heterozygous familial hypercholesterolemia have demonstrated significant reductions in their serum total and low-density lipoprotein cholesterol levels. While statins seem to be safe and well-tolerated in children, their long-term safety in this age group is not firmly established. This is an update of a previously published version of this Cochrane Review. **OBJECTIVES:** To assess the effectiveness and safety of statins in children with heterozygous familial hypercholesterolemia. **SEARCH METHODS:** Relevant studies were identified from the Group's Inborn Errors and Metabolism Trials Register and Medline. Date of most recent search: 04 November 2019. **SELECTION CRITERIA:** Randomized and controlled clinical studies including participants up to 18 years old, comparing a statin to placebo or to diet alone. **DATA COLLECTION AND ANALYSIS:** Two authors independently assessed studies for inclusion and extracted data. **MAIN RESULTS:** We found 26

Literature update week 45 (2019)

potentially eligible studies, of which we included nine randomized placebo-controlled studies (1177 participants). In general, the intervention and follow-up time was short (median 24 weeks; range from six weeks to two years). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points (high-quality evidence). There may be little or no difference in liver function (serum aspartate and alanine aminotransferase, as well as creatinine kinase concentrations) between treated and placebo groups at any time point (low-quality evidence). There may be little or no difference in myopathy (as measured in change in creatinine levels) (low-quality evidence) or clinical adverse events (moderate-quality evidence) with statins compared to placebo. One study on simvastatin showed that this may slightly improve flow-mediated dilatation of the brachial artery (low-quality evidence), and on pravastatin for two years may have induced a regression in carotid intima media thickness (low-quality evidence). No studies reported rhabdomyolysis (degeneration of skeletal muscle tissue) or death due to rhabdomyolysis, quality of life or compliance to study medication. **AUTHORS' CONCLUSIONS:** Statin treatment is an effective lipid-lowering therapy in children with familial hypercholesterolemia. Few or no safety issues were identified. Statin treatment seems to be safe in the short term, but long-term safety remains unknown. Children treated with statins should be carefully monitored and followed up by their pediatricians and their care transferred to an adult lipidologist once they reach 18 years of age. Large long-term randomized controlled trials are needed to establish the long-term safety issues of statins.

[16] Corina A, Abrudan MB, Nikolic D et al. **Effects of Aging and Diet on Cardioprotection and Cardiometabolic Risk Markers.** Current pharmaceutical design 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31692432>

ABSTRACT

The prevalence of several diseases increases by age, including cardiovascular diseases, the leading cause of morbidity and mortality worldwide. Aging, as a complex process characterized by graduated senescence, triggers various pathways such as oxidative stress, systemic inflammation, metabolism dysfunction, but also telomere shortening, mitochondrial dysfunction and deregulated autophagy. A better understanding of the senescence underlying mechanisms may lead to the development of new therapeutic targets and strategies for the age-related pathologies and extend the healthy lifespan. Modulating lifestyle risk factors and adopting healthy dietary patterns remain powerful tools which may delay the aging process, decrease age-associated co-morbidities and mortality, increase life expectancy, and, consequently, prevent the development of the cardiovascular disease. Furthermore, such a strategy represents the most cost-effective approach, and the subjects' quality of life may be significantly improved. An integrated, personalized approach targeting at cardiometabolic aging and frailty is suggested in daily clinical practice. However, it should be started from an early age, while there is a need for further well designed and controlled studies in order to elucidate a link between the time of feeding, longevity and cardiovascular prevention. In the future, it is expecting that the pharmacological treatment in cardioprotective management will be necessary accompanied by equally important lifestyle interventions and adjunctive exercise.

[17] Kim YJ, Jeong IK, Kim SG et al. **Changes in the Quality of Life in Patients with Type 2 Diabetes Mellitus According to Physician and Patient Behaviors.** Diabetes Metab J 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31701689>

ABSTRACT

Literature update week 45 (2019)

BACKGROUND: Diabetes mellitus (DM) is the most common chronic metabolic disorder with an increasing prevalence worldwide. According to a previous study, physicians' treatment patterns or patients' behaviors change when they become aware of the risk for cardiovascular (CV) disease in patients with DM. However, there exist controversial reports from previous studies in the impact of physicians' behaviors on the patients' quality of life (QoL) improvements. So we investigate the changes in QoL according to physicians and patients' behavioral changes after the awareness of CV risks in patients with type 2 DM. **METHODS:** Data were obtained from a prospective, observational study where 799 patients aged ≥ 40 years with type 2 DM were recruited at 24 tertiary hospitals in Korea. Changes in physicians' behaviors were defined as changes in the dose/type of antihypertensive, lipid-lowering, and anti-platelet therapies within 6-month after the awareness of CV risks in patients. Changes in patients' behaviors were based on lifestyle modifications. Audit of Diabetes Dependent Quality of Life comprising 19-life-domains was used. **RESULTS:** The weighted impact score change for local or long-distance journey ($P=0.0049$), holidays ($P=0.0364$), and physical health ($P=0.0451$) domains significantly differed between the two groups; patients whose physician's behaviors changed showed greater improvement than those whose physician's behaviors did not change. **CONCLUSION:** This study demonstrates that changes in physicians' behaviors, as a result of perceiving CV risks, improve QoL in some domains of life in DM patients. Physicians should recognize the importance of understanding CV risks and implement appropriate management.

[18] *Pelaez-Jaramillo MJ, Valencia-Enciso N, Cardenas-Mojica AA et al. Impact of a Formulation Containing Unusual Polyunsaturated Fatty Acids, Trace Elements, Polyphenols and Plant Sterols on Insulin Resistance and Associated Disturbances. Diabetes Ther* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31691133>

ABSTRACT

INTRODUCTION: To evaluate the effect of a lipid-based formulation containing unusual polyunsaturated fatty acids, trace elements, polyphenols and plant sterols on insulin resistance and its associated disturbances among adults at risk of diabetes. **METHODS:** This was an 8-week, three-arm, open-label randomized clinical trial. We studied individuals aged ≥ 18 years old with diabetes risk given by a body mass index ≥ 25 kg/m² or a FinnRisc score $\geq 13/20$. Participants were randomly assigned to receive: 7 ml sunflower oil (control group), 3.5 ml of the study formulation + 3.5 ml of sunflower oil (low-dose group) or 7 ml of study formulation (high-dose group). **RESULTS:** We randomized 25 individuals. After one withdrawal in the high-dose group, the study sample comprised nine patients in the control, nine in the low-dose and six in the high-dose groups. The insulin sensitivity increased significantly and in a dose-dependent fashion, up to 10% in the high-dose group. At week 8 the low-dose group exhibited lower glycemic excursions during the oral glucose tolerance test (OGTT), especially 1 h after the glucose challenge (32 mg/dl or 23% lower vs. control group). The incremental area under the glucose curve in the OGTT was 17.1% lower in the low-dose group vs. the control group. Waist circumference increased in the control group, remained constant in the low-dose group and decreased in the high-dose group. C-reactive protein decreased in both formulation groups, up to 50% in the high-dose group. Participants in the formulation groups exhibited increased secretion of GLP-1 and plasma irisin at week 8 vs. the control group. **CONCLUSION:** The formulation induced favorable changes in insulin sensitivity, glucose tolerance, abdominal obesity and inflammation. These effects and their durability will need to be assessed in larger studies. **TRIAL REGISTRATION:** NCT03512665. **FUNDING:** Team Foods Colombia.

Literature update week 45 (2019)

[19] *Stakhneva EM, Meshcheryakova IA, Demidov EA et al. A Proteomic Study of Atherosclerotic Plaques in Men with Coronary Atherosclerosis. Diagnostics (Basel, Switzerland) 2019; 9.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31703357>

ABSTRACT

BACKGROUND: To study the changes in protein composition of atherosclerotic plaques at different stages of their development in coronary atherosclerosis using proteomics. **METHODS:** The object of research consisted of homogenates of atherosclerotic plaques from coronary arteries at different stages of development, obtained from 15 patients. Plaque proteins were separated by two-dimensional electrophoresis. The resultant protein spots were identified by the matrix-assisted laser desorption ionization method with peptide mass mapping. **RESULTS:** Groups of differentially expressed proteins, in which the amounts of proteins differed more than twofold ($p < 0.05$), were identified in pools of homogenates of atherosclerotic plaques at three stages of development. The amounts of the following proteins were increased in stable atherosclerotic plaques at the stage of lipidosis and fibrosis: vimentin, tropomyosin beta-chain, actin, keratin, tubulin beta-chain, microfibril-associated glycoprotein 4, serum amyloid P-component, and annexin 5. In plaques at the stage of fibrosis and calcification, the amounts of mimecan and fibrinogen were increased. In unstable atherosclerotic plaque of the necrotic-dystrophic type, the amounts of human serum albumin, mimecan, fibrinogen, serum amyloid P-component and annexin were increased. **CONCLUSION:** This proteomic study identifies the proteins present in atherosclerotic plaques of coronary arteries by comparing their proteomes at three different stages of plaque development during coronary atherosclerosis.

[20] *Miname MH, Bittencourt MS, Pereira AC et al. Vascular age derived from coronary artery calcium score on the risk stratification of individuals with heterozygous familial hypercholesterolaemia.*

European heart journal cardiovascular Imaging 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31702778>

ABSTRACT

AIMS: The objective of this study was to evaluate if vascular age derived from coronary artery calcium (CAC) score improves atherosclerosis cardiovascular disease (ASCVD) risk discrimination in primary prevention asymptomatic heterozygous familial hypercholesterolaemia (FH) patients undergoing standard lipid-lowering therapy. **METHODS AND RESULTS:** Two hundred and six molecularly confirmed FH individuals (age 45 +/- 14 years, 36% males, baseline LDL-cholesterol 6.2 +/- 2.2 mmol/L; 239 +/- 85mg/dL) were followed by 4.4 +/- 2.9 years (median: 3.7 years, interquartile ranges 2.7-6.8). CAC measurement was performed, and lipid-lowering therapy was optimized according to FH guidelines. Vascular age was derived from CAC and calculated according to the Multi Ethnic Study of Atherosclerosis algorithm. Risk estimation based on the Framingham equations was calculated for both biological (bFRS) and vascular (vaFRS) age. During follow-up, 15 ASCVD events (7.2%) were documented. The annualized rate of events for bFRS <10%, 10-20%, and >20% was respectively: 8.45 [95% confidence interval (CI) 3.17-22.52], 23.28 (95% CI 9.69-55.94), and 28.13 (95% CI 12.63-62.61) per 1000 patients. The annualized rate of events for vaFRS <10%, 10-20%, and >20% was respectively: 0, 0, and 50.37 (95% CI 30.37-83.56) per 1000 patients. vaFRS presented a better discrimination for ASCVD events compared to bFRS 0.7058 (95% CI 0.5866-0.8250) vs. vaFRS 0.8820 (95% CI 0.8286-0.9355), $P = 0.0005$. **CONCLUSION:** CAC derived vascular age can improve ASCVD risk discrimination in

Literature update week 45 (2019)

primary prevention FH subjects. This tool may help further stratify risk in FH patients already receiving lipid-lowering medication who might be candidates for further treatment with newer therapies.

[21] Aykan DA, Seyithanoglu M. **The Effects of Administration of Vitamin D, Infliximab, and Leflunomide on Testosterone Concentrations in Rats under Atorvastatin Therapy.** The Eurasian journal of medicine 2019; 51:224-227.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31692672>

ABSTRACT

Objective: Statins inhibit the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme and thus reduce plasma cholesterol levels. Although decreased cholesterol level is the main target of anti-lipidemic drugs, cholesterol has an important role in the synthesis of lipid-based hormones such as testosterone. In this study, the alterations in serum testosterone levels were examined in rats under atorvastatin therapy and their responses to vitamin D, infliximab, and leflunomide supplementation were evaluated. Materials and Methods: Wistar rats were treated with atorvastatin (100 mg/kg) for 21 days to induce inhibition of the HMG-CoA reductase enzyme activity. Following statin therapy, rats received vitamin D (0.2 mug/kg/day) orally for 15 days, infliximab (7 mg/kg/day) intraperitoneally in two doses, or leflunomide (10 mg/kg/day) orally in two doses. Subsequently, the alterations in serum testosterone levels were measured by ELISA. Results: Atorvastatin led to a decrease in the testosterone level compared to the vehicle group. Administration of vitamin D, infliximab, and leflunomide under HMG-CoA inhibition insignificantly increased the testosterone level compared to the atorvastatin control group. Furthermore, it appears that rats under statin administration respond better to treatment with leflunomide by achieving a greater induction in testosterone levels than with vitamin D or infliximab. Conclusion: Our data provide evidence that administration of vitamin D, infliximab, and leflunomide in rats under atorvastatin treatment may ameliorate the serum testosterone levels.

[22] Labenz C, Prochaska JH, Huber Y et al. **Cardiovascular Risk Categories in Patients With Nonalcoholic Fatty Liver Disease and the Role of Low-Density Lipoprotein Cholesterol.** Hepatology communications 2019; 3:1472-1481.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31701071>

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in patients with nonalcoholic fatty liver disease (NAFLD). The current analysis expands the knowledge on atherogenic lipid profiles in NAFLD by modeling changes in low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) in a prospectively enrolling real-life study cohort to inform physicians on the cardiovascular (CV) event risk based on these changes. A total of 304 patients with histologically confirmed NAFLD were included (mean age, 52 years; equal sex distribution). Of these, 129 (42.4%) patients exhibited a NAFLD activity score ≥ 4 and 186 (61.2%) had at least intermediate fibrosis $\geq F2$. The median TC levels were 209 mg/dL (interquartile range [IQR], 183, 239), LDL-C 131 mg/dL (IQR, 103, 152), and high-density lipoprotein cholesterol (HDL-C) 45 mg/dL (IQR, 38, 52). Only 16.9% of patients received lipid-lowering therapy. According to the LDL/HDL ratio, 69 (23.7%) patients exhibited a high CV risk. The 10-year CV event risk according to the Framingham risk score (FRS) was low in 91 (41.2%), intermediate in 59 (26.7%), and high in 71 (32.1%) patients and higher in the $\geq F2$ NAFLD population. A moderate increase in LDL-C levels by 20 mg/dL led to a transition of 20% of patients into the high-risk group when assessing the LDL/HDL ratio. According to the FRS, 6 (2.7%) patients moved from low to intermediate

Literature update week 45 (2019)

and 11 (4.9%) from intermediate to high CV risk. Conclusion: Patients with NAFLD exhibit a substantial CV event risk and are frequently undertreated with lipid-lowering medication. Moderate increases in LDL-C would result in worsening of the CV event risk in approximately 7.8% of all patients without a history of CVD.

[23] Marx N. **[New ESC guidelines 2019 "Diabetes, prediabetes and cardiovascular diseases" : Paradigm shift in reduction of cardiovascular risk in patients with diabetes mellitus].** Herz 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31686123>

ABSTRACT

At the last meeting of the European Society of Cardiology (ESC) in 2019 the new version of the ESC guidelines on "Diabetes, prediabetes and cardiovascular diseases", which were written in collaboration with the European Association for the Study of Diabetes (EASD), were presented. The recommendations of these guidelines included the novel evidence generated over the last 6 years in large cardiovascular outcome trials with novel antidiabetic drugs. This led to a completely novel positioning of medications for lowering blood glucose levels in the reduction of cardiovascular events for patients with diabetes mellitus. This overview article summarizes the most important recommendations of these new guidelines.

[24] Nuglozeh E, Fazaludeen MF, Hasona N et al. **Genotyping and Frequency of PCSK9 Variations Among Hypercholesterolemic and Diabetic Subjects.** Indian journal of clinical biochemistry : IJCB 2019; 34:444-450.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31686731>

ABSTRACT

Non-synonymous single-nucleotide polymorphism (SNPs) in the gene for proprotein convertase subtilisin/kexin type 9 (PCSK9) can influence cholesterol and glucose metabolism, leading to increased risk of cardiovascular disease and diabetes. To determine the frequency of four common PCSK9 SNPs, L10Ins, A56V, I474V, and E670G, in a population sample (n = 98) of the Hail region of Kingdom of Saudi Arabia. Blood was collected from participants; serum cholesterol, blood glucose and glycated hemoglobin were determined; genomic DNA was extracted and PCR amplicons from SNP-containing PCSK9 exons were subjected to Sanger sequencing. Out of 98 participants. 10 (10.20%) carried none of the SNPs, 2 (2.04%) the L10ins/A56V linked SNPs, 35 (35.71%) the I474V SNP, 22 (22.45%) both the I474V and E670G SNPs, and 29 (29.59%) the E670G SNP. Of the 30 eucholesterolemic diabetics patients, 11 (36.66%) carried the I474V SNP, 10 (33.33%) the E679G SNP and 6 (20%) the I474V/E679G. SNPs. Of 63 diabetic patients, 26 (41.26%) carry I474V SNP and 22 (34.92%) carry E670G SNP. Our data demonstrated that the I474V and E670G PCSK9 variants are very frequent in the Hail region of Saudi Arabia and are found at even higher frequency among diabetics. Further investigations are needed to determine whether these variations or another variant segregating with them can explain its apparent association with diabetes in this population.

[25] Espirito Santo LR, Faria TO, Silva CSO et al. **Socioeconomic status and education level are associated with dyslipidemia in adults not taking lipid-lowering medication: a population-based study.** International health 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31693111>

ABSTRACT

Literature update week 45 (2019)

BACKGROUND: Socio-economic disparities account for changes in the lipid profile in developing countries. We aimed to investigate the association between blood lipids and socio-economic and educational strata in adults not taking lipid-lowering medications. **METHODS:** A cross-sectional, population-based study enrolled 1614 individuals not taking lipid-lowering medications. Sociodemographic characteristics, monthly income, education level and the number of consumer goods available at home were obtained and individuals were classified into five socio-economic categories. Blood lipids were obtained in fasting participants. **RESULTS:** In men, the higher the socio-economic or educational stratum, the higher the total cholesterol, low-density lipoprotein cholesterol (LDL-c) and triglyceride (TG) levels and the lower the high-density lipoprotein cholesterol (HDL-c), after controlling for age, body mass index, hypertension, smoking habit and physical activity. In women, the higher socio-economic strata were associated with elevated total cholesterol and HDL-c, while lower total cholesterol, LDL-c and TG levels were found in those with higher education levels. Also, individuals in the upper socio-economic strata had higher levels of total cholesterol and LDL-c, showing more than two times higher odds of having multiple alterations in blood lipids (men: OR 2.99 [95% CI 1.23 to 5.07]; women: OR 2.31 [95% CI 1.09 to 5.83]). **CONCLUSIONS:** Dyslipidemia is highly prevalent in developing countries. Individuals in the highest socio-economic category are the ones at higher risk for dyslipidemia. This phenomenon calls for strategies to stimulate healthy diet habits and a physically active lifestyle to minimize health problems.

[26] *Churov A, Summerhill V, Grechko A et al. MicroRNAs as Potential Biomarkers in Atherosclerosis. International journal of molecular sciences* 2019; 20.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31703274>

ABSTRACT

Atherosclerosis is a complex multifactorial disease that, despite advances in lifestyle management and drug therapy, remains to be the major cause of high morbidity and mortality rates from cardiovascular diseases (CVDs) in industrialized countries. Therefore, there is a great need in reliable diagnostic/prognostic biomarkers and effective treatment alternatives to reduce its burden. It was established that microRNAs (miRNAs/miRs), a class of non-coding single-stranded RNA molecules, can regulate the expression of genes at the post-transcriptional level and, accordingly, coordinate the cellular protein expression. Thus, they are involved not only in cell-specific physiological functions but also in the cellular and molecular mechanisms of human pathologies, including atherosclerosis. MiRNAs may be significant in the dysregulation that affects endothelial integrity, the function of vascular smooth muscle and inflammatory cells, and cellular cholesterol homeostasis that drives the initiation and growth of an atherosclerotic plaque. Besides, distinct expression patterns of several miRNAs are attributed to atherosclerotic and cardiovascular patients. In this article, the evidence indicating the multiple critical roles of miRNAs and their relevant molecular mechanisms related to atherosclerosis development and progression was reviewed. Moreover, the effects of miRNAs on atherosclerosis enabled to exploit them as novel diagnostic biomarkers and therapeutic targets that may lead to better management of atherosclerosis and CVDs.

[27] *Taheri F, Taheri M, Basiri A et al. Effects of short-term atorvastatin use in patients with calcium stones: A randomized placebo-controlled clinical trial. Investigative and clinical urology* 2019; 60:472-479.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31692870>

ABSTRACT

Purpose: A few experimental and observational studies have reported that atorvastatin prevents calcium oxalate stone formation. Our study is the first to investigate the effect of atorvastatin on 24-hour urinary metabolites, urinary malondialdehyde (U-MDA) (an oxidative stress marker) and urinary neutrophil gelatinase-associated lipocalin (U-NGAL) (a renal tubular injury marker) in patients with calcium stones and hyperoxaluria. Materials and Methods: This randomized, double-blind, placebo-controlled, parallel-group clinical trial included 32 adults with recurrent calcium stone formation and hyperoxaluria. All participants received a 3-month course of either atorvastatin (20 mg/d) or placebo of an identical shape. Both groups received the usual nutritional care based on the European Association of Urology guidelines. Results: Twenty-eight participants completed the study. Serum levels of total and low-density lipoprotein cholesterol decreased in the atorvastatin group, and these changes were significantly different between groups ($p < 0.001$). No statistically significant differences were observed between intergroup changes of the 24-hour urinary metabolite analysis, the U-MDA to creatinine ratio and the U-NGAL to creatinine ratio. Conclusions: Atorvastatin administration at a dose of 20 mg/d for 3 months did not affect 24-hour urinary metabolite, U-MDA and U-NGAL levels in recurrent calcium stone formers. However, this study could not disprove the preventive role of atorvastatin in kidney stone formation. Future studies should consider a larger sample size, longer follow-up, different drug doses, and measurements of multiple biomarkers of oxidative stress and tubular injury.

[28] Kawada-Watanabe E, Yamaguchi J, Sekiguchi H et al. Targeting high-sensitivity C-reactive protein levels in acute coronary syndrome patients undergoing contemporary lipid-lowering therapy: a sub-analysis of the HIJ-PROPER trial. *J Cardiol* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31699568>

ABSTRACT

BACKGROUND: The effects of high-sensitivity C-reactive protein (hs-CRP) levels on clinical outcomes in chronic-phase acute coronary syndrome (ACS) patients undergoing aggressive lipid-lowering therapy remain unclear. We examined the effects of hs-CRP levels on the prognosis of ACS patients who underwent aggressive lipid-lowering therapy and determined treatment targets for hs-CRP value. METHODS: This post-hoc sub-analysis of a prospective randomized control trial (HIJ-PROPER) included 1734 ACS patients with dyslipidemia, who were divided into hs-CRP quartiles after 3 months of treatment. Primary endpoints were combined all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and ischemia-driven coronary revascularization. Secondary endpoint was all-cause death. RESULTS: The median follow-up period was 3.7 years. Overall, 1415 patients were evaluated retrospectively. No significant among-group differences were noted in low-density lipoprotein cholesterol (LDL-C) levels over time ($p = 0.44$). Kaplan-Meier analyses revealed that the incidence of the primary and secondary endpoints was significantly higher in the highest hs-CRP group than in the other groups [hazard ratio (HR) = 1.52, 95% confidence interval (CI) = 1.16-2.00, $p < 0.01$; HR = 5.30, 95% CI = 2.47-11.32, $p < 0.01$, respectively]. The cut-off hs-CRP level to predict all-cause death was 0.74 mg/L (receiver operating characteristic curve: sensitivity: 68%, specificity: 62%). Multivariate analyses revealed that hs-CRP ≥ 0.74 mg/L at 3 months was correlated with an increased risk of all-cause death (adjusted HR = 3.68, 95% CI = 2.22-6.10, $p < 0.01$). CONCLUSION: Elevated hs-CRP levels independently predicted a worse prognosis, regardless of LDL-C levels, suggesting that interventions against elevated inflammatory responses plus intensive lipid-lowering therapy and coronary revascularization are encouraging options for secondary prevention in ACS patients. TRIAL

Literature update week 45 (2019)

REGISTRATION: This trial is registered with the UMIN Clinical Trials Registry number UMIN000002742. Trial name: Proper level of lipid lowering with pitavastatin and ezetimibe in acute coronary syndrome (HIJ-PROPER) URL: <https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr-view.cgi?recptno=R000003334>.

[29] Wu H, Xu L, Ballantyne CM. **sDietary and pharmacological fatty acids and cardiovascular health.** *The Journal of clinical endocrinology and metabolism* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31678992>

ABSTRACT

CONTEXT: The effects of dietary intake of different fatty acids and pharmacological use of fatty acids, specifically long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs), on cardiovascular health and atherosclerotic cardiovascular disease (ASCVD) prevention have been examined in a large number of observational studies and clinical trials. This review summarizes recent data and discusses potential mechanisms. EVIDENCE ACQUISITION: The review is based on the authors' knowledge of the field supplemented by a PubMed search using the terms "seafood," "fish oil," "saturated fatty acids," "omega-3 fatty acids," "eicosapentaenoic acid," "docosahexaenoic acid," "polyunsaturated fatty acids," "monounsaturated fatty acids," and "ASCVD." EVIDENCE SYNTHESIS: We mainly discuss the recent clinical trials that examine the effects of different types of dietary fatty acids and pharmacological use of n-3 PUFA products on ASCVD prevention and the potential mechanisms. CONCLUSIONS: While replacement of dietary saturated fat with unsaturated fat, polyunsaturated fat in particular, or intake of LC n-3 PUFA-rich seafood has generally shown benefit for ASCVD prevention and is recommended for cardiovascular benefits, data on effects of n-3 PUFA products on ASCVD health are inconsistent. However, recent clinical trials support benefits of prescription EPA in ASCVD prevention. n-3 PUFAs may contribute to ASCVD prevention through multiple mechanisms, including lowering plasma triglyceride levels, anti-inflammatory effects, and other effects.

[30] Kostapanos MS, Cacciottolo PJ, Hubsch A et al. **Investigating the lowest threshold of vascular benefits from LDL cholesterol lowering with a PCSK9 mAb inhibitor (alirocumab) in healthy volunteers - a mechanistic physiological study (INTENSITY-LOW): protocol and study rationale.** *Journal of drug assessment* 2019; 8:167-174.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31692938>

ABSTRACT

Objective: Whether reducing low density lipoprotein cholesterol (LDL-C) is associated with cardiovascular benefits in low risk normocholesterolaemic subjects is unknown. The INTENSITY LOW [Investigating the lowest threshold of vascular benefits from LDL-cholesterol lowering with a PCSK9 mAb inhibitor (alirocumab) in healthy volunteers] study aims to assess whether lowering LDL-C by alicumab monotherapy can improve endothelial-dependent vascular function compared with placebo (primary objective) in low-risk normocholesterolaemic healthy individuals. Changes in endothelial-dependent or endothelial-independent vascular function, arterial stiffness and biomarkers of systemic inflammation by alicumab, atorvastatin or their combination are secondary objectives. Study design and methods: This is a single-center, randomized, two-period, single-blind, placebo-controlled clinical trial. The study was registered on clinicaltrials.gov (N03273972). It will include 30 healthy low-risk subjects with LDL-C < 4.1 mmol/l. After passing the screening visit (Visit 1), eligible participants will be randomized 1:1 to either subcutaneous alicumab 150 mg or placebo. These will be administered as single doses in 2 visits 14 days apart (Visits 2 and 3). Atorvastatin 20 mg once

Literature update week 45 (2019)

nightly will be prescribed for 14 days at Visit 3 in both groups through to Visit 4. At baseline (Visit 2) and during all post-dose visits (Visits 3-4), endothelial function will be assessed using venous occlusion plethysmography. Specifically, changes in forearm blood flow responses to intra-arterial infusions of acetylcholine, sodium nitroprusside and L-N(G)-monomethyl-arginine acetate will be assessed as surrogates of endothelial-dependent and -independent vasodilatation. Additionally, arterial stiffness and carotid intima-media thickness will be evaluated at the same timepoints. The above-mentioned changes will be correlated with changes in lipid and systemic inflammation biomarkers.

[31] Lee HS, Noh JY, Shin OS et al. **Matrix metalloproteinase-13 in atherosclerotic plaque is increased by influenza A virus infection.** *The Journal of infectious diseases* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31693113>

ABSTRACT

BACKGROUND: Influenza virus infection triggers acute cardiovascular events. Several studies have demonstrated that influenza A virus infection was associated with immune cell influx and increased production of inflammatory cytokines in the atherosclerotic plaque lesion, but the underlying mechanism for these findings is not clear. METHODS: We examined the expression levels of matrix metalloproteinases by influenza A virus infection in human cells using quantitative RT-PCR, Western blot and human MMP-13 ELISA assay. In an animal study, protein expression in the plaque lesions of ApoE-deficient mice were analyzed by immunohistochemistry and Western blot. RESULTS: We confirmed that matrix metalloproteinase-13 was increased in influenza A virus-infected cells. In the aorta of infected ApoE-deficient mice, matrix metalloproteinase-13 was increased at 3 days after infection. Immunohistochemical staining results suggested that collagen was degraded in the matrix metalloproteinase-13 expression area and that macrophages were the main source of matrix metalloproteinase-13 expression. Furthermore, the expression of matrix metalloproteinase-13 was regulated by influenza A virus through activation of the p38 MAPK signal pathway. CONCLUSIONS: In this study, we demonstrated that p38 MAPK-mediated matrix metalloproteinase-13 expression by influenza A virus infection led to destabilization of vulnerable atherosclerotic plaques in artery. (191 words).

[32] Kiourtzidis M, Kuhn J, Schutkowski A et al. **Inhibition of Niemann-Pick C1-like protein 1 by ezetimibe reduces uptake of deuterium-labeled vitamin D in mice.** *J Steroid Biochem Mol Biol* 2019; 197:105504.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31682937>

ABSTRACT

For a long time, orally ingested vitamin D was assumed to enter the body exclusively via simple passive diffusion. Recent data from in vitro experiments have described Niemann-Pick C1-like protein 1 (Npc1l1) as an important sterol transporter for vitamin D absorption. However, short-term applications of ezetimibe, which inhibits Npc1l1, were not associated with reduced vitamin D uptake in animals and humans. The current study aimed to elucidate the effect of long-term inhibition of Npc1l1 by ezetimibe on the uptake and storage of orally administered triple deuterated vitamin D₃ (vitamin D₃-d₃). Therefore, 30 male wild-type mice were randomly assigned into three groups and received diets with 25mg/kg of vitamin D₃-d₃ that contained 0 (control group), 50 or 100mg/kg ezetimibe for six weeks. Mice fed diets with 50 or 100mg/kg ezetimibe had lower circulating levels of cholesterol than control mice (-12 %, -15 %, P<0.01). In contrast, the concentrations of 7-dehydrocholesterol in serum (P<0.001)

Literature update week 45 (2019)

and liver ($P<0.05$) were higher in mice treated with ezetimibe than in control mice, indicating an increased sterol synthesis to compensate for cholesterol reduction. Long-term application of ezetimibe significantly reduced the concentrations of vitamin D₃-d₃ in the serum and tissues of mice. The magnitude of vitamin D₃ reduction was comparable between the two ezetimibe groups. In comparison to the control group, mice treated with ezetimibe had lower concentrations of deuterated vitamin D₃ compared with the control group in serum (62 %, $P<0.001$), liver (79 %, $P<0.001$), kidney (54 %, $P<0.001$), adipose tissues (55 %, $P<0.001$) and muscle (41 %, $P<0.001$). Surprisingly, the serum concentration of deuterated 25-hydroxyvitamin D₃ was higher in the group fed 100mg/kg ezetimibe than in the control group ($P<0.05$). The protein expression of the vitamin D hydroxylases Cyp2r1, Cyp27a1, Cyp3a11, Cyp24a1 and Cyp2j3 in liver and Cyp27b1 and Cyp24a1 in kidney remained largely unaffected by ezetimibe. To conclude, Npc1l1 appears to be crucial for the uptake of orally ingested vitamin D because long-term inhibition of Npc1l1 by ezetimibe strongly reduced the levels of deuterium-labeled vitamin D in the body; the observed rise in deuterated 25-hydroxyvitamin D₃ in serum of these mice can not be explained by the expression levels of the key enzymes involved in vitamin D hydroxylation.

[33] *Korani S, Bahrami S, Korani M et al. Parenteral systems for statin delivery: a review. Lipids in health and disease* 2019; 18:193.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31690335>

ABSTRACT

The oral route of drug administration is the most common and convenient route for dosing statin drugs, and, in fact, most medications, because of ease of drug delivery, patient compliance, and cost-effectiveness. However, the oral administration of statin drugs has disadvantages such as hepatic first-pass metabolism and degradation within the gastrointestinal tract that limit their overall bioavailability. This review introduces several diverse non-oral delivery methods for the administration of statins. These alternative delivery systems and routes of administration are varied and are capable of improving the bioavailability and therapeutic efficacy of statin drugs.

[34] *Bulut A, Avci B. Carotid intima-media thickness values are significantly higher in patients with prediabetes compared to normal glucose metabolism. Medicine (Baltimore)* 2019; 98:e17805.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31689862>

ABSTRACT

Carotid intima-media thickness (C-IMT) increases in patients with adult type-2 diabetes mellitus (DM) and is used for early detection of macrovascular complications. We aimed to investigate the change of C-IMT in prediabetes and type-2 DM patients compared to subjects with normal glucose metabolism (NGM). A total of 180 individuals (60 subjects with NGM, 60 patients with prediabetes and 60 patients with type-2 DM) were included in this study. Routine laboratory and micro-macrovascular involvement were investigated. Urine albumin-creatinine ratio (ACR) was measured for urinary albuminuria detection. In addition to routine laboratory examination, right-left common and internal C-IMT (CC-IMT and IC-IMT) were measured. Systolic and diastolic blood pressure values were found to be higher in prediabetes and type-2 DM groups than NGM group. The prevalence of nephropathy and presence of CAD were higher in type-2 DM groups than prediabetes. Glucose, glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood urea nitrogen, creatinine, high sensitive C reactive protein (hs-CRP) levels and urinary ACR were significantly higher in patients

Literature update week 45 (2019)

within prediabetes and type-2 DM groups than NGM group. Glucose, HbA1c and hs-CRP levels were found to be higher in type-2 DM groups than prediabetes. Estimated glomerular filtration rate and high-density lipoprotein (HDL) cholesterol level was found to be lower in patients within prediabetes and type-2 DM groups than NGM group. Right-left-mean CC-IMT and IC-IMT values were found to be higher in prediabetes and type-2 DM groups than NGM group. Left IC-IMT, left CC-IMT, and mean IC-IMT values were found to be higher in type-2 DM patients compared to prediabetes. LDL and HDL cholesterols, HbA1c, and hs-CRP levels were independently associated with IC-IMT and CC-IMT. C-IMT values were significantly higher in impaired glucose metabolism compared to NGM. C-IMT measurement may be used as part of routine screening of macrovascular complication in patients with prediabetes and newly diagnosed type-2 DM.

[35] *Cicero AFG, Fogacci F, Banach M. Red Yeast Rice for Hypercholesterolemia. Methodist DeBakey cardiovascular journal* 2019; 15:192-199.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31687098>

ABSTRACT

The extract of red yeast rice (RYR) is the most effective cholesterol-lowering nutraceutical on the market. In particular, its effectiveness is directly related to the amount of monacolin K within the extract (up to 10 mg/day). Consuming monacolin K on a daily basis reduces low-density lipoprotein (LDL) cholesterol plasma levels between 15% and 25% within 6 to 8 weeks. Certainly, the decrease in LDL-cholesterol is accompanied by a similar reduction in total cholesterol, non-high-density lipoprotein cholesterol, plasma apolipoprotein B, matrix metalloproteinases 2 and 9, and high-sensitivity C-reactive protein. Furthermore, the RYR lipid-lowering effect is associated with significant improvements in pulse wave velocity and endothelial function, which are validated and reliable biomarker tools able to detect vascular aging. Although it has a mechanism of action similar to statins, a daily consumption of between 3 and 10 mg monacolin K has only minimal associated risks, and mild myalgias are seen only in the frailest patients (those who also cannot tolerate minimal dosages of statin). The monacolin K found in RYR is a safe and effective supplement for managing mild to moderate hypercholesterolemia in people with no additional cardiovascular risk factors.

[36] *Sunkara A, Raizner A. Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment. Methodist DeBakey cardiovascular journal* 2019; 15:179-184.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31687096>

ABSTRACT

Vitamins and minerals are dietary supplements used by almost half of the US adult population based on the presumption that they help prevent or treat cardiovascular disease. Many studies, including randomized trials, have investigated the possible role of these substances in cardiovascular disease. We reviewed the available data on multivitamins/multiminerals, antioxidants, folic acid, vitamin E, niacin (B3), and beta-carotene. Despite extensive investigation, the evidence to date fails to support the use of exogenous supplements of vitamins and minerals for the prevention or treatment of cardiovascular disease. Here, we review some of the common supplements used by adults for cardiovascular health and the available evidence for risks/benefits.

Literature update week 45 (2019)

[37] *van Ingen E, Foks AC, Kroner MJ et al. Antisense Oligonucleotide Inhibition of MicroRNA-494 Halts Atherosclerotic Plaque Progression and Promotes Plaque Stabilization. Molecular therapy. Nucleic acids* 2019; 18:638-649.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31689618>

ABSTRACT

We have previously shown that third-generation antisense (3GA) inhibition of 14q32 microRNA (miRNA)-494 reduced early development of atherosclerosis. However, patients at risk of atherosclerotic complications generally present with advanced and unstable lesions. Here, we administered 3GAs against 14q32 miRNA-494 (3GA-494), miRNA-329 (3GA-329), or a control (3GA-ctrl) to mice with advanced atherosclerosis. Atherosclerotic plaque formation in LDLr(-/-) mice was induced by a 10-week high-fat diet and simultaneous carotid artery collar placement. Parallel to 3GA-treatment, hyperlipidemia was normalized by a diet switch to regular chow for an additional 5 weeks. We show that, even though plasma cholesterol levels were normalized after diet switch, carotid artery plaque progression continued in 3GA-ctrl mice. However, treatment with 3GA-494 and, in part, 3GA-329 halted plaque progression. Furthermore, in the aortic root, intra-plaque collagen content was increased in 3GA-494 mice, accompanied by a reduction in the intra-plaque macrophage content. Pro-atherogenic cells in the circulation, including inflammatory Ly6C(hi) monocytes, neutrophils, and blood platelets, were decreased upon miRNA-329 and miRNA-494 inhibition. Taken together, treatment with 3GA-494, and in part with 3GA-329, halts atherosclerotic plaque progression and promotes stabilization of advanced lesions, which is highly relevant for human atherosclerosis.

[38] *Komal F, Mahr Un N, Khan MK et al. Evaluation of the efficacy of different sources of omega-3 fatty acids in polycystic ovarian syndrome (PCOS) induced rats. Pak J Pharm Sci* 2019; 32:1781-1788.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31680073>

ABSTRACT

The study was planned to check the beneficial effects of various sources of omega-3 fatty acids (synthetic, flaxseed oil, fish oil) on 45 Wistar female rats. The rats were divided into five groups and assigned to different diets i.e. NC (Negative control), PC (Positive control), SO (Synthetic omega-3 250mg/kg/orally/daily), FO (flaxseed oil 250mg/kg/orally/daily) and F (fish oil 250mg/kg/orally/diet). Animals fed on different diets were induced PCOS by an intramuscular (IM) injection of estradiol-valerate (4mg/rat/IM) except NC group. Results of the lipid profile indicated that F showed highest increase in HDL level (35.67+/-1.45), while cholesterol, LDL, triglycerides, blood glucose and body weight were reduced in all three treatment groups. In case of a hormonal profile, testosterone, luteinizing hormone (LH) and insulin levels showed a significant reduction after treatments. It can be concluded from the study that different sources of omega-3 fatty acids can be a new approach to treat the symptoms of PCOS.

[39] *Ustinova M, Silamikelis I, Kalnina I et al. Metformin strongly affects transcriptome of peripheral blood cells in healthy individuals. PloS one* 2019; 14:e0224835.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31703101>

ABSTRACT

Metformin is a commonly used antihyperglycaemic agent for the treatment of type 2 diabetes mellitus. Nevertheless, the exact mechanisms of action, underlying the various therapeutic effects of metformin, remain elusive. The goal of this study was to evaluate the alterations in longitudinal whole-

Literature update week 45 (2019)

blood transcriptome profiles of healthy individuals after a one-week metformin intervention in order to identify the novel molecular targets and further prompt the discovery of predictive biomarkers of metformin response. Next generation sequencing-based transcriptome analysis revealed metformin-induced differential expression of genes involved in intestinal immune network for IgA production and cytokine-cytokine receptor interaction pathways. Significantly elevated faecal sIgA levels during administration of metformin, and its correlation with the expression of genes associated with immune response (CXCR4, HLA-DQA1, MAP3K14, TNFRSF21, CCL4, ACVR1B, PF4, EPOR, CXCL8) supports a novel hypothesis of strong association between metformin and intestinal immune system, and for the first time provide evidence for altered RNA expression as a contributing mechanism of metformin's action. In addition to universal effects, 4 clusters of functionally related genes with a subject-specific differential expression were distinguished, including genes relevant to insulin production (HNF1B, HNF1A, HNF4A, GCK, INS, NEUROD1, PAX4, PDX1, ABCC8, KCNJ11) and cholesterol homeostasis (APOB, LDLR, PCSK9). This inter-individual variation of the metformin effect on the transcriptional regulation goes in line with well-known variability of the therapeutic response to the drug.

[40] *Kulshreshtha A, Singh S, Ahmad M et al. Simvastatin mediates inhibition of exosome synthesis, localization and secretion via multicomponent interventions. Scientific reports* 2019; 9:16373.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31704996>

ABSTRACT

Discovery of exosomes as modulator of cellular communication has added a new dimension to our understanding of biological processes. Exosomes influence the biological systems by mediating trans-communication across tissues and cells, which has important implication for health and disease. In absence of well-characterized modulators of exosome biogenesis, an alternative option is to target pathways generating important exosomal components. Cholesterol represents one such essential component required for exosomal biogenesis. We initiated this study to test the hypothesis that owing to its cholesterol lowering effect, simvastatin, a HMG CoA inhibitor, might be able to alter exosome formation and secretion. Simvastatin was tested for its effect on exosome secretion under various in-vitro and in-vivo settings and was found to reduce the secretion of exosome from various cell-types. It was also found to alter the levels of various proteins important for exosome production. Murine model of Acute Airway Inflammation was used for further validation of our findings. We believe that the knowledge acquired in this study holds potential for extension to other exosome dominated pathologies and model systems.

[41] *Sposito AC, Carvalho LSF, Moura FA et al. Statin Short-term Inhibition of Insulin Sensitivity and Secretion During Acute Phase of ST-Elevation Myocardial Infarction. Scientific reports* 2019; 9:16401.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31704948>

ABSTRACT

Hyperglycemia during myocardial infarction (MI) has a strong and direct association with mortality. In stable patients and experimental models, statins favor the elevation of glycaemia. The present study investigated whether short-course treatment with statins during MI can influence glucose homeostasis and thus the clinical outcome. In this prospective study, euglycemic hyperinsulinemic clamp (EHC) was performed at second (D2) and sixth (D6) day after MI in patients randomized to simvastatin (S)10 or 80 mg/day during hospitalization (n = 27). In addition, patients (n = 550) were treated without (WS) or with simvastatin (S) at 20, 40 or 80 mg/day had HOMA2S on admission (D1) and fifth (D5) day after MI.

Literature update week 45 (2019)

According to EHC, insulin sensitivity increased by 20 +/- 60% in S10 and decreased by -6 +/- 28% in S80 (p = 0.025). Consistently, the changes in HOMA2S between D1 and D5 were 40 +/- 145% (WS), 22 +/- 117% (S20), 16 +/- 61% (S40) and -2% +/- 88% (S80) (p = 0.001). In conclusion, statin during the acute phase of MI reduces insulin sensitivity in a dose-dependent manner.

[42] *Wu BJ, Li Y, Ong KL et al. The Cholesteryl Ester Transfer Protein Inhibitor, des-Fluoro-Anacetrapib, Prevents Vein Bypass-induced Neointimal Hyperplasia in New Zealand White Rabbits. Scientific reports* 2019; 9:16183.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31700015>

ABSTRACT

Coronary artery bypass grafting is among the most commonly performed of all cardiovascular surgical procedures. However, graft failure due to stenosis reduces the long-term benefit of the intervention. This study asks if elevating plasma high density lipoprotein cholesterol (HDL-C) levels by inhibition of cholesteryl ester transfer protein (CETP) activity with des-fluoro-anacetrapib, an analog of the CETP inhibitor anacetrapib, prevents vein bypass-induced neointimal hyperplasia. NZW rabbits were placed on a normal chow diet or chow containing 0.14% (wt/wt) des-fluoro-anacetrapib for 6 weeks. Bypass grafting of the jugular vein to the common carotid artery was performed 2 weeks after starting dietary des-fluoro-anacetrapib supplementation. The animals were euthanised 4 weeks post-bypass grafting. Relative to control, dietary supplementation with des-fluoro-anacetrapib reduced plasma CETP activity by 89 +/- 6.9%, increased plasma apolipoprotein A-I levels by 24 +/- 5.5%, increased plasma HDL-C levels by 93 +/- 26% and reduced intimal hyperplasia in the grafted vein by 38 +/- 6.2%. Des-fluoro-anacetrapib treatment was also associated with decreased bypass grafting-induced endothelial expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), endothelial dysfunction, and smooth muscle cell (SMC) proliferation in the grafted vein. In conclusion, increasing HDL-C levels by inhibiting CETP activity is associated with inhibition of intimal hyperplasia in grafted veins, reduced inflammatory responses, improved endothelial function, and decreased SMC proliferation.

[43] *Huang CC, Charng MJ. Clinical Evaluation Of Evolocumab For The Treatment Of Homozygous Familial Hypercholesterolemia In Chinese Patients. Therapeutics and clinical risk management* 2019; 15:1209-1216.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31686828>

ABSTRACT

Evolocumab, which can lower low-density lipoprotein (LDL) cholesterol levels by approximately 60% and prevent cardiovascular events in patients with cardiovascular disease, is a monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Some studies have investigated its efficacy and safety in the treatment of the homozygous form of familial hypercholesterolemia (HoFH), and others have focused on its efficacy and safety in Asians with high cardiovascular risk. Although no direct evolocumab clinical trials have been conducted in Chinese HoFH patients, its efficacy and safety in the Chinese population should be similar to those in other ethnic groups.