[1] *Elkind-Hirsch KE, Seidemann E, Harris R*. **A randomized trial of dapagliflozin and metformin, alone and combined, in overweight women after gestational diabetes mellitus**. Am J Obstet Gynecol MFM 2020; 2:100139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33345876

ABSTRACT

BACKGROUND: Women with a history of gestational diabetes mellitus are at a substantially increased risk of gestational diabetes mellitus recurrence and type 2 diabetes. Weight gain, particularly increased central adiposity after delivery, is strongly associated with deterioration of pancreatic beta cell compensation for insulin resistance. Weight management after gestational diabetes mellitus could have a significant benefit in these women who are at a high risk of developing type 2 diabetes. OBJECTIVE: This study aimed to evaluate the treatment efficacy of dapagliflozin and metformin, alone and in combination, on body weight and anthropometric, cardiovascular, and metabolic parameters in overweight women with a recent history of gestational diabetes mellitus. STUDY DESIGN: This was a prospective, single-blind, randomized, outpatient clinical trial with 3 parallel treatment groups. Overweight or obese (body mass index>25) females (n=66; ≥18-45 years) with gestational diabetes mellitus in pregnancy in the past 12 months were randomized in a single-blind manner to dapagliflozin, metformin, or dapagliflozin-metformin for 24 weeks. Body weight, height, body mass index, waist circumference, waist-to-height ratio, and blood pressure were determined at baseline and trial completion. Oral glucose tolerance tests were performed at baseline and 24 weeks to assess glycemia and mean blood glucose and calculate insulin sensitivity and secretion measures. Plasma lipid fractions, thyroid-stimulating hormone, and liver enzymes were also assessed in the fasting sample at the beginning and completion of the study trial. RESULTS: The study was completed by 49 participants (74%). Significant reduction of weight, waist circumference, and waist-to-height ratio and improved glycemia and insulin sensitivity index derived from oral glucose tolerance test were found with dapagliflozin-metformin vs metformin monotherapy. Both dapagliflozin and dapagliflozin-metformin therapy were superior to metformin in increasing high-density lipoprotein levels, reducing triglyceride concentrations, lowering the triglyceride-to-high-density lipoprotein cholesterol ratio, and improving glucose excursion after an oral glucose tolerance test. The early insulin response to a glucose challenge significantly improved with only dapagliflozin-metformin compared with single-drug treatments. CONCLUSION: This is the first report comparing the efficacy of a sodium-glucose cotransporter 2 inhibitor alone and in combination with metformin in this patient population. We found that combination dapagliflozin-metformin treatment over a 24-week period had a greater positive effect on body weight, waist circumference, and glycemic, cardiovascular, and metabolic parameters than metformin monotherapy in overweight or obese at-risk women with a recent history of gestational diabetes mellitus.

[2] *Chung S, Ko YG, Kim JS et al.* **Effect of FIXed-dose combination of ARb and statin on adherence and risk factor control: The randomized FIXAR study**. Cardiology journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33346375

ABSTRACT

BACKGROUND: The efficacy of fixed-dose combinations (FDCs) in improving adherence and risk factor control for cardiovascular disease has not been reported consistently. Here, we compared adherence and efficacy between an olmesartan/rosuvastatin FDC and the usual regimen. METHODS: In this 6-month, open-label, randomized, active-control study, we screened 154 patients;

of these, 150 were randomly assigned to receive either olmesartan/rosuvastatin FDC or the usual regimen with separate angiotensin receptor blockers and statins. In total, 135 patients completed the study (median age: 68 years; male: 68.9%). The primary outcome was patients' adherence; the secondary outcomes were changes in blood pressure (BP) and lipid parameters. RESULTS: During follow-up, adherence in both groups was high and similar between the groups (98.9% and 98.3% in the FDC and usual regimen groups, respectively, p = 0.328). Changes in systolic (-8 and -5 mmHg, respectively, p = 0.084) and diastolic BP (-5 and -2 mmHg, p = 0.092) did not differ significantly, although they were numerically greater in the FDC group. Changes in low-density lipoprotein cholesterol (LDL-C) were greater in the FDC group (-13 and -4 mg/dL, respectively, p = 0.019), whereas changes in other lipid parameters were similar between the groups. The test drugs were well tolerated, showing no difference in safety between the groups. CONCLUSIONS: Patients' adherence was excellent and similar in the groups, whereas the reduction in the LDL-C level was greater in the FDC group. We provide comprehensive information on the adherence and efficacy of an FDC compared to the usual regimen in Korean patients with high cardiovascular risk.

[3] *Alhabeeb H, Sohouli MH, Lari A et al.* **Impact of orange juice consumption on cardiovascular disease risk factors: a systematic review and meta-analysis of randomized-controlled trials**. Critical reviews in food science and nutrition 2020:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33350317
ABSTRACT
Cardiovascular disease (CVD) is the greatest cause of premature death and disability globally. Numerous therapeutic strategies have been developed to improve and prevent the adverse cardiovascular events, including nutritional approaches. This systematic review and meta-analysis summarized the evidence on orange juice consumption on CVD risk factors. Four databases were searched up to September 2020. Ten randomized controlled trials were included in the final analysis. Pooled results demonstrated a significant effect of orange juice on glucose (WMD: -2.92 mg/dl, 95% CI: -5.327, -0.530, p = 0.017), insulin (WMD: -1.229 μU/ml, 95% CI: -2.083, -0.374, p = 0.005), HOMA-IR (WMD: -0.464, 95% CI: -0.747, -0.181, p = 0.001), total cholesterol (WMD: -9.84 mg/dl, 95% CI: -15.43, -4.24, p = 0.001), LDL-C (WMD: -9.14 mg/dl, 95% CI: -15.79, -2.49, p = 0.007), and CRP (WMD: -0.467 mg/l, 95% CI: -0.815, -0.120, p = 0.008) compared to control group. However, the effect of orange juice on body composition factors and other CVD risk factors was not significant compared to control group. These lowering effects of glucose, HOMA-IR, total cholesterol, and LDL-C were robust in subgroups with orange juice consumption ≥500 ml/day. This meta-analysis suggests that orange juice may be beneficial in improving several CVD risk factors.

[4] *Whittemore R, Siverly L, Wischik DL, Whitehouse CR*. **An Umbrella Review of Text Message Programs for Adults With Type 2 Diabetes**. Diabetes Educ 2020; 46:514-526.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33353511
ABSTRACT
PURPOSE: The purpose of this umbrella review was to synthesize the evidence from published systematic reviews on the effectiveness of text message programs for adults with type 2 diabetes (T2DM) on glycemic management (A1C), self-management, and other clinical outcomes. The effect of directionality of the program was also explored. METHODS: A systematic search was conducted using multiple databases. Inclusion criteria were systematic review of text message programs for

adults with T2DM, evaluated A1C, and English language. Quality assessment was completed using AMSTAR-2 guidelines. Data were extracted by multiple coders, and results were synthesized. RESULTS: The final sample included 9 systematic reviews published between 2011 and 2019, with 72 unique international studies. Text message programs focused on diabetes self-management and reducing health risks through educational and motivational content with some providing personalized feedback. A meta-analysis of program effect on A1C was conducted in 5 reviews with a pooled difference in A1C from -0.38% to -0.8%. Adults with T2DM of shorter duration and lower A1C had better treatment effects. Evidence on unidirectional versus bidirectional programs is conflicting; however, both improve outcomes. Evidence of text message programs targeting medication engagement was inconclusive. Some programs improved blood pressure, lipids, self-management, self-efficacy, and health behaviors. High satisfaction and an average of 9.6% to 18.7% attrition was reported. CONCLUSIONS: Text messaging programs can improve T2DM outcomes, are a highly accessible mode of communication, are relatively inexpensive, and are an underutilized adjunct to clinical care.

[5] *di Mauro G, Zinzi A, Scavone C et al.* **PCSK9 Inhibitors and Neurocognitive Adverse Drug Reactions: Analysis of Individual Case Safety Reports from the Eudravigilance Database**. Drug Saf 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33351170
ABSTRACT
INTRODUCTION: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9Is) were associated with a risk of neurocognitive adverse drug reactions (ADRs). OBJECTIVE: We aimed to investigate the occurrence of neuropsychiatric ADRs related to PCSK9Is. METHODS: We analyzed Individual Case Safety Reports (ICSRs) sent through the European pharmacovigilance database that reported alirocumab or evolocumab as the suspected drug and at least one neurological or psychiatric ADR. The reporting odds ratio (ROR) was computed to compare the probability of reporting ICSRs with neuropsychiatric ADRs between alirocumab, evolocumab and statins. RESULTS: Overall, 2041 ICSRs with alirocumab and/or evolocumab as the suspected drug described the occurrence of neuropsychiatric ADRs. The most reported preferred terms for both drugs were headache, insomnia and depression. No difference between alirocumab and evolocumab was observed for the RORs of ICSRs with ADRs belonging to the System Organ Classes (SOCs) 'Nervous system disorders' or 'Psychiatric disorders' (ROR 1.02, 95% confidence interval 0.91-1.14; and 1.12, 95% CI 0.94-1.34, respectively), while evolocumab and alirocumab had a higher reporting probability of ICSRs with ADRs belonging to the SOC 'Nervous system disorders' compared with atorvastatin and fluvastatin. A lower reporting probability was instead found for ICSRs with ADRs belonging to the SOC 'Psychiatric disorders' for evolocumab and alirocumab versus simvastatin, pravastatin and rosuvastatin. CONCLUSION: Our results demonstrated that 22.7% of all ICSRs reporting alirocumab or evolocumab as suspect drugs described the occurrence of neuropsychiatric ADRs. The ROR showed that evolocumab and alirocumab had a higher reporting probability of neurological ADRs compared with statins. Further data from real-life contexts are needed.

[6] *Wang Q, Oliver-Williams C, Raitakari OT et al.* **Metabolic profiling of angiopoietin-like protein 3 and 4 inhibition: a drug-target Mendelian randomization analysis**. European heart journal 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33351885

ABSTRACT

AIMS : Angiopoietin-like protein 3 (ANGPTL3) and 4 (ANGPTL4) inhibit lipoprotein lipase (LPL) and represent emerging drug targets to lower circulating triglycerides and reduce cardiovascular risk. To investigate the molecular effects of genetic mimicry of ANGPTL3 and ANGPTL4 inhibition and compare them to the effects of genetic mimicry of LPL enhancement. METHODS AND RESULTS : Associations of genetic variants in ANGPTL3 (rs11207977-T), ANGPTL4 (rs116843064-A), and LPL (rs115849089-A) with an extensive serum lipid and metabolite profile (208 measures) were characterized in six cohorts of up to 61 240 participants. Genetic associations with anthropometric measures, glucose-insulin metabolism, blood pressure, markers of kidney function, and cardiometabolic endpoints via genome-wide summary data were also explored. ANGPTL4 rs116843064-A and LPL rs115849089-A displayed a strikingly similar pattern of associations across the lipoprotein and lipid measures. However, the corresponding associations with ANGPTL3 rs11207977-T differed, including those for low-density lipoprotein and high-density lipoprotein particle concentrations and compositions. All three genotypes associated with lower concentrations of an inflammatory biomarker glycoprotein acetyls and genetic mimicry of ANGPTL3 inhibition and LPL enhancement were also associated with lower C-reactive protein. Genetic mimicry of ANGPTL4 inhibition and LPL enhancement were associated with a lower waist-to-hip ratio, improved insulin-glucose metabolism, and lower risk of coronary heart disease and type 2 diabetes, whilst genetic mimicry of ANGPTL3 was associated with improved kidney function. CONCLUSIONS : Genetic mimicry of ANGPTL4 inhibition and LPL enhancement have very similar systemic metabolic effects, whereas genetic mimicry of ANGPTL3 inhibition showed differing metabolic effects, suggesting potential involvement of pathways independent of LPL. Genetic mimicry of ANGPTL4 inhibition and LPL enhancement were associated with a lower risk of coronary heart disease and type 2 diabetes. These findings reinforce evidence that enhancing LPL activity (either directly or via upstream effects) through pharmacological approaches is likely to yield benefits to human health.

[7] *Sun JT, Chen Z, Nie P et al.* **Lipid Profile Features and Their Associations With Disease Severity and Mortality in Patients With COVID-19**. Frontiers in cardiovascular medicine 2020; 7:584987.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33344516

ABSTRACT

Background: Emerging studies have described and analyzed epidemiological, clinical, laboratory, and radiological features of COVID-19 patients. Yet, scarce information is available regarding the association of lipid profile features and disease severity and mortality. Methods: We conducted a prospective observational cohort study to investigate lipid profile features in patients with COVID-19. From 9 February to 4 April 2020, a total of 99 patients (31 critically ill and 20 severely ill) with confirmed COVID-19 were included in the study. Dynamic alterations in lipid profiles were recorded and tracked. Outcomes were followed up until 4 April 2020. Results: We found that high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein A-1 (apoA-1) levels were significantly lower in the severe disease group, with mortality cases showing the lowest levels ($p < 0.0001$). Furthermore, HDL-C and apoA-1 levels were independently associated with disease severity (apoA-1: odds ratio (OR): 0.651, 95% confidence interval (CI): 0.456-0.929, $p = 0.018$; HDL-C: OR: 0.643, 95% CI: 0.456-0.906, $p = 0.012$). For predicting disease severity, the areas under the receiver operating

characteristic curves (AUCs) of HDL-C and apoA-1 levels at admission were 0.78 (95% CI, 0.70-0.85) and 0.85 (95% CI, 0.76-0.91), respectively. For in-hospital deaths, HDL-C and apoA-1 levels demonstrated similar discrimination ability, with AUCs of 0.75 (95% CI, 0.61-0.88) and 0.74 (95% CI, 0.61-0.88), respectively. Moreover, patients with lower serum concentrations of apoA-1 (<0.95 g/L) or HDL-C (<0.84 mmol/l) had higher mortality rates during hospitalization (log-rank $p < 0.001$). Notably, levels of apoA-1 and HDL-C were inversely proportional to disease severity. The survivors of severe cases showed significant recovery of apoA-1 levels at the end of hospitalization (vs. midterm apoA-1 levels, $p = 0.02$), whereas the mortality cases demonstrated continuously lower apoA-1 levels throughout hospitalization. Correlation analysis revealed that apoA-1 and HDL-C levels were negatively correlated with both admission levels and highest concentrations of C-reactive protein and interleukin-6. Conclusions: Severely ill COVID-19 patients featured low HDL-C and apoA-1 levels, which were strongly correlated with inflammatory states. Thus, low apoA-1 and HDL-C levels may be promising predictors for severe disease and in-hospital mortality in patients suffering from COVID-19.

[8] *Jarauta E, Bea-Sanz AM, Marco-Benedi V, Lamiquiz-Moneo I*. **Genetics of Hypercholesterolemia: Comparison Between Familial Hypercholesterolemia and Hypercholesterolemia Nonrelated to LDL Receptor**. Frontiers in genetics 2020; 11:554931.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33343620
ABSTRACT
Severe hypercholesterolemia (HC) is defined as an elevation of total cholesterol (TC) due to the increase in LDL cholesterol (LDL-C) >95th percentile or 190 mg/dl. The high values of LDL-C, especially when it is maintained over time, is considered a risk factor for the development of atherosclerotic cardiovascular disease (ASCVD), mostly expressed as ischemic heart disease (IHD). One of the best characterized forms of severe HC, familial hypercholesterolemia (FH), is caused by the presence of a major variant in one gene (LDLR, APOB, PCSK9, or ApoE), with an autosomal codominant pattern of inheritance, causing an extreme elevation of LDL-C and early IHD. Nevertheless, an important proportion of serious HC cases, denominated polygenic hypercholesterolemia (PH), may be attributed to the small additive effect of a number of single nucleotide variants (SNVs), located along the whole genome. The diagnosis, prevalence, and cardiovascular risk associated with PH has not been fully established at the moment. Cascade screening to detect a specific genetic defect is advised in all first- and second-degree relatives of subjects with FH. Conversely, in the rest of cases of HC, it is only advised to screen high values of LDL-C in first-degree relatives since there is not a consensus for the genetic diagnosis of PH. FH is associated with the highest cardiovascular risk, followed by PH and other forms of HC. Early detection and initiation of high-intensity lipid-lowering treatment is proposed in all subjects with severe HC for the primary prevention of ASCVD, with an objective of LDL-C <100 mg/dl or a decrease of at least 50%. A more aggressive reduction in LDL-C is necessary in HC subjects who associate personal history of ASCVD or other cardiovascular risk factors.

[9] *Brandts J, Ray KK*. **Clinical implications and outcomes of the ORION Phase III trials**. Future cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33345605
ABSTRACT

Inclisiran is a siRNA inhibiting hepatic PCSK9 synthesis. As a first-in-class therapy, inclisiran has been assessed within the ORION trial program for its low-density lipoprotein cholesterol (LDL-C) lowering efficacy and clinical safety. Phase II and III trials have shown that inclisiran lowers LDL-C by about 50% with an infrequent dosing schedule in patients with established atherosclerotic cardiovascular disease and those at high risk, including patients with heterozygous familial hypercholesterolemia. Ongoing Phase III trials will provide evidence on longer-term safety and effectiveness, and inclisiran's efficacy in patients with homozygous familial hypercholesterolemia. Furthermore, the ORION-4 trial will assess inclisiran's impact on cardiovascular outcomes.

[10] *Mszar R, Gopal DJ, Chowdary R et al.* **Racial/Ethnic Disparities in Screening for and Awareness of High Cholesterol Among Pregnant Women Receiving Prenatal Care**. Journal of the American Heart Association 2021; 10:e017415.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33345544

ABSTRACT

Background Atherosclerotic cardiovascular disease remains a leading cause of morbidity and mortality among women, with younger women being disproportionately affected by traditional cardiovascular risk factors such as dyslipidemia. Despite recommendations for lipid screening in early adulthood and the risks associated with maternal dyslipidemia during pregnancy, many younger women lack access to and utilization of early screening. Accordingly, our objective was to assess the prevalence of and disparities in lipid screening and awareness of high cholesterol as an atherosclerotic cardiovascular disease risk factor among pregnant women receiving prenatal care. Methods and Results We invited 234 pregnant women receiving prenatal care at 1 of 3 clinics affiliated with the University of Pennsylvania Health System to complete our survey. A total of 200 pregnant women (86% response rate) completed the survey. Overall, 59% of pregnant women (mean age 32.2 [±5.7] years) self-reported a previous lipid screening and 79% of women were aware of high cholesterol as an atherosclerotic cardiovascular disease risk factor. Stratified by racial/ethnic subgroups, non-Hispanic Black women were less likely to report a prior screening (43% versus 67%, P=0.022) and had lower levels of awareness (66% versus 92%, P<0.001) compared with non-Hispanic White women. Non-Hispanic Black women were more likely to see an obstetrician/gynecologist for their usual source of non-pregnancy care compared with non-Hispanic White women (18% versus 5%, P=0.043). Those seeing an obstetrician/gynecologist for usual care were less likely to report a prior lipid screening compared with those seeing a primary care physician (29% versus 63%, P=0.007). Conclusions Significant racial/ethnic disparities persist in lipid screening and risk factor awareness among pregnant women. Prenatal care may represent an opportunity to enhance access to and uptake of screening among younger women and reduce variations in accessing preventive care services.

[11] *Furuhashi M, Sakuma I, Morimoto T et al.* **Differential Effects of DPP-4 Inhibitors, Anagliptin and Sitagliptin, on PCSK9 Levels in Patients with Type 2 Diabetes Mellitus who are Receiving Statin Therapy**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33342939

ABSTRACT

AIM: Proprotein convertase subtilisin/kexin type 9 (PCSK9) degrades the low-density lipoprotein (LDL) receptor, leading to hypercholesterolemia and cardiovascular risk. Treatment with a statin leads

to a compensatory increase in circulating PCSK9 level. Anagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, was shown to decrease LDL cholesterol (LDL-C) levels to a greater extent than that by sitagliptin, another DPP-4 inhibitor, in the Randomized Evaluation of Anagliptin versus Sitagliptin On low-density lipoproteiN cholesterol in diabetes (REASON) trial. We investigated PCSK9 concentration in type 2 diabetes mellitus (T2DM) and the impact of treatment with anagliptin or sitagliptin on PCSK9 level as a sub-analysis of the REASON trial. METHODS: PCSK9 concentration was measured at baseline and after 52 weeks of treatment with anagliptin (n=122) or sitagliptin (n=128) in patients with T2DM who were receiving statin therapy. All of the included patients had been treated with a DPP-4 inhibitor prior to randomization. RESULTS: Baseline PCSK9 level was positively, but not significantly, correlated with LDL-C and was independently associated with platelet count and level of triglycerides. Concomitant with reduction of LDL-C, but not hemoglobin A1c (HbA1c), by anagliptin, PCSK9 level was significantly increased by treatment with sitagliptin (218±98 vs. 242±115 ng/mL, P=0.01), but not anagliptin (233±97 vs. 250±106 ng/mL, P=0.07). CONCLUSIONS: PCSK9 level is independently associated with platelet count and level of triglycerides, but not LDL-C, in patients with T2DM. Anagliptin reduces LDL-C level independent of HbA1c control in patients with T2DM who are on statin therapy possibly by suppressing excess statin-mediated PCSK9 induction and subsequent degradation of the LDL receptor.

[12] *Saiki A, Watanabe Y, Yamaguchi T et al.* **CAVI-Lowering Effect of Pitavastatin May Be Involved in the Prevention of Cardiovascular Disease: Subgroup Analysis of the TOHO-LIP**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33342941
ABSTRACT
AIM: In the TOHO Lipid Intervention Trial Using Pitavastatin (TOHO-LIP), a multicenter randomized controlled trial, pitavastatin significantly reduced cardiovascular (CV) events compared to atorvastatin in patients with hypercholesterolemia. To investigate the mechanism by which pitavastatin preferentially prevents CV events, we investigated the relationship between CV events and cardio-ankle vascular index (CAVI) using the TOHO-LIP database. METHODS: For the subgroup analysis, we selected patients from a single center, Toho University Sakura Medical Center. After excluding those who had CV events at baseline or during the first year, 254 patients were enrolled. The primary end point was the same as that of TOHO-LIP, and three-point major cardiac adverse events (3P-MACE) was added as secondary end point. RESULTS: The cumulative 5-year incidence of 3P-MACE (pitavastatin 1.6%, atorvastatin 6.1%, P=0.038) was significantly lower in pitavastatin group (2 mg/day) than in atorvastatin group (10 mg/day). CAVI significantly decreased only in pitavastatin group during the first year (9.50-9.34, P=0.042), while the change in low-density lipoprotein cholesterol (LDL-C) did not differ between the two groups. The change in CAVI during the first year positively correlated with 3P-MACE and tended to be an independent predictor of 3P-MACE in Cox proportional hazards model (hazard ratio, 1.736; P=0.079). The annual change in CAVI throughout the observation period was significantly higher in subjects with CV events compared to those without. CONCLUSIONS: In this subgroup analysis, the reduction in CV events tended to be associated with the CAVI-lowering effect of pitavastatin, which was independent of the LDL-C-lowering effect.

[13] *Leggott K, Lyon C, Claus L, Prasad S*. **PURL: Consider this Rx for patients with high triglycerides?** The Journal of family practice 2020; 69:518-525.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33348346

ABSTRACT

A daily dose of this prescription fish oil may be worth a trial in light of the cardiovascular benefits it affords statin-treated patients with high triglycerides.

[14] *Hearps AC, Angelovich TA, Trevillyan JM et al.* **Rosuvastatin therapy in people with HIV at intermediate cardiovascular risk does not decrease biomarkers of inflammation and immune activation**. The Journal of infectious diseases 2020.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33350447

ABSTRACT

BACKGROUND: Statins may help prevent cardiovascular disease (CVD) in people with HIV (PWH) with chronic inflammation due to their pleotropic lipid lowering and anti-inflammatory properties. METHODS: The impact of 48 weeks of rosuvastatin therapy on inflammation and immune activation in a double-blind, placebo-controlled trial in PWH at moderate CVD risk was assessed. RESULTS: Rosuvastatin not alter plasma levels of IL-6, soluble (s)TNF-RII, CXCL10, sCD14 or sVCAM-1 ($p \geq 0.1$ for all). Proportions of CD16 + monocyte subsets were increased in PWH receiving rosuvastatin. CONCLUSIONS: The potential benefits of statin use in PWH with normal lipid levels requires further clinical outcome research.

[15] *Welzel L, Bergin DH, Schidlitzki A et al.* **Systematic evaluation of rationally chosen multitargeted drug combinations: a combination of low doses of levetiracetam, atorvastatin and ceftriaxone exerts antiepileptogenic effects in a mouse model of acquired epilepsy**. Neurobiology of disease 2020; 149:105227.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33347976

ABSTRACT

Epileptogenesis, the gradual process that leads to epilepsy after brain injury or genetic mutations, is a complex network phenomenon, involving a variety of morphological, biochemical and functional brain alterations. Although risk factors for developing epilepsy are known, there is currently no treatment available to prevent epilepsy. We recently proposed a multitargeted, network-based approach to prevent epileptogenesis by rationally combining clinically available drugs and provided first proof-of-concept that this strategy is effective. Here we evaluated eight novel rationally chosen combinations of 14 drugs with mechanisms that target different epileptogenic processes. The combinations consisted of 2-4 different drugs per combination and were administered systemically over 5 days during the latent epileptogenic period in the intrahippocampal kainate mouse model of acquired temporal lobe epilepsy, starting 6 h after kainate. Doses and dosing intervals were based on previous pharmacokinetic and tolerability studies in mice. The incidence and frequency of spontaneous electrographic and electroclinical seizures were recorded by continuous (24/7) video linked EEG monitoring done for seven days at 4 and 12 weeks post-kainate, i.e., long after termination of drug treatment. Compared to vehicle controls, the most effective drug combination consisted of low doses of levetiracetam, atorvastatin and ceftriaxone, which markedly reduced the incidence of electrographic seizures (by 60%; $p<0.05$) and electroclinical seizures (by 100%; $p<0.05$) recorded at 12 weeks after kainate. This effect was lost when higher doses of the three drugs were administered, indicating a synergistic drug-drug interaction at the low doses. The potential mechanisms underlying

this interaction are discussed. We have discovered a promising novel multitargeted combination treatment for modifying the development of acquired epilepsy.