Literature update week 01 (2020)

[1] *Khan SU, Khan MU, Riaz H et al.* **Meta-analysis of the Relation of Body Mass Index to Cardiovascular Outcomes in Patients Receiving Intensive Low-Density Lipoprotein Cholesterol Lowering Therapy**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31898964
ABSTRACT
The impact of body mass index (BMI) on cardiovascular outcomes in patients receiving intensive low-density lipoprotein cholesterol (LDL-C) lowering therapy is uncertain. We performed meta-analysis of 29 randomized controlled trials using PubMed, Embase, and CENTRAL through April 2019. Therapies were grouped as more intensive LDL-C lowering therapy (statins, ezetimibe+statin or PCSK9 inhibitors) and less intensive LDL-C lowering therapy (less potent active control or placebo). Random effects meta-regressions and meta-analyses were performed to evaluate association of BMI with cardiovascular endpoints. In 265,766 patients, for every 1 kg/m(2) increase in BMI, more intensive therapy compared with less intensive therapy was associated with hazard ratio (HR) of 1.07 for cardiovascular mortality (95% confidence interval 1.02 to 1.13); HR of 1.03 for all-cause mortality (0.99 to 1.06) HR of 1.06 for myocardial infarction (1.02 to 1.09), HR of 1.08 (1.03 to 1.12) for revascularization and HR of 1.04 for MACE (1.01 to 1.07). Meta-analysis showed that patients with BMI <25 kg/m(2) had the highest risk reduction in mortality and cardiovascular outcomes compared with patients with BMI >/=30 kg/m(2) (p-interaction </=0.05). In conclusion, patients with normal BMI treated with intensive LDL-C lowering regimens may derive a larger clinical benefit compared with patients with larger BMI. The results could be due to the higher mortality rate of obese patients that may artificially lower the efficacy of therapy, or due to a true therapeutic limitation in these patients.

[2] *Mariano C, Alves AC, Medeiros A et al.* **The FH Phenotype: Monogenic Familial Hypercholesterolaemia, Polygenic Hypercholesterolaemia and Other Causes**. Clinical genetics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31893465
ABSTRACT
Familial Hypercholesterolaemia (FH) is a monogenic disorder characterised by high LDL-C concentrations and increased cardiovascular risk. However, in clinically defined FH cohorts worldwide, an FH-causing variant is only found in 40-50% of the cases. The aim of this work was to characterise the genetic cause of the FH phenotype in Portuguese clinical FH patients. Methods and Results Between 1999 and 2017, 731 index patients (311 children and 420 adults) who met the Simon Broome diagnostic criteria had been referred to our laboratory. LDLR, APOB, PCSK9, APOE, LIPA, LDLRAP1, ABCG5/8 genes were analysed by PCR amplification and Sanger sequencing. The 6-SNP LDL-C genetic risk score (GRS) for polygenic hypercholesterolaemia was validated in the Portuguese population and cases with a GRS over the 25th percentile were considered to have a high likelihood of polygenic hypercholesterolaemia. An FH-causing mutation was found in 39% of patients (94% in LDLR, 5% APOB and 1% PCSK9), while at least 29% have polygenic hypercholesterolaemia and 1% have other lipid disorders. A genetic cause for the FH phenotype was found in 503 patients (69%). All known causes of the FH phenotype should be investigated in FH cohorts to ensure accurate diagnosis and appropriate management.

[3] *Wang FM, Zhang Y*. **High Lipoprotein(a) Level Is Independently Associated with Adverse Clinicopathological Features in Patients with Prostate Cancer**. Disease markers 2019; 2019:9483935.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31885745

ABSTRACT
Background: The effect of lipoprotein(a) (Lp(a)) on prostate cancer (PCa) is unclear. The aim of this study was to investigate the association between serum Lp(a) levels and clinicopathological features in patients with PCa. Methods: A total of 376 consecutive pathologically diagnosed PCa patients were enrolled and were classified as a low-intermediate-risk group or a high-risk group. The association of Lp(a) and the other lipid parameters including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), TC/HDL-C, LDL-C/HDL-C, and remnant cholesterol (RC) with clinicopathological parameters was tested by univariate and multivariate logistic regression analyses. Results: The high-risk PCa patients tended to have higher Lp(a) levels (p = 0.022) while there was no significant difference regarding the other lipid parameters (p > 0.05) compared to low-intermediate-risk counterparts. Patients with PSA >/= 100 ng/ml had significantly higher Lp(a) levels than subjects with PSA < 100 ng/ml (p = 0.002). Univariate logistic regression analyses revealed that high Lp(a) levels were correlated with high-risk PCa (Q4 vs. Q1, HR = 2.687, 95% CI: 1.113-6.491, p = 0.028), while the other lipid parameters were not correlated with high-risk PCa. In the stepwise multivariate regression analysis, the association between Lp(a) levels and high-risk PCa remained significant (Q4 vs. Q1, HR = 2.890, 95% CI: 1.148-7.274, p = 0.024) after adjusting for confounding factors including age, body mass index, hypertension, diabetes, coronary artery disease, and lipid-lowering drugs. Conclusions: This is the first study showing the positive association between high Lp(a) and adverse clinicopathological features of PCa. PCa patients with high Lp(a) tends to be more aggressive and should receive more attention in clinical practice.

[4] *Parhofer KG, Laufs U*. **The Diagnosis and Treatment of Hypertriglyceridemia**. Deutsches Arzteblatt international 2019; 116:825-832.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31888796

ABSTRACT
BACKGROUND: Hypertriglyceridemia affects 15-20% of the adult population and is associated with overweight, metabolic syndrome, and diabetes mellitus. It is often discovered incidentally. METHODS: This review is based on pertinent publications retrieved by a selective literature search, including current guidelines on hypertriglyceridemia. RESULTS: Elevated triglyceride (TG) levels are causally linked to cardiovascular disease; TG levels above 1000 mg/dL (11.4 mmol/L) can induce acute pancreatitis. The individual risk of cardiovascular disease and of pancreatitis must be estimated in order to decide whether, and how, hypertriglyceridemia should be treated. Lifestyle modifications (cessation of alcohol consumption, reduced intake of rapidly metabolized carbohydrates), weight loss, and blood sugar control are the most effective ways to lower TG levels. The need to lower the low-density lipoprotein (LDL) concentration must be determined on the basis of the cardiovascular risk, independently of the success of the lifestyle changes. Few patients need specific drug treatment to lower the TG level. Fibrates can lower TG concentrations, but their efficacy in combination with statins has not been clearly shown in endpoint studies. A daily dose of 2-4 g omega-3 fatty acids can also lower TG levels. To date, only a single large-scale randomized, blinded trial has shown the efficacy of 4 g of eicosapentaenoic acid ethyl ester per day in lowering the risk in high-risk patients (number needed to treat = 21). Patients with the very rare purely genetic types of hypertriglyceridemia (familial chylomicronemia syndrome) should be treated in specialized outpatient clinics. CONCLUSION: Hypertriglyceridemia is causally linked to cardiovascular disease and pancreatitis. Lifestyle modifications play a paramount role in its treatment.

[5] *Dopheide JF, Veit J, Ramadani H et al.* **Adherence to statin therapy favours survival of patients with symptomatic peripheral artery disease**. European heart journal. Cardiovascular pharmacotherapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31886861
ABSTRACT
AIMS : We hypothesized that adherence to statin therapy determines survival in patients with peripheral artery disease (PAD). METHODS AND RESULTS : Single-centre longitudinal observational study with 691 symptomatic PAD patients. Mortality was evaluated over a mean follow-up of 50 +/- 26 months. We related statin adherence and low-density lipoprotein cholesterol (LDL-C) target attainment to all-cause mortality. Initially, 73% of our PAD patients were on statins. At follow-up, we observed an increase to 81% (P < 0.0001). Statin dosage, normalized to simvastatin 40 mg, increased from 50 to 58 mg/day (P < 0.0001), and was paralleled by a mean decrease of LDL-C from 97 to 82 mg/dL (P < 0.0001). The proportion of patients receiving a high-intensity statin increased over time from 38% to 62% (P < 0.0001). Patients never receiving statins had a significant higher mortality rate (31%) than patients continuously on statins (13%) or having newly received a statin (8%; P < 0.0001). Moreover, patients on intensified statin medication had a low mortality of 9%. Those who terminated statin medication or reduced statin dosage had a higher mortality (34% and 20%, respectively; P < 0.0001). Multivariate analysis showed that adherence to or an increase of the statin dosage (both P = 0.001), as well as a newly prescribed statin therapy (P = 0.004) independently predicted reduced mortality. CONCLUSION : Our data suggest that adherence to statin therapy is associated with reduced mortality in symptomatic PAD patients. A strategy of intensive and sustained statin therapy is recommended.

[6] *Karazniewicz-Lada M, Krzyzanska D, Danielak D et al.* **Impact of genetic variants of selected cytochrome P450 isoenzymes on pharmacokinetics and pharmacodynamics of clopidogrel in patients co-treated with atorvastatin or rosuvastatin**. Eur J Clin Pharmacol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31897532
ABSTRACT
PURPOSE: Impaired antiplatelet effect of clopidogrel (CLP) can result from drug-drug interactions and genetic polymorphisms of drug-metabolizing enzymes. The aim of the study was to evaluate the effect of genetic polymorphisms of ABCB1 and the selected cytochrome P450 isoenzymes on the pharmacodynamics and pharmacokinetics of CLP and its metabolites in patients co-treated with atorvastatin or rosuvastatin. METHODS: The study involved 50 patients after coronary angiography/angioplasty treated with CLP and atorvastatin (n = 25) or rosuvastatin (n = 25) for at least 6 months. Plasma concentrations of CLP, diastereoisomers of thiol metabolite (inactive H3 and active H4), and inactive CLP carboxylic acid metabolite were measured by UPLC-MS/MS method. Identification of the CYP2C19*2, CYP2C19*17, CYP3A4*1G, CYP1A2*1F, and ABCB1 C3435T genetic polymorphisms was performed by PCR-RFLP, while platelet reactivity units (PRU) were tested using the VerifyNow P2Y12 assay. RESULTS: There were significant differences in the pharmacokinetic parameters of the H4 active metabolite of CLP in the atorvastatin and rosuvastatin group divided according to their CYP2C19 genotype. There were no significant associations between CYP3A4, CYP1A2, and ABCB1 genotypes and pharmacokinetic parameters in either statin groups. In the multivariate analysis, CYP2C19*2 genotype and non-genetic factors including BMI, age, and diabetes significantly affected platelet reactivity in the studied groups of patients (P < 0.01). In the atorvastatin

group, CYP2C19*2, CYP3A4*1G, and ABCB1 C3435T TT genotypes were independent determinants of PRU values (P < 0.01). CONCLUSION: The CYP2C19*2 allele is the primary determinant of the exposition to the H4 active metabolite of clopidogrel and platelet reactivity in patients co-treated with atorvastatin or rosuvastatin.

[7] *Lee WD, Kim BK, Park JY et al.* **Combined use of rosuvastatin and ezetimibe improves hepatic steatosis in patients with dyslipidemia**. European journal of gastroenterology & hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895906
ABSTRACT
BACKGROUND AND AIMS: Rosuvastatin plus ezetimibe are beneficial for the management of dyslipidemia. We investigated whether rosuvastatin plus ezetimibe improves hepatic steatosis in patients with dyslipidemia. METHODS: Between January and August 2018, 114 patients with dyslipidemia treated for 6 months with rosuvastatin plus ezetimibe were analyzed in this retrospective cohort study. The degree of hepatic steatosis was assessed using the hepatic steatosis index (HSI). Hepatic steatosis improvement and presence of fatty liver were defined as a >/=5% reduction in HSI score and HSI >/=36, respectively. RESULTS: The mean age of the study population (50 males and 64 females) was 57.4 years. At baseline, the mean BMI total cholesterol level, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and HSI were 25.1 kg/m, 207.4 mg/dL, 126.1 mg/dL, 52.9 mg/dL, 146.4 mg/dL, and 36.1, respectively. During the 6-month treatment, hepatic steatosis burden was constant (mean HSI = 36.3 and 36.4 at 3 and 6 months, respectively). On multivariate analyses, ultrasonographic fatty liver and HSI >/=36 were selected as independent predictors of hepatic steatosis improvement. However, when 53 (46.5%) patients with fatty liver (HSI >/= 36) were selected, hepatic steatosis burden was significantly improved (mean HSI = 40.8, 39.3, and 39.7 at baseline, 3 months, and 6 months, respectively). CONCLUSIONS: The use of rosuvastatin plus ezetimibe for the management of dyslipidemia did not improve hepatic steatosis burden in all patients with dyslipidemia, but it improved hepatic steatosis burden in the subgroup with fatty liver.

[8] *Delgado GE, Kramer BK, Scharnagl H et al.* **Bile Acids in Patients with Uncontrolled Type 2 Diabetes Mellitus - The Effect of Two Days of Oatmeal Treatment**. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31896155
ABSTRACT
BACKGROUND: Beta-glucans are effective in binding bile acids (BA) thereby lowering cholesterol concentration. This might contribute to the beneficial effects of the consumption of beta-glucan-rich foods like oatmeal on glucose homeostasis. OBJECTIVE: We measured BA serum concentrations in patients with uncontrolled type 2 diabetes (T2DM) to investigate the effect of two days of oatmeal treatment on BA concentration as compared to a conventional T2DM-adapted diet. METHODS: The OatMeal And Insulin Resistance study was performed as a randomized, open label crossover dietary intervention study with consecutive inclusion of 15 patients in an inpatient clinical setting. Bile acids were measured by high-resolution mass spectrometry. For statistical analysis, the differences in the concentration of serum BA and laboratory parameters between the fifth day and the third day of each inpatient stay were calculated and the effect compared between both phases by using the Wilcoxon test. RESULTS: Whereas there was a mean decrease in total BA following oatmeal treatment (-0.82+/-

1.14 micromol/l), there was no decrease following the control treatment. Glycocholic acid was lower after oatmeal treatment but higher following control treatment (-0.09+/-0.17 vs. 0.05+/-0.11 micromol/l). The reduction in total BA was directly correlated with a decrease in proinsulin during the oatmeal phase. Decreases in blood lipids or apolipoproteins were mostly greater after oatmeal treatment, but these differences were not statistically significant. CONCLUSION: Two days of oatmeal diet led to significant reductions in total BA as compared to a diabetes-adapted control diet. The magnitude of BA reduction was directly correlated with a decrease in proinsulin.

[9] *Pasta A, Cremonini AL, Pisciotta L et al.* **PCSK9 inhibitors for treating hypercholesterolemia**. Expert opinion on pharmacotherapy 2020:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31893957
ABSTRACT
Introduction: Scientific evidence on subjects treated with statin or other lipid-lowering treatments has established that treatments aiming to lower low-density lipoprotein cholesterol (LDL-C) can reduce atherosclerosis. PCSK9 inhibitors (PCSK9-i), thanks to their efficacy in reducing LDL-C constitute a further step in the treatment of dyslipidemia and cardiovascular (CV) diseases.Areas covered: The purpose of this narrative review is to summarize the current knowledge of PCSK9-i, with particular regard to pharmacodynamic, pharmacokinetic, and clinical data on evolocumab and alirocumab.Expert opinion: PCSK9-I are effective in reducing atherosclerotic events through their significant LDL-C-lowering action similarly to statins. Furthermore, these drugs can be considered safe and well-tolerated. However, some controversies remain with regard to their efficacy in reducing mortality and the paucity of data on both pleiotropic effects and long-term safety of these drugs. However, future studies will focus on understanding the effects of very low cholesterol levels on health. At present, we know that the genetic model of PCSK9 deficiency is characterized by very low LDL-C levels without particular health problems. Yet, we do not know the effect of prolonged PCSK9 inhibition induced by antibody action during the lifetime of normal subjects.

[10] *Lensen KDF, Voskuyl AE, Comans EFI et al.* **Should vascular wall (18)F-FDG uptake be adjusted for the extent of atherosclerotic burden?** The international journal of cardiovascular imaging 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31898005
ABSTRACT
Vascular wall (18)F-FDG uptake is often used as a surrogate marker of atherosclerotic plaque inflammation. A potential caveat is that vascular wall (18)F-FDG uptake is higher simply because more atherosclerosis is present. To determine if the degree of inflammation is high or low relative to the extent of atherosclerosis, vascular wall (18)F-FDG uptake may require statistical adjustment for a non-inflammatory marker reflecting the extent of atherosclerosis, e.g. calcification. Adjustments is probably needed if (1) vascular wall (18)F-FDG uptake correlates sufficiently strongly with arterial calcification and (2) adjustment for extent of calcification affects determinants of vascular (18)F-FDG uptake. This study addresses these questions. (18)F-FDG PET/low-dose-CT scans of 99 patients were used. Cardiovascular risk factors were assessed and PET/CT scans were analysed for standardized (18)F-FDG uptake values and calcification. ANOVA was used to establish the association between vascular (18)F-FDG uptake and calcification. Multiple linear regression (with and without calcification as independent variable) was used to show whether determinants of vascular (18)F-FDG uptake were affected by the degree of calcification. (18)F-FDG uptake was related to increased calcification in the aortic arch,

descending and abdominal aorta. However, (18)F-FDG uptake showed considerable overlap between categories of calcification. Age and body mass index were main determinants of vascular (18)F-FDG uptake. In multiple regression analyses, most standardized beta coefficients of these determinants were not affected by adjustment for the degree of calcification. Although vascular (18)F-FDG uptake is related to total atherosclerotic burden, as reflected by vascular calcification, the association is weak and unlikely to affect the identification of determinants of atherosclerotic inflammation implicating no need for adjustment in future studies.

[11] *Cao Q, Du H, Fu X et al.* **Artemisinin attenuated atherosclerosis in high-fat diet-fed ApoE-/- mice by promoting macrophage autophagy via AMPK/mTOR/ULK1 pathway**. Journal of cardiovascular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895870
ABSTRACT
Artemisinin is an endoperoxide sesquiterpene lactone from Artemisia annua L with multiple beneficial effects, including anti-inflammation, anti-oxidant and vascular protection. Recent studies have found that inflammation along with autophagy deficiency in macrophages are the possible reasons for foam cell accumulation in the intima, which leads to atherosclerotic plaque formation. The primary aim of this study was to explore the inhibiting effect of artemisinin on atherosclerosis in high-fat diet (HFD)-fed ApoE mice and investigate the probable mechanism. Artemisinin (50, 100 mg/kg, intragastric administration) treatment effectively inhibited foamy macrophage transformation and decreased atherosclerotic plaque formation in atherosclerotic mice. Moreover, artemisinin promoted AMP activated protein kinase (AMPK) activation, inhibited mammalian target of rapamycin (mTOR) and uncoordinated-51-like kinases 1 (ULK1) phosphorylation, increased LC-3II accumulation and P62 degradation, and thereby enhancing macrophage autophagy. Besides, the inhibiting effect of artemisinin on mTOR and ULK1 phosphorylation could be abrogated by AMPK knockdown, suggesting AMPK was the essential target of artemisinin on promoting macrophage autophagy. Our study indicated that artemisinin alleviated atherosclerotic lesions by accelerating macrophage autophagy via AMPK/mTOR/ULK1 pathway.

[12] *Yang XJ, Liu F, Feng N et al.* **Berberine Attenuates Cholesterol Accumulation in Macrophage Foam Cells by Suppressing AP-1 Activity and Activation of the Nrf2/HO-1 Pathway**. Journal of cardiovascular pharmacology 2020; 75:45-53.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895879
ABSTRACT
Atherosclerosis is a chronic inflammation condition resulting from the interaction between lipoproteins, monocyte-derived macrophages, T lymphocytes, and other cellular elements in the arterial wall. Macrophage-derived foam cells play a key role in both early and advanced stage of atherosclerosis. Previous studies have shown that berberine could inhibit foam cell formation and prevent experimental atherosclerosis. However, its underlying molecular mechanisms have not been fully clarified. In this study, we explored the cholesterol-lowering effects of berberine in macrophage-derived foam cells and investigated its possible mechanisms in prevention and treatment of atherosclerosis. Here, we demonstrated that berberine could inhibit atherosclerosis in apolipoprotein E-deficient mice and induce cholesterol reduction as well as decrease the content of macrophages. Berberine can regulate oxLDL uptake and cholesterol efflux, thus suppresses foam cell formation.

Mechanisms study showed that berberine can suppress scavenger receptor expression via inhibiting the activity of AP-1 and upregulate ATP-binding cassette transporter via activating Nrf2/HO-1 signaling in human macrophage. In summary, berberine significantly inhibits atherosclerotic disease development by regulating lipid homeostasis and suppressing macrophage foam cell formation.

[13] *Kim BS, Lim JS, Jeong JU et al.* **Regression of asymptomatic intracranial arterial stenosis by aggressive medical management with a lipid-lowering agent**. Journal of cerebrovascular and endovascular neurosurgery 2019; 21:144-151.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31886149
ABSTRACT
Objective: The incidence rate of stroke as a result of intracranial arterial stenosis (ICAS) is higher in Asian countries than in the West. We aimed to analyze the regression, lack of change, or progression of asymptomatic ICAS after the administration of rosuvastatin and associated factors. Methods: The patients who had undergone computed tomography angiography (CTA) at our hospital and had been diagnosed with ICAS with no ischemic event in the stenosed vascular territory were included in the study. They were administered 20mg of rosuvastatin per day. After a follow-up period of at least 6 months after treatment, the patients were examined using CTA again and the clinical information and imaging results were analyzed. Results: In total, 48 patients were diagnosed with asymptomatic ICAS. During the final follow-up examination, it was found that the stenotic lesion regressed in 30 patients, whereas it remained unchanged or progressed without any adverse effects in 18 patients. In univariate analysis, the regressed group showed significantly higher differences in the levels of total cholesterol and low-density lipoprotein (LDL) between their initial and final values (both, p=0.031 for both). In the multivariate analysis, a significantly higher difference in the levels of LDL between its initial and final measurement was seen in the regressed group (p=0.035, odds ratio(OR) 3.9). Conclusions: Rosuvastatin was found to have better lipid-lowering effects for total cholesterol and particularly LDL in patients whose ICAS had regressed. We concluded that rosuvastatin administration can be recommended for the treatment of patients with asymptomatic ICAS.

[14] *Woodward A, Broom D, Harrop D et al.* **The effects of physical exercise on cardiometabolic outcomes in women with polycystic ovary syndrome not taking the oral contraceptive pill: a systematic review and meta-analysis**. Journal of diabetes and metabolic disorders 2019; 18:597-612.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31890686
ABSTRACT
Purpose: Women with polycystic ovary syndrome (PCOS) exhibit many metabolic abnormalities that are associated with an increased cardiovascular disease risk. Exercise may promote improvements in lipid profile and insulin sensitivity in women with PCOS. There is however, a knowledge gap on the optimal dose of exercise, regarding duration, intensity, type, and frequency of exercise. The aim of this systematic review and meta-analysis was to define effective types of exercise to improve cardiometabolic profile in PCOS. Methods: We included randomised controlled trials (RCT), quasi-RCT, and controlled clinical trials focusing on reproductive-aged women diagnosed with PCOS. Eligible interventions included those with at least two weeks of supervised exercise sessions. Primary outcomes were blood lipids, blood glucose, blood pressure, measures of abdominal adiposity, and inflammation markers. Secondary outcomes were total and free testosterone, sex hormone binding globulin, and measures of insulin resistance. Nine electronic databases were searched from inception

to present for English language publications. The Cochrane Risk Assessment tool was used to assess bias in the included studies. Outcomes were quantitatively synthesised and a meta- analysis was performed. Pooled effect estimates and 95% confidence intervals were presented. Results: This systematic review identified three trials, including 231 participants with PCOS, that examined the effect of structured, supervised exercise on cardiometabolic outcomes. Analysis of pooled data indicated statistical favourable effects of exercise on total cholesterol, fasting glucose, waist circumference and waist-to-hip ratio, systolic blood pressure, C-reactive protein, total testosterone, and sex hormone binding globulin using post-intervention scores. Conclusions: Moderate aerobic exercise interventions >/=3 months in duration, with a frequency of 3/week for at least 30-min, may have favourable effects on various cardiometabolic risk factors in women with PCOS. However, results should be interpreted with caution. Many of the outcomes were based on studies with serious methodological limitations, and only one "gold-standard" RCT was identified.PROSPERO ID: CRD42018086117.

[15] *Takagi H, Tanimoto K, Shimazaki A et al.* **A Novel Acetyl-CoA Carboxylase 2 Selective Inhibitor Improves Whole-Body Insulin Resistance and Hyperglycemia in Diabetic Mice through Target-Dependent Pathways**. The Journal of pharmacology and experimental therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31900320

ABSTRACT

Excess intramyocellular lipid (IMCL) deposition in skeletal muscle is closely associated with insulin resistance. Pharmacological inhibition of acetyl-CoA carboxylase (ACC) 2 offers a promising approach to treat insulin resistance through stimulation of mitochondrial fatty acid oxidation (FAO) and reduction of IMCL deposition. Previously reported experimental ACC2 inhibitors exhibited plasma glucose-lowering effect in diabetic rodents. However, their antidiabetic action may be potentially biased by off-target effects on triglyceride metabolism or by neurological side effects. In this study, we investigated a safety profile, target dependency of its action and antidiabetic efficacy of compound 2e, a novel olefin derivative potent ACC2 selective inhibitor. Four-day administration of supra-pharmacological dose of compound 2e did not exhibit any obvious side effects in Sprague-Dawley rats. In db/db mice, single administration of compound 2e led to significantly elevated FAO and reduced IMCL deposition in skeletal muscle. In ACC2 knockout mice, treatment with pharmacological doses of compound 2e did not reduce plasma triglyceride levels, while A-908292, a previously reported ACC2 inhibitor, caused a significant triglyceride reduction, showing that compound 2e was devoid of off-target triglyceride-lowering activity. Chronic treatment of db/db mice with compound 2e improved hyperglycemia but did not decrease plasma triglyceride levels. Additionally, compound 2e showed significant improvements of whole-body insulin resistance in the clamp study and insulin tolerance test. Collectively, compound 2e demonstrated a good safety profile and significant antidiabetic effects through inhibition of ACC2-dependent pathways. These findings provide further evidence that selective inhibition of ACC2 is an attractive strategy against insulin resistance and type 2 diabetes. SIGNIFICANCE STATEMENT: This study shows that pharmacological inhibition of ACC2 leads to significant improvements in whole-body glucose homeostasis, independently of off-target metabolic pathways and toxicity which were observed in previously reported ACC2 inhibitors. These findings support the concept that ACC2 selective inhibitors will be a novel remedy for treatment of type 2 diabetes.

[16] *Szczuko M, Hawrylkowicz V, Kikut J, Drozd A*. **The implications of vitamin content in the plasma in reference to the parameters of carbohydrate metabolism and hormone and lipid profiles in PCOS**. J Steroid Biochem Mol Biol 2019; 198:105570.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31883924
ABSTRACT
So far, there have been no analyses of correlations between the level of water-soluble vitamins in women with polycystic ovary syndrome (PCOS) and hormone and lipid profiles as well as carbohydrate metabolism. The unpopular concept that PCOS may also be conditioned by a chronic infection leads to a suspicion that water-soluble vitamins may be involved in the struggle against PCOS. This is why the aim of this research was to determine whether there are any indications that could confirm this hypothesis. The study included 64 women of Caucasian race: 50 patients aged 29.52+/-7.01 years with PCOS, diagnosed according to the Rotterdam criteria. The control group consisted of 14 women aged 30.23+/-6.3 years with correct BMI. HPLC Infinity1260 Binary LC (Agilent Technologies, Waldbronn, Germany) was used to analyze nine vitamins. The vitamins were separated using the gradient method, a buffer of 25mM HK2PO4 with pH equal to 7.0, and 100 % methanol buffer. The acquired results were compared using Statistica 12.0 (Statsoft, Tulsa, Oklahoma, USA). Non-parametric tests were used: Mann-Whitney tests for comparisons between groups (PCOS and control group, CG), in which $p<0.05$ was considered statistically significant. Subsequently, we performed a correlation matrix of the biochemical parameters of blood with vitamins at $p</=0.05$. Higher concentrations of ascorbic acid were observed in PCOS. The content of the remaining vitamins was higher in the control group, and the statistical differences were significant in reference to thiamine, riboflavin, pyridoxine and folic acid in comparison to the control group. A significant positive correlation was observed between vitamin C and testosterone/insulin, another between riboflavin and androstenedione/testosterone, next between biotin and thyrotropic hormone (TSH), between pantothenic acid and dehydroepiandrosteron (DHEA-SO4), and finally between pyridoxine and androstenedione. A negative correlation was observed in the case of niacin with sex hormone binding protein (SHBG) and high density lipoprotein (HDL). Water-soluble vitamins play an important role in the therapy of women with PCOS through the reduction of antioxidative stress and low-intensity inflammation caused by various factors, including chronic infection.

[17] *Bach RG, Cannon CP, Blazing MA*. **Interpreting the Benefit of Simvastatin-Ezetimibe in Patients 75 Years or Older-Reply**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895449
ABSTRACT

[18] *Li D, McCaw ZR, Wei LJ*. **Interpreting the Benefit of Simvastatin-Ezetimibe in Patients 75 Years or Older**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895431
ABSTRACT

[19] *Weingartner O, Sijbrands EJG, Lutjohann D*. **Interpreting the Benefit of Simvastatin-Ezetimibe in Patients 75 Years or Older**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895451
ABSTRACT

[20] *Dolgalev IV, Brazovskaya NG, Ivanova AY et al.* **[Impact of hypertension, overweight, hypertriglyceridemia and their combination for mortality rate according to the results of a 27-year cohort prospective study]**. Kardiologiia 2019; 59:44-52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31884940

ABSTRACT
AIM: To study influence of hypertension, overweight, hypertriglyceridemia and their combinations for all-cause and cardiovascular mortality risk formation. Methods. The prevalence of hypertension, overweight and hypertriglyceridemia was studied (1988-1991) by 27-year prospective cohort study of unorganized population of Tomsk (1546 persons - 916 female and 630 male). The predictive value of these risk factors for all-cause and cardiovascular mortality risk formation were researched in 2015. Hypertension was diagnosed in persons with blood pressure greater or equal to 140/90 mm Hg, overweight was diagnosed in people with body mass index 25 kg/m2, hypertriglyceridemia was diagnosed in individuals having high blood level of triglycerides (greater or equal to 1.7). Results. Influence of hypertension for all-cause (relative risk (RR) 2.2) and cardiovascular mortality (RR 3.38) risk formation was detected. A hypertension related elevation of mortality risk was observed both among women and men and in all age groups with the exception of men 40-59 years (the results for cardiovascular mortality in these persons was statistically insignificant). We established that hypertension had the independent significant contribution for mortality risk formation. It is shown that RR of all-cause mortality 1.25 times (cardiovascular mortality 1.8 times) more in overweight persons. Increase of relative mortality risk was detected in overweight women, especially in women 20-39 years old. Hypertriglyceridemia increases relative risk of all-cause mortality 1.46 times, relative risk of cardiovascular mortality 2.15 times, especially in individuals 40-59 years old. It was revealed that hypertriglyceridemia is significant risk factor for all-cause mortality formation only in women. Combination of hypertension and overweight increases the risk of all-cause mortality 2.23 times and the risk of cardiovascular mortality 4.0 times, combination of hypertension and hypertriglyceridemia - 2.83 and 5.06 times, combination of overweight and hypertriglyceridemia - 1.73 and 2.99 times, respectively. We detected the additional risk of hypertriglyceridemia in individuals with overweight for all-cause (RR 1.53) and cardiovascular (RR 2.18) mortality risk formation compared with overweight persons with normal level of triglycerides and also the additional risk of hypertriglyceridemia (RR 1.51 and 2.04, respectively) in individuals with hypertension compared with normotensive persons (p<0,05). The additional risk of overweight in individuals with hypertension for all-cause mortality was found only in women (RR 3.23). Conclusion. The independent significant impact of hypertension for all-cause and cardiovascular mortality risk formation was revealed by the results of 27-year prospective study. Combination of hypertension and hypertriglyceridemia increases the risk of all-cause mortality 2.8 times and the risk of cardiovascular mortality 5.1 times, combination of hypertension and overweight - 2.2 and 4 times, combination of overweight and hypertriglyceridemia - 1.7 and 3 times, respectively. We detected the additional risk of hypertriglyceridemia for all-cause mortality in overweight people (RR 1.5) and in individuals with hypertension (RR 1.5). Also, the additional risk of hypertriglyceridemia for cardiovascular mortality risk formation in overweight people (RR 2.2) and in persons with hypertension (RR 2.0) was found.

[21] *Pogosova NV, Yufereva YM, Kachanova NP et al.* **[An exploration of potential approaches to improve the diagnosis of subclinical atherosclerosis in patients with high cardiovascular risk]**. Kardiologiia 2019; 59:53-62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31884941
ABSTRACT
PURPOSE: The search for optimal approaches to the diagnosis of subclinical atherosclerosis using a wide range of traditional and psychosocial risk factors (RFs), as well as clinical and instrumental diagnostic methods in patients (pts) with high or very high cardiovascular (CV) risk. METHODS: This cross-sectional study enrolled52 pts, aged 40 to 65 years with high or very high CV risk (5-9 and >/=10% by the Systematic Coronary Risk Estimation Scale [SCORE], respectively). All participants underwent cardiac computed tomography (CT)angiography and calcium scoring. Traditional RFs (family history of premature CVD, smoking, overweight/obesity and abdominal obesity, hypertension, type 2 diabetes mellitus, lipids parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) and lipids-related markers (apolipoprotein A1, apolipoprotein B, ApoB/ApoA1 ratio), biomarkers of inflammation (high-sensitivity C-reactive protein [hs CRP], fibrinogen), indicator carbohydrate metabolism (glucose), ankle-brachial index, stress-test, carotid plaques according to ultrasound, arterial stiffness were evaluated in all pts. Psychological RFs were evaluated using Hospital Anxiety and Depression Scale and DS-14 for type D personality. RESULTS: All pts were divided into 2 groups according to the CT angiography results: pts in the main group (n=21) had any non-obstructive lesions or calcium score >0, pts in the control group (n=31) had intact coronary arteries. The groups did not differ in age or gender. It was found that patients with subclinical atherosclerosis significantly more often have a very high (>/=10%) CV risk (42.9% vs.16.3%, p<0.05), a long (>/=5 years) history of arterial hypertension (47.6% vs. 12.9% , p<0.01) and longer duration of antihypertensive therapy (61.9% vs. 29.0%, p<0.05), higher heart rate in rest (87. +/- 14 vs. 77 +/- 10 beats/min, p<0.01), increased arterial stiffness according to aortic pulse wave velocity (85.7% vs. 61.3%, p<0.05) and high level of hs-CRP (100% vs. 90.3%, p<0.05). CONCLUSION: Using in routine clinical practice of additional anamnestic (hypertension lasting >/= 5 years and the intake of any antihypertensive drugs) and clinical-instrumental parameters (high heart rate in rest, hs CRP and arterial stiffness in pts with high and very high CV risk increases effectiveness of early detection of subclinical atherosclerosis.

[22] *Massy ZA, Ferrieres J, Bruckert E et al.* **Achievement of Low-Density Lipoprotein Cholesterol Targets in CKD**. Kidney international reports 2019; 4:1546-1554.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31890996
ABSTRACT
Introduction: We describe the characteristics of patients with moderate/advanced chronic kidney disease (CKD) according to receipt of lipid-lowering therapy (LLT), and whether they achieved low-density lipoprotein cholesterol (LDL-C) targets for high- and very high-risk patients. Methods: CKD-REIN (NCT03381950), a prospective cohort study conducted in 40 nephrology clinics in France, enrolled 3033 patients with moderate (stage G3) or advanced (stage G4/G5) CKD (2013-2016) who had not been on chronic dialysis or undergone kidney transplantation. Data were collected from patients' interviews and medical records. Patients were followed up at 1 year. Results: Among 2542 patients (mean [SD] age 67 [13] years, 34% women) with LDL-C measurements at baseline (mean [SD] LDL-C 2.7 [1.1] mmol/l; cholesterol 4.8 [1.3] mmol/l), 63% were on LLT; 24% were at high (CKD stage G3, no

cardiovascular disease [CVD] or diabetes) and 74% at very high (CKD stage G3 with diabetes or CVD, or CKD stage G4/5) cardiovascular risk. Among high-risk patients, 45% of those on statin and/or ezetimibe achieved the LDL-C treatment target (<2.6 mmol/l). Among very high-risk patients, the percentage at goal (<1.8 mmol/l) was 38% for CKD stage G3 and 29% for stage G4/5. There was a trend toward higher achievement of LDL-C targets with increasing LLT intensity (adjusted odds ratios for moderate vs. low intensity 1.20; 95% confidence interval 0.92-1.56; high vs. low intensity 1.46; 1.02-2.09; P trend = 0.036). Conclusion: Many patients with CKD stage G3-G5 who are eligible for LLT are not treated, and those on LLT rarely achieve LDL-C targets.

[23] *Toyoda Y, Takada T, Yamanashi Y, Suzuki H*. **Pathophysiological importance of bile cholesterol reabsorption: hepatic NPC1L1-exacerbated steatosis and decreasing VLDL-TG secretion in mice fed a high-fat diet**. Lipids in health and disease 2019; 18:234.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31883528
ABSTRACT
BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide, although its pathogenesis remains to be elucidated. A recent study revealed that hepatic Niemann-Pick C1-Like 1 (NPC1L1), a cholesterol re-absorber from bile to the liver expressed on the bile canalicular membrane, is an exacerbation factor of NAFLD. Indeed, transgenic mice with hepatic expression of human NPC1L1 under a liver-specific promoter (L1-Tg mice) developed steatosis with a high-fat diet (HFD) containing cholesterol within a few weeks. However, the mechanism underlying diet-induced hepatic NPC1L1-mediated lipid accumulation is poorly defined. METHODS: To achieve a deeper understanding of steatosis development in L1-Tg mice, the biochemical features of hepatic NPC1L1-mediated steatosis were investigated. Hemizygous L1-Tg mice and wild-type littermate controls fed a HFD or control-fat diet were used. At the indicated time points, the livers were evaluated for cholesterol and triglyceride (TG) contents as well as mRNA levels of hepatic genes involved in the maintenance of lipid homeostasis. The hepatic ability to secrete very low-density lipoprotein (VLDL)-TG was also investigated. RESULTS: Unlike the livers of wild-type mice that have little expression of hepatic Npc1l1, the livers of L1-Tg mice displayed time-dependent changes that indicated steatosis formation. In steatosis, there were three different stages of development: mild accumulation of hepatic cholesterol and TG (early stage), acceleration of hepatic TG accumulation (middle stage), and further accumulation of hepatic cholesterol (late stage). In the early stage, between WT and L1-Tg mice fed a HFD for 2 weeks, there were no significant differences in the hepatic expression of Pparalpha, Acox1, Fat/Cd36, Srebf1, and Srebf2; however, the hepatic ability to secrete VLDL-TG decreased in L1-Tg mice ($P < 0.05$). Furthermore, this decrease was completely prevented by administration of ezetimibe, an NPC1L1-selective inhibitor. CONCLUSION: Hepatic NPC1L1 exacerbates diet-induced steatosis, which was accompanied by decreased hepatic ability of VLDL-TG secretion. The obtained results provide a deeper understanding of L1-Tg mice as a promising NAFLD animal model that is able to re-absorb biliary-secreted cholesterol similar to humans. Furthermore, this work supports further studies of the pathophysiological impact of re-absorbed biliary cholesterol on the regulation of hepatic lipid homeostasis.

[24] *Yu M, Liang C, Kong Q et al.* **Efficacy of combination therapy with ezetimibe and statins versus a double dose of statin monotherapy in participants with hypercholesterolemia: a meta-analysis of literature**. Lipids in health and disease 2020; 19:1.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31900179

ABSTRACT

BACKGROUND: The aim of this study was to compare and summarize the lipid-altering effects of combination therapy with ezetimibe and statins (E/S) and a double dose of statin (D/S) monotherapy on patients with hypercholesterolemia. METHODS: We conducted search on 2 medical databases, PubMed and EMBASE to identify all relevant studies. A meta-analysis was performed to clarify the efficacy in the two groups. Only double-blind Randomized controlled study (RCTs) of efficacy evaluation in the two groups with ezetimibe and statins and a double dose of statin in participants with hypercholesterolemia that examined low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and high-density lipoprotein (HDL) were included. Two reviewers extracted data from all primary studies independently. The primary data were the level of LDL-C, TC and HDL-C concentrations at the end point and are expressed as mean and standard deviation (SD). RESULTS: A total of 11 double-blind, active or placebo-controlled studies with 1926 hypercholesterolemia adults randomized to ezetimibe 10 mg added to ongoing statins (N = 994) or statin titration (doubling) (N = 932) were pooled for the global meta-analysis. The effect size between treatment groups within individual studies was assessed by weighted mean difference (MD) using a random- or fixed-effect model. The result showed that the participants in E/S group get obvious lower LDL-C [MD = -13.14 mg/dL, 95%CI (-16.83, -9.44), p = 0.00001] and TC concentration [MD = -23.79 mg/dL, 95%CI (-38.65, -8.93), p = 0.002] from baseline to follow-up, comparing to the D/S group. Besides, no significant between-group differences were observed for concentrations of HDL-C [MD = 0.46 mg/dL, 95%CI (- 1.14, 2.06), p = 0.57]. According to subgroup analysis, the combination of ezetimibe and atorvastatin (10 mg) [MD = -16.98 mg/dL, p < 0 .0001] or simvastatin (20 mg) [MD = -17.35 mg/dL, p < 0 .0001] showed stronger ability of reducing LDL-C than combination of ezetimibe and rosuvastatin (10 mg) [MD = -9.29 mg/dL, p = 0.05]. The efficacy of short-term (endpoint time between 6 to 16 week) and long-term (52 week) treatment in the LDL-C between two groups did not show significant differences. Besides, only participants from Asia treated with combination therapy were associated with a significant lower LDL-C concentration [MD = -14.7 mg/dL, p < 0 .0001]. CONCLUSIONS: The addition of ezetimibe to statin appears to be more effective on reducing LDL-C and TC concentrations than doubling the statin dose. Moreover, the ability to reduce cholesterol levels of combinations therapy with ezetimibe and different statins or to participants from different geographic location may vary, based on this meta-analysis, while more samples are needed to verify.

[25] *Novotny R, Chlupac J, Kristek J et al.* **Uterus transplant graft's arterial atherosclerotic remodeling veracity**. Medicine (Baltimore) 2020; 99:e18612.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31895813

ABSTRACT

BACKGROUND: Uterus transplantation is a complex, multi-step experimental procedure used for the treatment of uterus absence or uterus anomaly that prevents embryo implantation or pregnancy completion. METHOD: To date, only 51 uterus transplants worldwide had been performed. When simplified, it is vascularized composite allograft transplantation. While it is still an experimental procedure with encouraging results for the future, there are still many issues that have to be clarified. The most serious complications of uterus transplantation are graft rejection or grafts vascular failure. RESULTS: So far, no reference to the atherosclerotic arterial infiltration of the uterus arteries was suggested and studied as one of the main causes of graft's failure. CONCLUSION: In this review we

summarized current knowledge and possible role of uterus arterial damage, including atherosclerotic changes on the graft's survival.

[26] *Cao B, Bi G, Wang Y*. **Pharmacology of atorvastatin on myocardial ischemia-reperfusion in rats and drug effect analysis**. Pak J Pharm Sci 2019; 32:2443-2447.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31894032
ABSTRACT
Statins are the most important drugs in the treatment of atherosclerosis. In this paper, the authors analyze the protective effect of atorvastatin on myocardial ischemia-reperfusion in rats and its drug effect. The results showed that the ratio of myocardial infarction area to total ischemia area in atorvastatin group was smaller than that in ischemia reperfusion group (P<0.01). Compared with the ischemia-reperfusion group, the MDA (16.23+/-4.05), TNF alpha (41.84 +/-5.61) and MPO (17.54+/-2.81) were decreased in atorvastatin group. The results showed that atorvastatin could improve many hemodynamic indexes including SBP, DBP, LVSP, LVEDP and so on. To sum up, atorvastatin can affect infarct size, improve hemodynamics and left ventricular function after myocardial ischemia-reperfusion injury.

[27] **Obesity and type 2 diabetes are associated with elevated PCSK9 levels in young women**. Pediatric diabetes 2020; 21:143.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31898388
ABSTRACT

[28] *Ahmadi Y, Mahmoudi N, Yousefi B, Karimian A*. **The effects of statins with a high hepatoselectivity rank on the extra-hepatic tissues; New functions for statins**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019; 152:104621.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31891788
ABSTRACT
Statins, as the most common treatment for hyperlipidemia, exert effects beyond their lipid-lowering role which are known as pleiotropic effects. These effects are mainly due to the inhibition of isoprenoids synthesis and consequently blocking prenylation of proteins involved in the cellular signaling pathways regulating cell development, growth, and apoptosis. Statins target cholesterol synthesis in the liver as the major source of cholesterol in the body and so reduce whole-body cholesterol. The reduced level of cholesterol forces other organs to an adaptive homeostatic reaction to increase their cholesterol synthesis capacity, however, this only occurs when statins have unremarkable access to the extra-hepatic tissues. In order to reduce the adverse effects of statin on the skeletal muscle, most recent efforts have been towards formulating new statins with the highest level of hepatoselectivity rank and the least level of access to the extra-hepatic tissues; however, the inaccessibility of statins for the extra-hepatic tissues may induce several biological reactions. In this review, we aim to evaluate the effects of statins on the extra-hepatic tissues when statins have unremarkable access to these tissues.

[29] *Wen YF, Culhane-Pera KA, Thyagarajan B et al.* **Potential Clinical Relevance of Differences in Allele Frequencies Found within Very Important Pharmacogenes between Hmong and East Asian Populations**. Pharmacotherapy 2019.

Literature update week 01 (2020)

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31884695

ABSTRACT

OBJECTIVES: Implementing pharmacogenetics for very important pharmacogenes (VIPs) holds the promise of improving clinical outcomes through optimal medication selection and dosing. However, significant differences in the frequency of actionable variants in VIPs may exist within subpopulations of a given ancestral group. Furthermore, these differences can potentially impact drug selection and dosing. The purpose of this study was to ascertain allele frequencies for VIPs and to predict medication requirements using Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines in Hmong and compare with published data for East Asians. METHODS: Using a community-based participatory action research approach, DNA collected from 194 Hmong adults living in the United States was analyzed for 22 genetic variants within eight VIPs (CYP2C9, CYP2C19, CYP4F2, DPYD, G6PD, SLCO1B1, TPMT, VKORC1). Allele frequencies for VIPs and predicted medication requirements using CPIC guidelines were compared between Hmong participants and East Asians. RESULTS: Significant differences in allele frequencies between the Hmong and East Asians were found for 23% (5/22) of the CPIC-actionable variants tested. Allele frequencies for VIPs in Hmong versus East Asians were 16.6% versus 3.4% in CYP2C9*3A, 42.2% versus 29.0% for CYP2C19*2, 0.3% versus 8.3% in CYP2C19*3, 6.5% versus 22.1% in CYP4F2*3, and 3.6% versus 0.1% in SLCO1B1*5, respectively. These differences significantly influenced predicted medication usage recommendations in warfarin, simvastatin, and phenytoin between Hmong and East Asians. CONCLUSIONS: Important differences in allele frequencies for key genetic variants influencing selection of medications and dosages were found between the Hmong and East Asians. The magnitude and nature of these differences can be expected to result in different medication recommendations for the Hmong relative to East Asians.

[30] *Ni T, Fu Y, Zhou W et al.* **Carotid plaques and neurological impairment in patients with acute cerebral infarction**. PloS one 2020; 15:e0226961.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31899784

ABSTRACT

OBJECTIVE: To determine whether the coexistence of carotid atherosclerosis plaque affects the neurological function of cerebral infarction. METHODS: A total of 1078 patients with acute cerebral infarction were enrolled, all patients were divided into carotid plaque group (n = 702) and non-carotid plaque group (n = 376). Meanwhile, all patients were divided into mild group (n = 624) and moderate to severe group (n = 454). The difference of the incidence of carotid plaque between the mild and moderate to severe group was analyzed. RESULTS: In the 1078 patients with cerebral infarction, the NIHSS score in the carotid plaque group was significantly higher than that in the non-carotid plaque group ($P<0.05$). The number of mild cases without carotid artery plaque group was larger than that of plaque group ($P<0.05$), and the number of moderate to severe cases in carotid plaque group was larger than that in non-plaque group ($P<0.05$). In patients with carotid atherosclerotic plaque, the risk of moderate to severe cerebral infarction was 2.11 times higher than that without carotid artery plaque. Lastly, patients with single plaques were 1.82 times more likely to develop moderate to severe cerebral infarction than those without carotid plaque, while patients with multiple carotid plaques were 2.41 times higher to get moderate or severe cerebral infarction than those without carotid plaque. CONCLUSIONS: The incidence of carotid atherosclerotic plaques may be related to neurological deficits in patients with acute cerebral infarction.

[31] *Michalikova D, Tyukos Kaprinay B, Liptak B et al.* **Natural substance rutin versus standard drug atorvastatin in a treatment of metabolic syndrome-like condition**. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 2019; 27:1196-1202.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31885479

ABSTRACT

Background: Metabolic syndrome is a cluster of metabolic risk factors. The clear causes of its development are not known yet and there is no comprehensive treatment of this disease. There is a trend to use natural substances in the treatment of various diseases, but their effects need to be well explored. We decided to test effect of rutin compared to the effect of the standard drug atorvastatin. Methods: As a model of metabolic syndrome we used males of hypertriacylglycerolemic rats in combination with high-fat-high-fructose diet. Rutin (100mg/kg) and atorvastatin (50mg/kg) were administered orally daily for 5weeks. Results: We determined biochemical parameters from blood: HDL-cholesterol, LDL-cholesterol, total cholesterol, triacylglycerols. Relaxation and contraction response of aorta was measured to determine vessel dysfunctions and possible predisposition to cardiovascular disease. The negative influence on cognitive functions could be associated with the development of metabolic cognitive syndrome. Therefore we aimed to monitor spatial memory by Morris water maze test. Both rutin and atorvastatin had a tendency to decrease levels of serum triacylglycerols, but only atorvastatin significantly reduced levels od LDL-cholesterol and increased HDL-cholesterol levels. Both compounds significantly reduced the phenylephrine-induced contractile response of the aorta and improved the relaxation response. Further, treated animals learned better compared to untreated rats in the Morris water maze. Conclusion: Based on our results we can assume that atorvastatin and rutin had positive effect on spatial memory and vessel reactivity. Atorvastatin optimized lipid profile of blood serum.

[32] *Kamel H, Pearce LA, Ntaios G et al.* **Atrial Cardiopathy and Nonstenosing Large Artery Plaque in Patients With Embolic Stroke of Undetermined Source**. Stroke 2020:Strokeaha119028154.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31893985

ABSTRACT

Background and Purpose- Atrial cardiopathy and atherosclerotic plaque are two potential mechanisms underlying embolic strokes of undetermined source (ESUS). The relationship between these two mechanisms among ESUS patients remains unclear. A better understanding of their association may inform targeted secondary prevention strategies. Methods- We examined the association between atrial cardiopathy and atherosclerotic plaque in the NAVIGATE ESUS trial (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial Versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source), which enrolled 7213 patients with recent ESUS during 2014 to 2017. For this analysis, we included patients with data on left atrial dimension, location of brain infarction, and cervical large artery plaque. The variables of primary interest were left atrial diameter and cervical plaque ipsilateral to brain infarction. Secondary markers of atrial cardiopathy were premature atrial contractions on Holter monitoring and newly diagnosed atrial fibrillation. For descriptive purposes, left atrial enlargement was defined as >/=4.7 cm. Multivariable logistic regression was used to examine the association between atrial cardiopathy markers and ipsilateral plaque after adjustment for age, sex, body mass index, hypertension, diabetes mellitus, current smoking, and hyperlipidemia. Results- Among 3983 eligible patients, 235 (5.9%) had left atrial enlargement, 939 (23.6%) had ipsilateral plaque, and 94 (2.4%) had both. Shared risk factors for left atrial enlargement and ipsilateral plaque

were male sex, white race, hypertension, tobacco use, and coronary artery disease. Despite shared risk factors, increasing left atrial dimension was not associated with ipsilateral plaque after adjustment for covariates (odds ratio per cm, 1.1 [95% CI, 1.0-1.2]; P=0.08). We found no consistent associations between secondary markers of atrial cardiopathy and ipsilateral plaque. Conclusions- In a large population of patients with ESUS, we did not observe a notable association between atrial cardiopathy and atherosclerotic plaque, and few patients had both conditions. These findings suggest that atrial cardiopathy and atherosclerotic plaque may be distinct, nonoverlapping risk factors for stroke among ESUS patients.

[33] *Hao JL, Xu LC, Huang TP et al.* **[Effects of apolipoprotein E on proliferation of mouse pulmonary arterial smooth muscle cells induced by hypoxia]**. Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chinese journal of applied physiology 2019; 35:414-417.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31894672
ABSTRACT
OBJECTIVE: To investigate the effects of apolipoprotein E (apoE) on the proliferation of pulmonary arterial smooth muscle cells (PASMCs) induced by hypoxia. METHODS: Primary culture of mouse PASMCs was prepared from male C57BL/6 mouse pulmonary artery by the method of tissue block anchorage. PASMCs were divided into four groups: normoxia group, normoxia with apoE administration group, hypoxia group and hypoxia with apoE administration group. The proliferation of PASMCs was observed by EdU incorporation. The protein levels of apoE, proliferating cell nuclear antigen (PCNA), protein kinase C (PKC) and phosphorylated protein kinase C (p-PKC) were analyzed by Western blot. RESULTS: The percentage of PASMCs proliferation of hypoxia group was significantly higher than that of normoxia group by 64.7% (P0.05), and the protein expression levels of PCNA and p-PKC of hypoxia group were up-regulated than those of normoxia group by 69.0% and 120.0%, while the protein expression of apoE was down-regulated by 51.0% (P0.05), respectively. The percentage of PASMCs proliferation of hypoxia with apoE administration group was significantly lower than that of hypoxia group by 19.6% (P0.05), and the protein expression levels of PCNA and p-PKC of hypoxia with apoE administration group were down-regulated than those of hypoxia group by 19.8% and 103.2% (P0.05), respectively. There was no significant difference among each group in the protein expression of PKC, nor do there any significant difference between normoxia group and hypoxia group in the protein expression of p-PKC (P0.05). CONCLUSION: ApoE can inhibit the proliferation of PASMCs induced by hypoxia, and the mechanism of its effect may be attributed to blocking PKC pathway.

[34] **[China cholesterol education program (CCEP) expert advice for the management of dyslipidaemias to reduce cardiovascular risk (2019)]**. Zhonghua nei ke za zhi 2020; 59:18-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31887831
ABSTRACT
The prevalence of dyslipidemia in Chinese adult is increasing dramatically, which poses a severe challenge to the prevention and treatment of atherosclerotic cardiovascular diseases. In recent years, a series of new research results have been published, providing a lot of new information for the management strategy of dyslipidemia. In order to apply these new research results to clinical practice for the further prevention and treatment of dyslipidemia more reasonably and effectively, the China Cholesterol Education Program (CCEP) Working Committee organized joint expert meeting and revised the "Expert Advice on Prevention and Treatment of Dyslipidemia in China Cholesterol Education

Program 2014", in which a new classification standard for cardiovascular risk stratification has been proposed, and the target value of lipid-lowering therapy has been updated.

[35] *Lyu XC, Cai GL, Xu QH et al.* **[Endothelial protective effect of simvastatin on coagulation system in septic rats]**. Zhonghua nei ke za zhi 2020; 59:52-57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31887837

ABSTRACT
Objective: To investigate the endothelial protective effects of simvastatin on the coagulation system in septic rats. Methods: A total of 54 SD male rats were divided into 3 groups. Six healthy rats were intraperitoneally injected with normal salineas control group. Twenty-four rats in septic group were intraperitoneally injected with normal saline followed by lipopolysaccharide 2.5 mg. Study group had 24 rats intraperitoneally injected with simvastatin followed by lipopolysaccharide. Plasma von Willebrand factor (vWF), thrombomodulin (TM), platelet activating factor (PAF) and antithrombin- (AT-) were tested at 1 h, 3 h, 6 h and 12 h after treatment. Scanning electron microscopy and transmission electron microscopy were used to observe the morphology and apoptosis of rat aorta endothelial cells. Results: Compared with healthy control group, vWF [(68.3+/-4.8) ng/ml, (59.2+/-5.1) ng/ml, (74.2+/-20.1) ng/ml, (53.5+/-4.0)ng/ml, respectively], TM [(1.4+/-0.3) ng/ml, (1.6+/-0.4) ng/ml, (2.8+/-0.9) ng/ml, (1.4+/-0.5) ng/ml, respectively], PAF [(29.1+/-6.5) pg/ml, (28.6+/-1.5) pg/ml, (28.7+/-2.7) pg/ml, (18.2+/-4.1) pg/ml, respectively] and AT- [(262.2+/-38.1)mug/ml, (233.0+/-70.4) mug/ml, (218.7+/-54.7) mug/ml, (162.2+/-37.2) mug/ml, respectively] were significantly increased in the sepsis group at 1 h, 3 h, 6 h and 12 h ($P<0.05$). Compared with the sepsis group, the plasma levels of PAF in simvastatin intervention group at 1 h [(15.6+/-2.5) pg/ml, 3 h(10.4+/-5.3) pg/ml, 6 h (9.3+/-1.4) pg/ml, 12 h(11.0+/-2.7) pg/ml] were significantly decreased, so were the TM level at 6 h (1.6+/-0.9) ng/ml, and the AT- levels at 1 h[(190.3+/-29.2) mug/ml],6 h [(104.4+/-33.6) mug/ml] and 12 h [(73.6+/-39.0) mug/ml, $P<0.05$]. Conclusion: In the condition of sepsis, toxins and over-activated inflammatory factors damage the vascular endothelium. A large amount of circulating vWF, TM, PAF, and AT- cause early hypercoagulability. Simvastatin significantly reduces plasma amount of these procoagulants, suggesting it smodification of coagulopathy and vascular protective effectsin a septic rat model.