Literature update week 31 (2019)

[1] *Li HH, Li J, Zhang XJ et al.* **23,24-Dihydrocucurbitacin B promotes lipid clearance by dual transcriptional regulation of LDLR and PCSK9**. Acta pharmacologica Sinica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31358898

ABSTRACT

23,24-Dihydrocucurbitacin B (designated as C95 in this article) is a cucurbitane triterpenoid that has been shown to possess a variety of pharmacological activities, such as anti-inflammatory and anti-HIV-1 activities etc. In this study, we investigated the effects of 23,24-dihydrocucurbitacin B on lipid regulation. We showed that 23,24-dihydrocucurbitacin B (1-5 muM) dose-dependently promoted DiI-LDL uptake in HepG2 cells by upregulating low-density lipoprotein receptor (LDLR) protein. In HepG2 cells, 23,24-dihydrocucurbitacin B (1-10 muM) dose-dependently enhanced LDLR promoter activity by elevating the mature form of SREBP2 (sterol regulatory element binding protein 2) protein levels on one hand, and inhibited PCSK9 (proprotein convertase subtilisin/kexin type 9) promoter activity by attenuating HNF1alpha (hepatocyte nuclear factor-1alpha) protein levels in nuclei on the other hand. Consequently, the expression of LDLR protein markedly increased, whereas the PCSK9-mediated LDLR protein degradation decreased. In a high-cholesterol LVG golden Syrian Hamster model, administration of 23,24-dihydrocucurbitacin B (30 mg . kg(-1) d(-1), intragastric, for 3 weeks) significantly decreased the serum LDL-cholesterol (LDL-C) levels. PCSK9 protein levels in the serum and liver tissues were significantly decreased, whereas LDLR protein levels in liver tissues were significantly increased in the treated animals as compared with the control animals. In conclusion, our study demonstrates for the first time that 23,24-dihydrocucurbitacin B exhibits dual transcriptional regulation of LDLR and PCSK9 in HepG2 cells by increasing SREBP2 protein levels and decreasing HNF1alpha protein levels in the nuclei. These results propose a new strategy to simultaneously manage LDLR and PCSK9 protein expression and provide a promising lead compound for drug development.

[2] *Chamberlain AM, Cohen SS, Killian JM et al.* **Lipid-Lowering Prescription Patterns in Patients With Diabetes Mellitus or Cardiovascular Disease**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31362878

ABSTRACT

The purpose of this study is to describe lipid-lowering therapy (LLT) prescriptions and low-density lipoprotein cholesterol (LDL-C) monitoring in patients with diabetes mellitus (DM) with or without concomitant cardiovascular disease (CVD). Olmsted County, Minnesota residents with a first-ever diagnosis of DM or CVD (ischemic stroke/transient ischemic attack, myocardial infarction, unstable angina pectoris, or revascularization procedure) between 2005 and 2012 were classified as having DM only, CVD only, or CVD+DM. All LLT prescriptions and LDL-C measurements were obtained for 2 years after diagnosis. A total of 4,186, 2,368, and 724 patients had DM, CVD, and CVD+DM, respectively. Rates of LDL-C measurement were 1.31, 1.66, and 1.88 per person-year and 14%, 32%, and 42% of LDL-C measurements were <70 mg/dl in those with DM, CVD, and CVD+DM. Within 3 months after diagnosis, 47%, 71%, and 78% of patients with DM, CVD, and CVD+DM were prescribed LLT. Most prescriptions were for moderate-intensity statins. Under one-fifth of patients with CVD and CVD+DM were prescribed high-intensity statins. Predictors of high-intensity statin prescriptions included male sex, having CVD or CVD+DM, increasing LDL-C, and LDL-C measured more recently (2012 to 2014 vs before

2012). In conclusion, a large proportion of patients at high CVD risk are not adequately treated with LLT. Despite often being considered a risk equivalent, patients with DM have substantially lower rates of LLT prescriptions and lesser controlled LDL-C than those with CVD or CVD+DM.

[3] *Ihdayhid AR, Goeller M, Dey D et al.* **Comparison of Coronary Atherosclerotic Plaque Burden and Composition as Assessed on Coronary Computed Tomography Angiography in East Asian and European-Origin Caucasians**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31351575

ABSTRACT

Recent evidence suggests plaque morphology evaluated on coronary computed tomography angiography has prognostic implications. East Asians have a lower prevalence of myocardial infarction and cardiovascular mortality compared with European-origin Caucasians. We aimed to compare coronary atherosclerotic burden and plaque composition in a matched cohort of Caucasian and East Asians patients with stable chest pain who underwent computed tomography angiography. Two-hundred symptomatic patients (age 58.8 +/- 7.9, male 51%) were matched for age, gender, body mass index, and diabetes (100 each ethnic group). A blinded core-laboratory quantified calcified and noncalcified plaque (NCP) volume and burden. Components of NCP were differentiated by plaque hounsfield unit (HU) thresholds which defined high-risk necrotic core (-30 to 30HU), fibrofatty plaque (31 to 130HU); and low-risk fibrous plaque (131 to 350HU). Composition of NCP components was derived as (NCP component volume/total NCP volume)x100%. Segment Involvement Score, percent diameter and area stenosis were comparable in both groups. Similarly, there was no difference in the volume and burden of total, calcified and NCP. Compared with Caucasians, East Asians demonstrated lower composition of plaque attenuation corresponding to necrotic core (3.5 vs 5.1%; p = 0.004) and fibrofatty plaque (29.6 vs 37.3%; p = 0.005), and higher fibrous plaque (65.7 vs 57.6%; p = 0.004). On multivariable analysis East Asian ethnicity was independently associated with lower composition of high-risk plaque after adjustment for risk factors and scan parameters. These findings were consistent in a propensity-matched sensitivity-analysis. In conclusion, based on this matched cohort, East Asian ethnicity is associated with significantly less composition of high-risk NCP (necrotic core and fibrofatty plaque) and a higher composition of low-risk fibrous plaque compared with Caucasians; which may confer a lower risk of cardiovascular events.

[4] *Zafar MI, Mills KE, Zheng J et al.* **Low-glycemic index diets as an intervention for diabetes: a systematic review and meta-analysis**. The American journal of clinical nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31374573

ABSTRACT

BACKGROUND: Low-glycemic index (GI) diets are thought to reduce postprandial glycemia, resulting in more stable blood glucose concentrations. OBJECTIVE: We hypothesized that low-GI diets would be superior to other diet types in lowering measures of blood glucose control in people with type 1 or type 2 diabetes, or impaired glucose tolerance. METHODS: We searched PubMed, the Cochrane Library, EMBASE, and clinical trials registries for published and unpublished studies up until 1 March, 2019. We included 54 randomized controlled trials in adults or children with impaired glucose tolerance, type 1 diabetes, or type 2 diabetes.

Continuous data were synthesized using a random effects, inverse variance model, and presented as standardized mean differences with 95% CIs. RESULTS: Low-GI diets were effective at reducing glycated hemoglobin (HbA1c), fasting glucose, BMI, total cholesterol, and LDL, but had no effect on fasting insulin, HOMA-IR, HDL, triglycerides, or insulin requirements. The reduction in fasting glucose and HbA1c was inversely correlated with body weight. The greatest reduction in fasting blood glucose was seen in the studies of the longest duration. CONCLUSIONS: Low-GI diets may be useful for glycemic control and may reduce body weight in people with prediabetes or diabetes.

[5] *Liberopoulos E, Rallidis L, Spanoudi F et al.* **Attainment of cholesterol target values in Greece: results from the Dyslipidemia International Study II**. Archives of medical science : AMS 2019; 15:821-831.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31360176
ABSTRACT
Introduction: Current European guidelines recommend treatment with lipid-lowering therapy (LLT) to a low-density lipoprotein cholesterol (LDL-C) target of < 70 mg/dl for patients at very high risk. LDL-C target attainment and use of LLTs in these patients in Greece is not known. Material and methods: The Dyslipidemia International Study (DYSIS) II was a multicenter observational study. The coronary heart disease (CHD) cohort was divided into two groups based on treatment status (on LLT for >/= 3 months or not on LLT). The acute coronary syndrome (ACS) cohort was evaluated at the time of admission and again 120 +/-15 days after admission. Results: In the CHD cohort (n = 499), 457 (91.6%) patients were on LLT. The LDL-C target value was attained by 26.5% of LLT users. Statin monotherapy was used by 77.5% of treated patients, with a mean +/- SD atorvastatin dose equivalent of 24 +/-16 mg/day. In the ACS cohort (n = 200), 159 (79.5%) patients were on LLT at admission. Mean +/- SD LDL-C levels were 108 +/-40 mg/dl at admission and 86 +/-25 mg/dl at follow-up. LDL-C target value attainment rates were 16.2% at admission and 25.0% at follow-up. At admission, statin monotherapy was used by 86.8% of treated patients. The mean +/- SD atorvastatin dose equivalent increased from 20 +/-14 mg/day at admission to 29 +/-15 mg/day at follow-up. The statin dose was associated with higher odds of LDL-C target value attainment (OR = 1.05, 95% CI: 1.02-1.08). Conclusions: The LDL-C target attainment by very high risk patients in Greece is suboptimal. Increasing the statin dose or combining it with non-statins may improve target value attainment.

[6] *Sun J, Zhang C, Zhang Z*. **Atorvastatin attenuates cardiac hypertrophy through AMPK/miR-143-3p/Bcl2 axis**. Archives of physiology and biochemistry 2019:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31353965
ABSTRACT
Atorvastatin is employed as a lipid lowering agent and its heart protective effect has been recently reported as well. However, the mechanism of atorvastatin in attenuating cardiac hypertrophy and inhibiting cardiac failure is unclear. In our study, cardiac hypertrophy was induced in rats using transverse aortic constriction (TAC) method and in cardiomyocytes using angiotensin II (Ang II). Atorvastatin significantly suppressed TAC-induced heart weight increase and cardiomyocytes apoptosis in rats. At a molecular level, we found that miR-143-3p was

significantly up-regulated, and the up-regulation could be inhibited by atorvastatin via activating AMPK pathway. Furthermore, it was validated that Bcl2 was one of the target genes of miR-143-3p. Taken together, the data indicated that miR-143-3p aggravated cardiac hypertrophy by inducing cardiomyocytes apoptosis through inhibiting Bcl2 expression. This study demonstrated the effects of atorvastatin in attenuating cardiac hypertrophy and inhibiting cardiac failure, which is depending on Bcl2 expression via miR-143-3p inhibition by AMPK activation.

[7] *Sato T, Horikawa M, Takei S et al.* **Preferential Incorporation of Administered Eicosapentaenoic Acid Into Thin-Cap Atherosclerotic Plaques**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119313093.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31366219
ABSTRACT
OBJECTIVE: n-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have beneficial effects on atherosclerosis. Although specific salutary actions have been reported, the detailed distribution of n-3 polyunsaturated fatty acids in plaque and their relevance in disease progression are unclear. Our aim was to assess the pharmacodynamics of EPA and DHA and their metabolites in atherosclerotic plaques. Approach and Results: Apolipoprotein E-deficient (Apoe(-/-)) mice were fed a western diet supplemented with EPA (1%, w/w) or DHA (1%, w/w) for 3 weeks. Imaging mass spectrometry analyses were performed in the aortic root and arch of the Apoe(-/-) mice to evaluate the distribution of EPA, DHA, their metabolites and the lipids containing EPA or DHA in the plaques. Liquid chromatography-mass spectrometry and histological analysis were also performed. The intima-media thickness of atherosclerotic plaque decreased in plaques containing freer EPA and EPAs attached with several lipids. EPA was distributed more densely in the thin-cap plaques than in the thick-cap plaques, while DHA was more evenly distributed. In the aortic root, the distribution of total EPA level and cholesteryl esters containing EPA followed a concentration gradient from the vascular endothelium to the media. In the aortic arch, free EPA and 12-hydroxy-EPA colocalized with M2 macrophage. CONCLUSIONS: Administered EPA tends to be incorporated from the vascular lumen side and preferentially taken into the thin-cap plaque.

[8] *Qiao L, Wang S, Jia Q et al.* **Clinical efficacy and safety of statin treatment after carotid artery stenting**. Artificial cells, nanomedicine, and biotechnology 2019; 47:3110-3115.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31352800
ABSTRACT
Objective: The randomized controlled trail was carried out to investigate the influence of statin pre-treatment on clinical efficacy of carotid artery stenting (CAS). Methods: 160 eligible patients were randomly divided into statin group (n = 82) and control group (n = 78). The patients in statin group received 40 mg atorvastatin daily 7 days before operation. Major endpoints included transient ischemic attack (TIA), stroke, death, myocardial infarction (MI), and other cardiac adverse events within 30 days after CAS. Results: Preoperative baseline information was similar between the statin and control groups ($p > 0.05$ for all). Within 48 h after operation, the occurrence rate of CIN (3.66% vs 8.97%, $p = .019$) and new infarction (4.88% vs. 14.10%, $p = .045$) were significantly lower in statin group than in control group. 30

days after CAS, the incidences of TIA (12.20% vs. 26.92%, p = .018), ischemic stroke (6.10% vs. 16.67%, p = .034), and other cardiac complications (7.32% vs. 19.23%, p = .026) were also significantly lower in statin group, than in the control group. Multiple analysis demonstrated that statin use exerted protective effect against ischemic stroke (OR = 0.038, 95% CI = 0.003-0.543, p = .016) and other cardiac complications (OR = 0.208, 95%CI = 0.063-0.694, p = .011). Conclusion: Pre-treatment with statin is an effective and safe strategy to prevent from perioperative complications and to improve postoperative outcomes in patients undergoing CAS.

[9] *Lim DH, Lee Y, Park GM et al.* **Serum uric acid level and subclinical coronary atherosclerosis in asymptomatic individuals: An observational cohort study**. Atherosclerosis 2019; 288:112-117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31352272
ABSTRACT
BACKGROUND AND AIMS: There are limited data on the association between serum uric acid (SUA) level and subclinical coronary atherosclerosis. This study investigated the influence of SUA level on subclinical coronary atherosclerosis, as detected by coronary computed tomography angiography (CCTA), in an asymptomatic population. METHODS: We evaluated 6431 asymptomatic individuals (mean age 53.6+/-7.6 years, 4691 men [72.9%]) with no prior history of coronary artery disease, who voluntarily underwent laboratory tests and CCTA as part of a general health examination. The participants were stratified into quartiles according to their SUA levels. Coronary atherosclerotic plaques (calcified, mixed, and non-calcified plaques) were assessed using CCTA. Logistic regression analysis was used to determine the association between SUA levels and subclinical coronary atherosclerosis. RESULTS: The prevalence of any atherosclerotic, calcified, mixed, and non-calcified plaques increased with SUA quartiles (all p<0.001). After adjustment for cardiovascular risk factors, there were no statistically significant differences in the adjusted odds ratios for calcified plaque (1.19; 95% CI 0.98-1.46; p=0.080) and mixed plaque (1.25; 95% CI 0.94-1.67; p=0.132) in the fourth SUA quartile compared to the first quartile. However, the adjusted odds ratios for any atherosclerotic plaque (1.39; 95% CI 1.16-1.68; p<0.001) and non-calcified plaque (1.38; 95% CI 1.11-1.72; p=0.004) were significantly higher in the fourth SUA quartile. CONCLUSIONS: In asymptomatic individuals, high SUA level was an independent predictor of non-calcified plaques, suggesting an increased cardiovascular risk.

[10] *de Jong M, Vos RC, de Ritter R et al.* **Sex differences in cardiovascular risk management for people with diabetes in primary care: a cross-sectional study**. BJGP open 2019; 3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31366676
ABSTRACT
BACKGROUND: Diabetes is a stronger risk factor for cardiovascular complications in women than men. AIM: To evaluate whether there are sex differences in cardiovascular risk management in patients with diabetes in primary care. DESIGN & SETTING: A cross-sectional study was undertaken using data from 12 512 individuals with diabetes within the Dutch Julius General Practitioners Network (JGPN) from 2013. METHOD: Linear and Poisson regression analyses were used to assess sex differences in risk factor levels, assessment, treatment, and

control. RESULTS: No sex differences were found in HbA1c levels and control, while small differences were found for cardiovascular risk management. Blood pressure levels were higher (mean difference [MD] 1.09 mmHg; 95% confidence intervals [CI] = 0.41 to 1.77), while cholesterol levels (MD -0.38 mmol/l; 95% CI = -0.42 to -0.34) and body mass index ([BMI] MD -1.79 kg/m(2); 95% CI = -2.03 to 1.56) were lower in men than women. Risk factor assessment was similar between sexes, apart from high-density lipoprotein cholesterol (HDL-c), which was more commonly assessed in women (risk ratio [RR] 1.16; 95% CI = 1.13 to 1.20). Among those with a treatment indication for prevention, women with cardiovascular disease (CVD) were less likely to receive lipid-lowering drugs (RR 0.84; 95% CI = 0.76 to 0.93) than men, while women without CVD were more likely to receive lipid-lowering drugs (RR 1.16; 95% CI = 1.04 to 1.2). Among those treated, women were more likely to achieve systolic blood pressure (SBP) control (RR 1.06; 95% CI = 1.02 to 1.10) and less likely to achieve low-density lipoprotein cholesterol (LDL-c) control (RR 0.88; 95% CI = 0.85 to 0.91) than men. CONCLUSION: In this Dutch primary care setting, sex differences in risk factor assessment and treatment of people with diabetes were small. However, women with diabetes were less likely to achieve control for LDL-c and more likely to achieve blood pressure control than men with diabetes.

[11] *Nykanen AI, Holmstrom EJ, Tuuminen R et al.* **Donor Simvastatin Treatment in Heart Transplantation: A Randomized and Blinded Clinical Trial**. Circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31352795
ABSTRACT

[12] *Kim S, Ko JW, Kim JR*. **Pharmacokinetic and Safety Profiles of a Fixed-Dose Combination of Amlodipine, Valsartan, and Atorvastatin: A 3-Period Replicate Crossover Study**. Clinical pharmacology in drug development 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31373174
ABSTRACT
The objective of study was to compare the pharmacokinetic and safety profiles of a fixed-dose combination (FDC) formulation of 5/160/20 mg amlodipine/valsartan/atorvastatin with those of separate formulations of a 5/160-mg amlodipine/valsartan tablet and a 20-mg atorvastatin tablet. This was a randomized, open-label, single-dose, 3-sequence, 3-period replicate crossover study with 42 subjects. Serial blood samples for pharmacokinetic assessment were collected up to 72 hours postdose. For establishing bioequivalence (BE) for amlodipine, valsartan, and atorvastatin, a reference-scaled average BE approach was used if applicable, as well as the conventional limit of 0.80-1.25. The 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) for the maximum plasma concentration (Cmax) and the area under the curve to the last measurable concentration (AUCt) between the FDC and separate formulations were within the 0.80-1.25 limit for all analytes but atorvastatin. The estimated within-subject standard deviation of the log-transformed values of the separate formulations, the reference intervention, was 0.3804 for the Cmax of atorvastatin, being set at 0.7489-1.3352 for the BE acceptance limit. For both the Cmax and AUCt for atorvastatin, the GMRs lay within 0.80-1.25, and the 90%CIs for the GMRs were within the BE acceptance limit. This 3-period replicate crossover study demonstrated the BE of the FDC formulation of amlodipine, valsartan, and atorvastatin and the separate formulations of an amlodipine/valsartan tablet and an

atorvastatin tablet. A similar incidence of treatment-emergent adverse events (TEAEs) was observed in both interventions, and headache was the most common TEAE.

[13] *Vasquez N, Joshi PH*. **Lp(a): Addressing a Target for Cardiovascular Disease Prevention**. Current cardiology reports 2019; 21:102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31367887
ABSTRACT
PURPOSE OF REVIEW: To review the current recommendations for lipoprotein(a) (Lp(a)) screening, the evidence behind the thresholds for increased cardiovascular disease (CVD) risk, and the available data supporting Lp(a) lowering. RECENT FINDINGS: Lp(a) is almost entirely genetically determined and has an independent causal association with CVD. Measurement of Lp(a) is challenging given the structural heterogeneity of apolipoprotein a (apo(a)), for which isoform-insensitive immunoassays should be used. Current guidelines do not recommend treatment to lower Lp(a) but rather focus on intensified preventive measures including low-density lipoprotein cholesterol (LDL-C) lowering in patients with high Lp(a). Evidence suggests that levels higher than 50 mg/dL (125 nmol/L) identify significantly increased CVD risk. Mendelian randomization studies suggest that in order to have a clinically significant reduction in coronary heart disease, Lp(a) levels should be reduced by at least 60-70 mg/dL to attain a significant benefit. Ongoing studies of targeted therapy with antisense oligonucleotides (ASO) have shown promising reductions in Lp(a) up to 80%, but a cardiovascular outcomes trial is needed. There is unquestionably an increased risk for CVD in patients with elevated Lp(a); however, measurement assay issues and the lack of Lp(a)-targeted therapies with proven outcome reduction limit the clinical utility of this important risk factor. Available evidence suggesting specific thresholds for clinically significant CVD risk are based on European or Caucasian populations, not accounting for important racial differences. Novel Lp(a)-targeted emerging therapies may need to account for an expected reduction of at least 60-70 mg/dL to achieve a clinically significant benefit.

[14] *Genkel VV, Kuznetcova AS, Shaposhnik, II*. **Biomechanical forces and atherosclerosis: From mechanism to diagnosis and treatment**. Current cardiology reviews 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31362692
ABSTRACT
The article provides an overview of current views on the role of biomechanical forces in the pathogenesis of atherosclerosis. The importance of biomechanical forces in maintaining vascular homeostasis is considered. We provide descriptions of mechanosensing and mechanotransduction. The roles of wall shear stress and circumferential wall stress in the initiation, progression and destabilization of atherosclerotic plaque are described. The data on the possibilities of assessing biomechanical factors in clinical practice and the clinical significance of this approach are presented. The article concludes with discussion current therapeutic approaches based on the modulation of biomechanical forces.

[15] *Szelenberger R, Kostka J, Saluk-Bijak J, Miller E*. **Pharmacological interventions and rehabilitation approach for enhancing brain self-repair and stroke recovery**. Curr Neuropharmacol 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31362657

ABSTRACT

Neuroplasticity is a natural process occurring in the brain for entire life. Stroke is the leading cause of long term disability and huge medical and financial problem throughout the world. Research conducted over the past decade focused mainly on neuroprotection in the acute phase of stroke while very little studies targets chronic stage. Recovery after stroke depends on the ability of our brain to reestablish structural and functional organization of neurovascular networks. Combining adjuvant therapies and drugs may enhance the repair processes and restore impaired brain functions. Currently, there are some drugs and rehabilitative strategies that can facilitate brain repair and improve clinical effect even years after stroke onset. Moreover, some of compounds such as citicoline, fluoxetine, niacin, levodopa etc. are already in clinical use or are being trial in clinical issues. Many studies testing also cell therapies, in our review we will focused on studies where cells have been implemented at the early stage of stroke. Next, we discuss pharmaceutical interventions. In this section selected methods of cognitive, behavioral and physical rehabilitation as well as adjuvant interventions for neuroprotection including non invasive brain stimulation and extremely low frequency electromagnetic field. The modern rehabilitation represents new model of physical interventions with limited therapeutic window up to six months after stroke. However, last studies suggest, that time window for stroke recovery is much longer than previous thought. This review attempts to present the progress in neuroprotective strategies, both pharmacological and non-pharmacological that can stimulate the endogenous neuroplasticity in post stroke patients.

[16] *Lan NSR, Fegan PG, Rankin JM et al.* **Implementing simple algorithms to improve glucose and lipid management in people with diabetes and acute coronary syndrome**. Diabetic medicine : a journal of the British Diabetic Association 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31365761

ABSTRACT

AIM: Diabetes mellitus is associated with increased risk of adverse outcomes following acute coronary syndrome. Translating evidence-based recommendations into practice is necessary to improve outcomes. We evaluated whether implementing algorithms to guide inpatient care improved glycaemic control, and increased use of sodium-glucose co-transporter 2 (SGLT2) inhibitors and lipid-lowering medication in a tertiary cardiac unit. METHOD: A 3-month audit (phase 1) was conducted to evaluate hyperglycaemia and dyslipidaemia management, and medication prescriptions. Consecutive people with diabetes admitted for acute coronary syndrome were prospectively identified. Target blood glucose level was defined as 5-10 mmol/l. A multidisciplinary committee designed and implemented decision-support algorithms plus education. A 3-month post-implementation audit (phase 2) was conducted. RESULTS: There were 104 people in phase 1 and 101 in phase 2, with similar characteristics [HbA1c 64 +/- 20 mmol/mol vs. 61 +/- 21 mmol/mol (8.0 +/- 1.8% vs. 7.8 +/- 1.9%]. Post implementation, the incidence of blood glucose levels > 10 mmol/l was lower [phase 1: 46.4% vs. phase 2: 31.8%, rate ratio (RR) = 0.77, 95% confidence intervals (CI) 0.60-0.98; P = 0.031], without a difference in blood glucose levels < 5mmol/l (phase 1: 4.9% vs. phase 2: 4.5%, RR = 1.20, 95% CI 0.70-2.08; P = 0.506). SGLT2 inhibitor prescriptions increased significantly (baseline to discharge: 12.5% to

15.4% vs. 7.9% to 24.8%; P = 0.007) but high-intensity statin prescriptions did not (baseline to discharge: 35.6% to 72.1% vs. 40.6% to 85.1%; P = 0.074). Prescription rates of non-statin lipid-lowering medications were not significantly increased. CONCLUSIONS: Implementing decision-support algorithms was associated with improved inpatient glycaemic control and increased use of cardioprotective therapies at discharge in people with diabetes and acute coronary syndrome.

[17] *Ma M, Bu L, Shi L et al.* **Effect of loading dose of atorvastatin therapy prior to percutaneous coronary intervention in patients with acute coronary syndrome: a meta-analysis of six randomized controlled trials**. Drug design, development and therapy 2019; 13:1233-1240.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31354240
ABSTRACT
Purpose: The study sought to summarize the evidence of pre-procedural atorvastatin therapy to improve the prognosis of acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). Patients and methods: We searched PubMed and Embase from inception to July 2018 for randomized controlled trials that compared loading dose atorvastatin pretreatment with no or low dose for the prevention of cardiovascular events. The primary end points were all-cause mortality and myocardial infarction (MI) at 30 days. The secondary end point was 30-day major adverse cardiovascular events (MACE), a composite of all-cause mortality, MI, and revascularization. Results: Six trials with 4,991 individuals were included in our meta-analysis. High-dose atorvastatin preloading before PCI was associated with a 27% relative reduction in MI (OR: 0.73, 95% CI, 0.56-0.94, P=0.015). All-cause mortality was nonsignificantly reduced by early treatment with high-potency atorvastatin (OR: 0.94, 95% CI, 0.69-1.30, P=0.725). There was a 20% reduction in MACE in the group of patients treated with statin loading prior to PCI (OR: 0.80, 95% CI, 0.66-0.97, P=0.026). When stratified according to the diagnosis of ACS, the results of MACE were only significant for those ST-elevation myocardial infarction patients undergoing PCI (OR: 0.67, 95% CI, 0.48-0.94, P=0.022) and were not noted in the group of non-ST elevation ACS patients (OR: 0.65, 95% CI, 0.35-1.22, P=0.179). Conclusion: High-dose atorvastatin pretreatment leads to a significant reduction in MI and MACE at 30 days in ACS patients undergoing PCI, especially in ST-segment elevation MI.

[18] *Sorathia N, Al-Rubaye H, Zal B*. **The Effect of Statins on the Functionality of CD4+CD25+FOXP3+ Regulatory T-cells in Acute Coronary Syndrome: A Systematic Review and Meta-analysis of Randomised Controlled Trials in Asian Populations**. European cardiology 2019; 14:123-129.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31360235
ABSTRACT
Acute coronary syndrome (ACS) is characterised by increased effector cells and decreased regulatory T-cells (Tregs). Statins have been shown to be clinically beneficial in ACS patients. This effect could be mediated via the induction of Tregs in ACS patients. The aim of this systemic review and meta-analysis was to evaluate whether statin therapy enhances the frequency of Tregs determined by CD4+CD25+FOXP3+ in this subset of patients. A comprehensive search of PubMed and Embase was performed. Studies were restricted to

randomised controlled trials that quantified CD4+CD25+FOXP3+ cell frequency by flow cytometric analysis before and after statin treatment in adults diagnosed with ACS. A minimum of at least two of the conventional markers to identify Tregs was compulsory. Four randomised controlled trials studies (439 participants) were included, all with low-to-moderate risk of bias. Pooled data showed a significant increase in Treg frequency after statin therapy in ACS patients. A further meta-regression and subgroup analysis also showed a negative dose-related effect, and a statin type-related effect (rosuvastatin versus atorvastatin), respectively. The results confirmed that statins positively alter the frequency of Tregs, which may indicate a potential mechanism of their therapeutic effect. However, there was a risk of information bias due to the markers used to identify Tregs, which was not fully explored, therefore, further randomised controlled trials should utilise markers of Tregs, such as the FOXP3 locus (Treg-specific demethylated region), for identification.

[19] *Ballantyne CM, Laufs U, Ray KK et al.* **Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy**. European journal of preventive cardiology 2019:2047487319864671.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357887

ABSTRACT

AIMS: The aim of this study was to evaluate the low-density lipoprotein cholesterol lowering efficacy and safety of a bempedoic acid 180 mg and ezetimibe 10 mg fixed-dose combination in patients with hypercholesterolemia and a high risk of cardiovascular disease receiving maximally tolerated statin therapy. METHODS: This phase 3, double-blind clinical trial enrolled adult patients at high risk of cardiovascular disease due to atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or multiple cardiovascular disease risk factors. Patients were randomly assigned (2:2:2:1) to treatment with the fixed-dose combination, bempedoic acid 180 mg, ezetimibe 10 mg or placebo added to stable background statin therapy for 12 weeks. The primary efficacy endpoint was the percentage change from baseline to week 12 in low-density lipoprotein cholesterol. RESULTS: Among the 301 patients included in the primary analysis, the mean baseline low-density lipoprotein cholesterol level was 3.87 mmol/L (149.8 mg/dL). At week 12, the fixed-dose combination lowered low-density lipoprotein cholesterol (-36.2%) significantly more than placebo (1.8% (placebo-corrected difference -38.0%); $P < 0.001$), ezetimibe alone (-23.2%; $P < 0.001$) or bempedoic acid alone (-17.2%; $P < 0.001$). The fixed-dose combination lowered low-density lipoprotein cholesterol levels similarly across subgroups, including patients receiving high-intensity, other-intensity or no statin therapy. Improvements with the fixed-dose combination were also observed in secondary efficacy endpoints, including high-sensitivity C-reactive protein. In this trial, fixed-dose combination treatment had a generally similar safety profile compared with bempedoic acid, ezetimibe or placebo. CONCLUSION: The bempedoic acid and ezetimibe fixed-dose combination significantly lowered low-density lipoprotein cholesterol versus placebo or other oral monotherapies and had a favourable safety profile when added to maximally tolerated statin therapy in patients with hypercholesterolemia and high cardiovascular disease risk. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT03337308.

[20] *Dykun I, Mincu R, Hendricks S et al.* **Efficacy of lipid-lowering therapy beyond statins to prevent cardiovascular events: a meta-analysis**. European journal of preventive cardiology 2019:2047487319866992.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357886
ABSTRACT

[21] *Zhang CY, Ren XM, Li HB et al.* **Simvastatin alleviates inflammation and oxidative stress in rats with cerebral hemorrhage through Nrf2-ARE signaling pathway**. European review for medical and pharmacological sciences 2019; 23:6321-6329.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31364139
ABSTRACT
OBJECTIVE: To investigate the regulatory effects of simvastatin on the inflammation and oxidative stress in rats with cerebral hemorrhage through the nuclear factor E2-related factor 2-antioxidant response element (Nrf2-ARE) signaling pathway. MATERIALS AND METHODS: A total of 120 healthy male rats weighing 280-300 g and 7-8 weeks old were selected to establish the traumatic brain injury (TBI) model. Rats were divided into group A (trauma operation, n=30), group B (no treatment, n=30), group C (drug administration after trauma operation, n=30), and group D (no trauma operation, drug administration, n=30). Cerebral edema content in brain tissues was measured by calculating the dry and wet weight. Neurological dysfunction was scored using the Garcia method. Positive levels of the Toll-like receptor 4 (TLR4) and interleukin-1beta (IL-1beta) were qualitatively analyzed via immunohistochemistry. Protein levels of TLR4 and IL-1beta were quantitatively analyzed via Western blotting. Moreover, the brain injury volume and neuronal apoptosis were evaluated via Nissl staining and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining, respectively. At 48 h after injury, activities of superoxide dismutase (SOD), reduced glutathione (GSH), and oxidized glutathione (GSSG) in brain tissues were detected, and levels of malondialdehyde (MDA) and nitric oxide (NO) were detected using the enzyme activity assay kits. Finally, relative levels of the Nrf2-ARE signaling pathway and its downstream molecules heme oxygenase-1 (HO-1) and NAD (P)H dehydrogenase, quinone 1 (NQO1) were detected via reverse Transcription-Polymerase Chain Reaction (RT-PCR) and Western blotting. RESULTS: Compared with those in group B, cerebral edema content in brain tissues significantly increased ($p<0.05$), the neurological dysfunction score significantly declined ($p<0.05$), and protein levels of TLR4 and IL-1beta were significantly upregulated in group A ($p<0.05$). In group C, relative levels of TLR4 and IL-1beta were down-regulated, cerebral edema content decreased, and the neurological dysfunction score significantly increased ($p<0.05$). After 48 h, activities of SOD, reduced GSH and GSSG and levels of MDA and NO all increased, and levels of MDA and NO declined in group C ($p<0.05$). Western blotting and RT-PCR showed that simvastatin could increase the transcriptional level of Nrf2. After simvastatin intervention, expression levels of downstream molecules HO-1 and NQO1 were upregulated. CONCLUSIONS: Simvastatin alleviates TLR4-mediated inflammatory injury, promotes neurological recovery and resists oxidative stress through the Nrf2-ARE signaling pathway, thus exerting a neuroprotective effect in TBI.

[22] *Amirfakhryan H*. **Vaccination against atherosclerosis: An overview**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31352027
ABSTRACT
Atherosclerosis, an inflammatory disorder involving innate and adaptive immune responses both atheroprotective and proatherogenic, is a life wasting, and economic demanding disorder continuing to be the leading cause of morbidity and mortality worldwide. Thus the need for a long-lasting and highly effective treatment has made researchers to find new strategies. Many efforts conducted to reduce the burden of the disease have been toward the modification of cardiovascular risk factors up to now. Vaccination against atherosclerosis has being investigated as a promising strategy to overcome the disorder. Several kinds of vaccination methods have been investigated mostly in mice, showed promising results in attenuation of atherosclerosis, inflammation, and lipid concentration. Finding proper antigens and adjuvants are the most conflicting parts of this strategy. Some antigens have been utilized include OxLDL, apoB100, CETP, PCSK9, HSP60, MHC-II-derived peptides, and interleukins. DNA-based vaccination method has opened a new window in this field. There is an increasing necessity for developing an effective, low-price, long-lasting, accessible, and convenient vaccination method. There are gaps of evidence like the selection of proper human sampling to test the vaccines, rout of delivery, safety, strength, scheduling, and determining side effects that all must be considered in clinical trials in the future.

[23] *Mazza A, Schiavon L, Rigatelli G et al.* **The Effects of a New Generation of Nutraceutical Compounds on Lipid Profile and Glycaemia in Subjects with Pre-hypertension**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31352663
ABSTRACT
INTRODUCION: Treatment strategies for patients with pre-hypertension and low-moderate cardiovascular (CV) risk may include nutraceutical compounds (NCs). AIM: To investigate the efficacy and safety of a new-generation of NC in lowering BP values and improving metabolic profile, in a group of hyper-cholesterolemic subjects with pre-hypertension. METHODS: 131 subjects with pre-hypertension (systolic BP 130-139 mmHg and/or diastolic BP 85-89 mmHg) without organ damage and history of CV diseases were enrolled. 66 subjects were treated with a once-daily oral formulation of a NC (red yeast rice, Berberine, Coenzyme Q10, folic acid and chrome) added to diet for 3 months, while 65 patients followed a diet only. Differences in serum total cholesterol (TC), low- and high-density lipoprotein cholesterol (LDLC and HDLC), triglycerides (TG), glycemia, creatine phosphokinase (CPK), aspartate aminotransferase (AST) alanine aminotransferase (ALT) and body mass index (BMI) were evaluated. RESULTS: At the end of treatment, significant reductions of TC, LDLC, TG glucose levels were observed in both treatment groups, while HDLC values increased in the active treatment group only. A greater reduction of TC, LDLC and glycemia was observed in the treatment group. TG levels were not different within the two groups. BP and BMI levels remained unchanged, as well AST, ALT; CPK slightly increased in both groups, but it remained in the normal range. CONCLUSIONS: In patients with pre-hypertension, NC supplementation was safe, well tolerated and effective in

improving lipid pattern and glucose levels and in preventing the progression to overt hypertension.

[24] *Williams JW, Elvington A, Kessler S et al.* **B Cell-Mediated Antigen Presentation through MHC Class II Is Dispensable for Atherosclerosis Progression**. ImmunoHorizons 2019; 3:37-44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31356175
ABSTRACT
Depletion of B cells attenuates plaque development and modulates T cell responses in mouse models of atherosclerosis, suggesting that Ag presentation by B cells may promote disease progression. Thus, we set out to determine the role of B cell-mediated MHC class II (MHC II) Ag presentation during atherosclerotic plaque development. We developed murine conditional MHC II deletion and expression systems under control of the B cell-restricted CD19 promoter in an experimental model of atherosclerosis. Mice lacking MHC II expression only on B cells exhibited systemic shifts in germinal center and marginal zone B cell populations, leading to a reduced Ab response compared with littermate control animals. However, all populations were present and normal cholesterol uptake was detected in the plasma following high-fat diet treatment. In a second model, in which conditional expression of MHC II is limited only to B cells, showed similar overall cellularity characteristics compared with mice with complete MHC II deficiency. High-fat diet feeding showed no major changes in atherosclerotic plaque size or plaque cellular content in either conditional deletion or conditional expression approaches, compared with control animals. By testing the necessity and sufficiency of MHC II on B cells in the progression of atherosclerosis, we determine that MHC II on B cells does not directly regulate lesion development in murine models.

[25] *Duni A, Liakopoulos V, Roumeliotis S et al.* **Oxidative Stress in the Pathogenesis and Evolution of Chronic Kidney Disease: Untangling Ariadne's Thread**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31362427
ABSTRACT
Amplification of oxidative stress is present since the early stages of chronic kidney disease (CKD), holding a key position in the pathogenesis of renal failure. Induction of renal pro-oxidant enzymes with excess generation of reactive oxygen species (ROS) and accumulation of dityrosine-containing protein products produced during oxidative stress (advanced oxidation protein products-AOPPs) have been directly linked to podocyte damage, proteinuria, and the development of focal segmental glomerulosclerosis (FSGS) as well as tubulointerstitial fibrosis. Vascular oxidative stress is considered to play a critical role in CKD progression, and ROS are potential mediators of the impaired myogenic responses of afferent renal arterioles in CKD and impaired renal autoregulation. Both oxidative stress and inflammation are CKD hallmarks. Oxidative stress promotes inflammation via formation of proinflammatory oxidized lipids or AOPPs, whereas activation of nuclear factor kappaB transcription factor in the pro-oxidant milieu promotes the expression of proinflammatory cytokines and recruitment of proinflammatory cells. Accumulating evidence implicates oxidative stress in various clinical models of CKD, including diabetic nephropathy, IgA nephropathy, polycystic kidney disease as well as the cardiorenal syndrome. The scope of this review is to tackle the issue of oxidative

stress in CKD in a holistic manner so as to provide a future framework for potential interventions.

[26] *Hafidi ME, Buelna-Chontal M, Sanchez-Munoz F, Carbo R*. **Adipogenesis: A Necessary but Harmful Strategy**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357412
ABSTRACT
Obesity is considered to significantly increase the risk of the development of a vast range of metabolic diseases. However, adipogenesis is a complex physiological process, necessary to sequester lipids effectively to avoid lipotoxicity in other tissues, like the liver, heart, muscle, essential for maintaining metabolic homeostasis and has a crucial role as a component of the innate immune system, far beyond than only being an inert mass of energy storage. In pathophysiological conditions, adipogenesis promotes a pro-inflammatory state, angiogenesis and the release of adipokines, which become dangerous to health. It results in a hypoxic state, causing oxidative stress and the synthesis and release of harmful free fatty acids. In this review, we try to explain the mechanisms occurring at the breaking point, at which adipogenesis leads to an uncontrolled lipotoxicity. This review highlights the types of adipose tissue and their functions, their way of storing lipids until a critical point, which is associated with hypoxia, inflammation, insulin resistance as well as lipodystrophy and adipogenesis modulation by Kruppel-like factors and miRNAs.

[27] *Wang T, Fu X, Chen Q et al.* **Arachidonic Acid Metabolism and Kidney Inflammation**. International journal of molecular sciences 2019; 20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357612
ABSTRACT
As a major component of cell membrane lipids, Arachidonic acid (AA), being a major component of the cell membrane lipid content, is mainly metabolized by three kinds of enzymes: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) enzymes. Based on these three metabolic pathways, AA could be converted into various metabolites that trigger different inflammatory responses. In the kidney, prostaglandins (PG), thromboxane (Tx), leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs) are the major metabolites generated from AA. An increased level of prostaglandins (PGs), TxA2 and leukotriene B4 (LTB4) results in inflammatory damage to the kidney. Moreover, the LTB4-leukotriene B4 receptor 1 (BLT1) axis participates in the acute kidney injury via mediating the recruitment of renal neutrophils. In addition, AA can regulate renal ion transport through 19-hydroxystilbenetetraenoic acid (19-HETE) and 20-HETE, both of which are produced by cytochrome P450 monooxygenase. Epoxyeicosatrienoic acids (EETs) generated by the CYP450 enzyme also plays a paramount role in the kidney damage during the inflammation process. For example, 14 and 15-EET mitigated ischemia/reperfusion-caused renal tubular epithelial cell damage. Many drug candidates that target the AA metabolism pathways are being developed to treat kidney inflammation. These observations support an extraordinary interest in a wide range of studies on drug interventions aiming to control AA metabolism and kidney inflammation.

[28] *Shahu A, Herrin J, Dhruva SS et al.* **Disparities in Socioeconomic Context and Association With Blood Pressure Control and Cardiovascular Outcomes in ALLHAT**. Journal of the American Heart Association 2019; 8:e012277.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31362591
ABSTRACT
Background Observational studies demonstrate that communities of low socioeconomic status have higher blood pressure and worse cardiovascular outcomes. Yet, whether the clinical outcomes resulting from antihypertensive therapy vary by socioeconomic context in a randomized clinical trial, in which participants are treated under a standard protocol, is unknown. Methods and Results We used data from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) to study the effect of socioeconomic context, defined as the county-level median household income, of study sites. We stratified sites into income quintiles and compared characteristics, blood pressure control, and cardiovascular outcomes among ALLHAT participants in the lowest- and highest-income quintiles. Among 27 862 qualifying participants, 2169 (7.8%) received care in the lowest-income sites (quintile 1) and 10 458 (37.6%) received care in the highest-income sites (quintile 5). Participants in quintile 1 were more likely to be women, to be black, to be Hispanic, to have fewer years of education, to live in the South, and to have fewer cardiovascular risk factors. After adjusting for baseline demographic and clinical characteristics, quintile 1 participants were less likely to achieve blood pressure control (<140/90 mm Hg) (odds ratio, 0.48; 95% CI, 0.37-0.63) and had greater all-cause mortality (hazard ratio [HR], 1.25; 95% CI, 1.10-1.41), heart failure hospitalizations/mortality (HR, 1.26; 95% CI, 1.03-1.55), and end-stage renal disease (HR, 1.86; 95% CI, 1.26-2.73), but lower angina hospitalizations (HR, 0.70; 95% CI, 0.59-0.83) and coronary revascularizations (HR, 0.71; 95% CI, 0.57-0.89). Conclusions Despite standardized treatment protocols, ALLHAT participants in the lowest-income sites experienced poorer blood pressure control and worse outcomes for some adverse cardiovascular events, emphasizing the importance of measuring and addressing socioeconomic context. Clinical Trial Registration URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000542.

[29] *Lee SE, Villines TC, Chang HJ*. **Should CT replace IVUS for evaluation of CAD in large-scale clinical trials: Effects of medical therapy on atherosclerotic plaque**. Journal of cardiovascular computed tomography 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31351840
ABSTRACT
Clinical trials assessing the effect of medical therapies on atherosclerotic plaques have hitherto employed invasive imaging techniques such as intravascular ultrasound (IVUS). This has limited the study population to high-risk patients in whom invasive coronary angiography is indicated; moreover, IVUS typically is performed utilizing a target lesion-based analysis. Recently, comprehensive quantitative analysis of all atherosclerotic plaques in the complete coronary artery network has become possible through the use of coronary computed tomography angiography (CCTA). Excellent inter-observer and inter-scan reproducibility of CCTA has been reported. Several studies have already tested the applicability of CCTA-measured plaque volume changes as an imaging surrogate endpoint in clinical trials and have found positive results. Further, substantial evidence supports the use of CCTA as a novel imaging surrogate

that can accurately assess the changes in plaque characteristics according to medical treatment. In this review, we summarize current evidences that support the use of CCTA as a novel imaging surrogate that can replace IVUS in evaluating the results of treatment. We also attempt to determine whether the technological advances in CCTA will extend its application beyond use as a diagnostic method in clinical practice to use in large-scale clinical trials.

[30] *Hafiane A*. **Vulnerable Plaque, Characteristics, Detection, and Potential Therapies**. Journal of cardiovascular development and disease 2019; 6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357630
ABSTRACT
Plaque development and rupture are hallmarks of atherosclerotic vascular disease. Despite current therapeutic developments, there is an unmet necessity in the prevention of atherosclerotic vascular disease. It remains a challenge to determine at an early stage if atherosclerotic plaque will become unstable and vulnerable. The arrival of molecular imaging is receiving more attention, considering it allows for a better understanding of the biology of human plaque and vulnerabilities. Various plaque therapies with common goals have been tested in high-risk patients with cardiovascular disease. In this work, the process of plaque instability, along with current technologies for sensing and predicting high-risk plaques, is debated. Updates on potential novel therapeutic approaches are also summarized.

[31] *Bradley CK, Shrader P, Sanchez RJ et al.* **The patient journey with proprotein convertase subtilisin/kexin type 9 inhibitors in community practice**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31371271
ABSTRACT
BACKGROUND: Trials have demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are effective as an adjunct to statin therapy, but access and cost issues have limited their use in community practice. OBJECTIVE: The aim of the study was to better understand patients' experiences when trying to obtain, fill, and use PCSK9 inhibitor therapy in community practice. METHODS: We conducted a patient survey to evaluate patient experiences with PCSK9 inhibitors including medication initiation, indication for treatment, insurance approval status, medication persistence, and reason for discontinuation. The survey was emailed to 4740 adults who used a patient access support program. RESULTS: Overall, 1327 of 4740 adults completed the survey (28.0% response rate). Of those, 75.0% were aged >60 years, 52.8% were male, and 92.4% were White. At the time of PCSK9 inhibitor prescription, 70.2% were not on a statin (with 84.4% of those not on a statin reporting statin intolerance). Overall, 74.6% of patients found the drug approval process to be "somewhat" or "very" burdensome. Among n = 1216 patients who initiated treatment, 33.7% discontinued by the time of the survey, with 50.0% taking the drug for 1 to 6 months. Patient out-of-pocket costs were the leading reported reason for discontinuation. CONCLUSIONS: Most PCSK9 inhibitor users in community practice were not on a statin, presumably because of statin intolerance. The drug approval process and costs continue to be strong reasons for lower initiation of PCSK9 agents, as well as higher discontinuation rates.

[32] *Dixon DL, Virani SS*. **Mortality reduction with PCSK9 inhibition: A case of cautious optimism**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31371269
ABSTRACT

[33] *Pavanello C, Pirazzi C, Bjorkman K et al.* **Individuals with familial hypercholesterolemia and cardiovascular events have higher circulating Lp(a) levels**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31371270
ABSTRACT
BACKGROUND: Cardiovascular disease (CVD) is a major cause of mortality and morbidity. Increased low-density lipoprotein cholesterol (LDL-C) level is its major risk factor. Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated LDL-C since birth and subsequent premature CVD. There is a heterogeneity in the CVD onset in patients with FH. This is potentially due to the presence of other independent risk factors. Lipoprotein(a) [Lp(a)] is an LDL-like particle and represents a strong risk factor for CVD. OBJECTIVE: Our objective was to understand the contribution of Lp(a) in the susceptibility to CVD in individuals with genetic diagnosis of FH. METHODS: We measured Lp(a) levels in 2 independent and well-characterized genetic-FH cohorts: the FH-Gothenburg cohort (n = 190) and the FH-CEGP Milan cohort (n = 160). The genetic diagnosis was performed by targeted next-generation sequencing (FH-Gothenburg and part of the FH-CEGP Milan cohort), or by Sanger sequencing. RESULTS: We show that among individuals with genetic diagnosis of FH, those with previous CVD had higher Lp(a) levels. In addition, analyzing the response to the lipid-lowering therapies, we have also shown that statins had the same LDL-C-lowering effect irrespective of the type of FH-causative mutation. However, when we examined the lipid-lowering effect of proprotein convertase subtilisin/kexin type 9 inhibition by antibodies, we observed a trend in a better reduction of the LDL-C level in carriers of nonsense mutations. CONCLUSION: In conclusion, our results suggest that Lp(a) contributes to CVD onset in individuals with genetic diagnosis of FH. Our finding supports the importance to identify an efficacious therapy to lower Lp(a) in patients with FH to prevent CVD onset or recurrence.

[34] *Sandesara PB, Dhindsa D, Hirsh B et al.* **PCSK9 inhibition in patients with heart transplantation: A case series**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31353230
ABSTRACT
PCSK9 inhibitors are potent low-density lipoprotein cholesterol-lowering medications. There is a lack of data regarding safety and efficacy of PCSK9 inhibitors in cardiac transplant patients. In this case series, we provide data supporting the low-density lipoprotein-lowering efficacy and short-term safety of PCSK9 inhibitors in three cardiac transplant patients.

[35] *Nguyen MT, Fernando S, Schwarz N et al.* **Inflammation as a Therapeutic Target in Atherosclerosis**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357404
ABSTRACT

Atherosclerotic coronary artery disease (CAD) results from build-up of cholesterol-rich plaques in the walls of the coronary arteries and is a leading cause of death. Inflammation is central to atherosclerosis. Uncontrolled inflammation makes coronary plaques "unstable" and vulnerable to rupture or erosion, leading to thrombosis and myocardial infarction (MI). As multiple inflamed plaques often co-exist in the coronary system, patients are at risk of repeated atherothrombotic cardiovascular events after MI, with rates of 10-12% at one year and 18-20% at three years. This is largely because current therapies for CAD, such as lipid-lowering statins, do not adequately control plaque inflammation. New anti-atherosclerotic agents are therefore needed, especially those that better target inflammation. The recent positive results for the anti-interleukin-1-beta (IL-1beta) monoclonal antibody, Canakinumab, in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) clinical trial has provided a major stimulant to the field. It highlights that not only is inflammation important from a pathogenic and risk prediction perspective in CAD, but that reducing inflammation can be beneficial. The challenge is now to find the best strategies to achieve this in real-world practice. This review outlines the role that inflammation plays in atherosclerosis and provides an update on anti-inflammatory therapies currently being investigated to target atherosclerosis.

[36] *Tarraga WA, Garda HA, Toledo JD, Gonzalez MC*. **Potential Inhibitors of the Activity of the Cholesterol-Ester Transfer Protein**. Journal of computational biology : a journal of computational molecular cell biology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31356116
ABSTRACT
The cholesterol-ester transfer protein (CETP) exchanges lipids between high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs). The excessive transport of lipids from HDLs to LDLs mediated by this protein can cause an alteration in the deposition of lipoproteins onto the arterial walls, thus promoting the development of arteriosclerosis. Different CETP inhibitors have been tested in recent years, but none has been confirmed as being effectively palliative for the disease. We employed in silico databases and molecular docking as a computational method to predict how potential CETP inhibitors could interact with the active site of the CETP protein. Upon previously comparing two computer software packages to determine which generated a greater number of accurate CETP-inhibitor-complex structures, we chose the more appropriate program for our studies. We then abstracted a series of databases of known CETP inhibitors and noninhibitors exhibiting different 50% concentrations of CETP-inhibitory (INH) activity, to generate virtual structures for docking with different combinations of the CETP receptor. From this process, we obtained as the most suitable structure 4F2A_1OB_C_PCW-it accordingly having a greater area under the receiver operating characteristic curve. The molecular docking of known compounds in comparison with the respective conformation of this inhibitor enabled us to obtain DeltaGs (in kcal/mol) from which data we made a first exploration of unknown compounds for CETP-INH activity. Thus, the 4F2A_1OB_C_PCW structure was docked with DrugBank-Approved commercial compounds in an extensive database, whose status had already been established from pharmacokinetics and toxicology. In this study, we present a group of potential compounds as CETP-inhibitor candidates.

[37] *Sarkeshikian SS, Ghadir MR, Alemi F et al.* **Atorvastatin in combination with conventional antimicrobial treatment of Helicobacter pylori eradication: A randomized controlled clinical trial**. Journal of gastroenterology and hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31359499
ABSTRACT
INTRODUCTION: Helicobacter pylori is one of the main causes of digestive diseases, which is difficult to treat and requires the administration of several antimicrobial agents. Considering the anti-inflammatory and antibacterial effect of atorvastatin, the present study aimed at adding this agent to a four-drug regimen in order to eradicate H. pylori. MATERIALS AND METHODS: A total of 220 patients with H. pylori infection were included in the current randomized, controlled clinical trial. In the current study, 110 patients in the control group received a 14-day regimen of amoxicillin, clarithromycin, bismuth, and esomeprazole, and 110 patients in the intervention group received 40 mg of atorvastatin daily plus the antibiotic regimen for 14 weeks. The treatment results were evaluated one month later using H. pylori stool antigen test. Data were collected using checklist and analyzed using Chi-square and the Fisher exact tests with SPSS version 18. RESULTS: H. pylori eradication rate in the intervention and control groups were 78.18% and 65.45%, respectively (P = 0.025), and there was a significant difference in terms of NUD between the groups (P = 0.049), but there was no significant difference in age, gender, and body mass index between two groups (P <0.05). CONCLUSION: The present study results showed that adding atorvastatin to the four-drug regimen of omeprazole, clarithromycin, bismuth, and amoxicillin is effective in the eradication of H. pylori. Also, the addition of atorvastatin to H. pylori eradication therapy is more effective in patients with non-ulcer dyspepsia (NUD).

[38] *Yang S, Xia YP, Luo XY et al.* **Exosomal CagA derived from Helicobacter pylori-infected gastric epithelial cells induces macrophage foam cell formation and promotes atherosclerosis**. Journal of molecular and cellular cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31352044
ABSTRACT
BACKGROUND: Seroepidemiological studies have highlighted a positive relation between CagA-positive Helicobacter pylori (H. pylori), atherosclerosis and related clinic events. However, this link has not been well validated. The present study was designed to explore the role of H. pylori PMSS1 (a CagA-positive strain that can translocate CagA into host cells) and exosomal CagA in the progression of atherosclerosis. METHODS: To evaluate whether H. pylori accelerates or even induces atherosclerosis, H. pylori-infected C57/BL6 mice and ApoE(-/-) mice were maintained under different dietary conditions. To identify the role of H. pylori-infected gastric epithelial cells-derived exosomes (Hp-GES-EVs) and exosomal CagA in atherosclerosis, ApoE(-/-) mice were given intravenous or intraperitoneal injections of saline, GES-EVs, Hp-GES-EVs, and recombinant CagA protein (rCagA). FINDINGS: CagA-positive H. pylori PMSS1 infection does not induce but promotes macrophage-derived foam cell formation and augments atherosclerotic plaque growth and instability in two animal models. Meanwhile, circulating Hp-GES-EVs are taken up in aortic plaque, and CagA is secreted in Hp-GES-EVs. Furthermore, the CagA-containing EVs and rCagA exacerbates macrophage-derived foam cell formation and lesion development in vitro and in vivo, recapitulating the pro-atherogenic effects of CagA-positive H.

pylori. Mechanistically, CagA suppresses the transcription of cholesterol efflux transporters by downregulating the expression of transcriptional factors PPARgamma and LXRalpha and thus enhances foam cell formation. INTERPRETATION: These results may provide new insights into the role of exosomal CagA in the pathogenesis of CagA-positive H. pylori infection-related atherosclerosis. It is suggested that preventing and eradicating CagA-positive H. pylori infection could reduce the incidence of atherosclerosis and related events.

[39] *Wu W, Liu J, Li A et al.* **Effect of Intensive Blood Pressure Control on Carotid Morphology and Hemodynamics in Chinese Patients with Hyperhomocysteinemia-Type Hypertension and High Risk of Stroke**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:5717-5726.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31369520
ABSTRACT
BACKGROUND Different blood pressure targets should be formulated for different groups of people. This study aimed to assess the effectiveness of intensive blood control in improving the carotid morphology and hemodynamics in Chinese patients with hyperhomocysteinemia-type hypertension and high risk of stroke. MATERIAL AND METHODS Chinese hypertensive patients with high risk of stroke were randomized to intensive (n=187) and standard (n=192; controls) blood pressure management groups. Systolic blood pressure (SBP) targets were 100< SBP </=120 and 120< SBP </=140 mmHg, respectively. All patients received folic acid 0.8 mg/d and atorvastatin 20 mg/d. Calcium antagonist was first used. If blood pressure was still uncontrolled, angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, ss-receptor blocker, and diuretics were added successively. Follow-up was 12 months. Carotid features, hemodynamics, and adverse events were examined. RESULTS There were no differences in sex, age, body mass index, blood lipids, baseline carotid parameters, and histories of smoking, diabetes, statin use, and stroke between the 2 groups. Carotid plaques after 12 months of treatment were 19.4+/-2.1 and 23.6+/-3.1 cm(2) for the intensive and control groups, respectively (P=0.038). Plaque scores were lower in the intensive group (1.75+/-0.52 vs. 2.45+/-0.47, P=0.023). Compared with controls, intensive management resulted in relatively higher Vd and significantly lower Vs/Vd, PI, and RI (all P<0.05). Major adverse events such as hypotension (n=5 (2.7%) vs. 3 (1.6%), P=0.020) and dizziness (n=20 (10.7%) vs. 16 (8.3%), P=0.041) were more frequent in the intensive group. CONCLUSIONS Intensive blood pressure management could be beneficial for Chinese patients with hyperhomocysteinemia-type hypertension and high risk of stroke.

[40] *Shiraishi H, Yamada K, Oki E et al.* **Open-label clinical trial of bezafibrate treatment in patients with fatty acid oxidation disorders in Japan; 2nd report QOL survey**. Molecular genetics and metabolism reports 2019; 20:100496.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31372341
ABSTRACT
Introduction: Fatty acid oxidation disorders (FAODs) are rare diseases caused by a defective mitochondrial fatty acid oxidation (FAO) enzyme. We recently reported that bezafibrate improved patient quality of life (QOL) based on the SF-36 questionnaire score in patients with FAODs during a 50-week, open-label, clinical trial. Herein we conducted further survey

assessments of the trial patients to define the long-term efficacy and safety of bezafibrate. Materials and methods: This trial was an open-label, non-randomized, and multicenter study of bezafibrate treatment in five patients with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and one patient with carnitine palmitoyltransferase-II (CPT-2) deficiency (median age, 15.9years; range, 5.8-26.4years). The bezafibrate administration was continued for a further 102-174weeks after the 24-week treatment described in our previous study. QOL was quantitated using the 36-Item Short Form Health Survey (SF-36) questionnaire, which constitutes eight components: physical functioning (PF), role limitation due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems, and mental health. Results: PF was elevated in all patients and continued to rise during the study, with the total QOL scores increased from baseline in five of the six cases. In particular, three patients older than 20years showed treatment efficacy, and all subcategories of QOL were elevated in two of these cases. Conclusion: Our findings supported one of the stated benefits of bezafibrate in improving QOL for patients with FAODs.

[41] *Li Y, Pan Y, Wu X et al.* **Dual-modality imaging of atherosclerotic plaques using ultrasmall superparamagnetic iron oxide labeled with rhodamine**. Nanomedicine (Lond) 2019; 14:1935-1944.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31355711
ABSTRACT
Aim: The diagnosis of vulnerable atherosclerotic plaques remains challenging. This study labeled ultrasmall superparamagnetic iron oxide with rhodamine (USPIO-R) and evaluated USPIO-R for imaging atherosclerotic plaques. Methods: Apolipoprotein E-deficient mice were fed a high-fat diet and underwent MRI before and after an intravenous injection of USPIO-R. Subsequently, an aortic specimen from the mice was removed and sliced for fluorescence imaging and Prussian blue and immunofluorescent staining. Results: T2 signal loss appeared and persisted in the aortic plaque postinjection, and spontaneous fluorescence from the plaque was observed. The accumulated mechanism of USPIO-R by plaque was the macrophage internalization by Prussian blue and immunofluorescence. Conclusion: USPIO-R is a promising dual-modality probe for diagnosing and monitoring vulnerable atherosclerotic plaques.

[42] *Bettiga A, Fiorio F, Di Marco F et al.* **The Modern Western Diet Rich in Advanced Glycation End-Products (AGEs): An Overview of Its Impact on Obesity and Early Progression of Renal Pathology**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31366015
ABSTRACT
Advanced glycation end-products (AGEs) are an assorted group of molecules formed through covalent bonds between a reduced sugar and a free amino group of proteins, lipids, and nucleic acids. Glycation alters their structure and function, leading to impaired cell function. They can be originated by physiological processes, when not counterbalanced by detoxification mechanisms, or derive from exogenous sources such as food, cigarette smoke, and air pollution. Their accumulation increases inflammation and oxidative stress through the activation of various mechanisms mainly triggered by binding to their receptors (RAGE). So far, the pathogenic role of AGEs has been evidenced in inflammatory and chronic diseases such as

chronic kidney disease, cardiovascular disease, and diabetic nephropathy. This review focuses on the AGE-induced kidney damage, by describing the molecular players involved and investigating its link to the excess of body weight and visceral fat, hallmarks of obesity. Research regarding interventions to reduce AGE accumulation has been of great interest and a nutraceutical approach that would help fighting chronic diseases could be a very useful tool for patients' everyday lives.

[43] *Chen X, Liu Y, Zhou Y et al.* **Effect of simvastatin on fracture healing of type 2 diabetic rats**. Panminerva medica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31355609
ABSTRACT

[44] *Absi M, Eid BG, Ashton N et al.* **Simvastatin causes pulmonary artery relaxation by blocking smooth muscle ROCK and calcium channels: Evidence for an endothelium-independent mechanism**. PloS one 2019; 14:e0220473.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31369604
ABSTRACT
Simvastatin reduces pulmonary arterial pressure and right ventricular hypertrophy in animal models of pulmonary arterial hypertension (PAH) and is thought to restore endothelial dysfunction. In vivo effects of drugs are complicated by several factors and little is known of the direct effects of statins on pulmonary arteries. This study investigated the direct effects of simvastatin on pulmonary arteries isolated from rats with or without monocrotaline-induced PAH. Simvastatin suppressed contractions evoked by the thromboxane A2 receptor agonist U46619 (30 nM), the alpha1-adrenergic agonist phenylephrine (5 muM) and KCl (50 mM) by ~50% in healthy and diseased arteries, but did not reduce contraction evoked by sarco/endoplasmic reticulum ATPase blockers. It relaxed hypertensive arteries in the absence of stimulation. Removing the endothelium or inhibiting eNOS did not prevent the inhibition by simvastatin. Inhibiting RhoA/rho kinase (ROCK) with Y27632 (10 muM) suppressed contractions to U46619 and phenylephrine by ~80% and prevented their inhibition by simvastatin. Y27632 reduced KCl-induced contraction by ~30%, but did not prevent simvastatin inhibition. Simvastatin suppressed Ca2+ entry into smooth muscle cells, as detected by Mn2+ quench of fura-2 fluorescence. The calcium antagonist, nifedipine (1 muM), almost abolished K+-induced contraction with less effect against U46619 and phenylephrine. We conclude that simvastatin relaxes pulmonary arteries by acting on smooth muscle to interfere with signalling through G-protein coupled receptors and voltage-dependent Ca2+ entry. Its actions likely include inhibition of ROCK-dependent Ca2+ sensitisation and voltage-gated Ca2+ channels. These are likely to contribute to the beneficial effects of simvastatin in animal models of PAH.

[45] *Schuster S, Rubil S, Endres M et al.* **Anti-PCSK9 antibodies inhibit pro-atherogenic mechanisms in APOE*3Leiden.CETP mice**. Scientific reports 2019; 9:11079.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31366894
ABSTRACT
LDL-cholesterol (LDL-C) is a causal pathogenic factor in atherosclerosis. Monoclonal anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) neutralizing antibodies are novel potent

LDL-lowering drugs which reduce cardiovascular events. To characterize their effect on atherogenesis, APOE*3Leiden.CETP mice were fed a high cholesterol/high fat diet (WTD) or normal chow (NC) for 18 weeks. Mice on WTD were injected with the human anti-PCSK9 antibody mAb1 (PL-45134, 10 mg*kg(-1) s.c.) or 0.9% saline every 10 days. PCSK9 inhibition decreased total cholesterol in serum of APOE*3Leiden.CETP mice and prevented the development of atherosclerosis. The plaque area in the aortic root was reduced by half and macrophage infiltration determined by Ly6c and Mac-3 staining was ameliorated. PCSK9 inhibition decreased markers of inflammation in mononuclear cells (Il-6, Tnfa mRNA), and in serum (CXCL-1,-10,-13; complement factor C5a) compared to control WTD fed animals. The number of circulating Sca-1/VEGF-R2 positive endothelial progenitor cells of the peripheral blood and spleen-derived diLDL/lectin double positive circulating angiogenic cells was increased. To conclude, the PCSK9-mediated anti-atherosclerotic effect involves the upregulation of pro-regeneratory endothelial progenitor cells, a reduction of inflammation and change of plaque composition.

[46] *Caron J, Pene V, Tolosa L et al.* **Low-density lipoprotein receptor-deficient hepatocytes differentiated from induced pluripotent stem cells allow familial hypercholesterolemia modeling, CRISPR/Cas-mediated genetic correction, and productive hepatitis C virus infection**. Stem cell research & therapy 2019; 10:221.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31358055
ABSTRACT
BACKGROUND: Familial hypercholesterolemia type IIA (FH) is due to mutations in the low-density lipoprotein receptor (LDLR) resulting in elevated levels of low-density lipoprotein cholesterol (LDL-c) in plasma and in premature cardiovascular diseases. As hepatocytes are the only cells capable of metabolizing cholesterol, they are therefore the target cells for cell/gene therapy approaches in the treatment of lipid metabolism disorders. Furthermore, the LDLR has been reported to be involved in hepatitis C virus (HCV) entry into hepatocytes; however, its role in the virus infection cycle is still disputed. METHODS: We generated induced pluripotent stem cells (iPSCs) from a homozygous LDLR-null FH-patient (FH-iPSCs). We constructed a correction cassette bearing LDLR cDNA under the control of human hepatic apolipoprotein A2 promoter that targets the adeno-associated virus integration site AAVS1. We differentiated both FH-iPSCs and corrected FH-iPSCs (corr-FH-iPSCs) into hepatocytes to study statin-mediated regulation of genes involved in cholesterol metabolism. Upon HCV particle inoculation, viral replication and production were quantified in these cells. RESULTS: We showed that FH-iPSCs displayed the disease phenotype. Using homologous recombination mediated by the CRISPR/Cas9 system, FH-iPSCs were genetically corrected by the targeted integration of a correction cassette at the AAVS1 locus. Both FH-iPSCs and corr-FH-iPSCs were then differentiated into functional polarized hepatocytes using a stepwise differentiation approach (FH-iHeps and corr-FH-iHeps). The correct insertion and expression of the correction cassette resulted in restoration of LDLR expression and function (LDL-c uptake) in corr-FH-iHeps. We next demonstrated that pravastatin treatment increased the expression of genes involved in cholesterol metabolism in both cell models. Moreover, LDLR expression and function were also enhanced in corr-FH-iHeps after pravastatin treatment. Finally, we demonstrated that both FH-iHeps and corr-FH-iHeps were as permissive to viral infection as primary human hepatocytes but that virus production in

FH-iHeps was significantly decreased compared to corr-FH-iHeps, suggesting a role of the LDLR in HCV morphogenesis. CONCLUSIONS: Our work provides the first LDLR-null FH cell model and its corrected counterpart to study the regulation of cholesterol metabolism and host determinants of HCV life cycle, and a platform to screen drugs for treating dyslipidemia and HCV infection.

[47] *Yan Y, Lv X, Ma J et al.* **Simvastatin Alleviates Intestinal Ischemia/Reperfusion Injury by Modulating Omi/HtrA2 Signaling Pathways**. Transplantation proceedings 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31351770
ABSTRACT
PURPOSE: The objective of this research was to survey the therapeutic action of simvastatin (Sim) on intestinal ischemia/reperfusion injury (II/RI) by modulating Omi/HtrA2 signaling pathways. METHODS: Sprague Dawley rats were pretreated with 40 mg/kg Sim and then subjected to 1 hour of ischemia and 3 hours of reperfusion. The blood and intestinal tissues were collected, pathologic injury was observed, the contents of serum tumor necrosis factor-alpha and interleukin-6 (IL-6) were estimated, and superoxide dismutase, methane dicarboxylic aldehyde, and cysteinyl aspartate specific proteinase-3 (caspase-3) levels, as well as the expressions of Omi/HtrA2 and caspase-3, were measured in the intestinal tissues. RESULTS: Sim preconditioning mitigated the damnification of intestinal tissues by decreasing oxidative stress, inflammatory damage, and apoptosis and downregulating the expression of Omi/HtrA2 compared to the ischemia/reperfusion group, while Sim+Ucf-101 significantly augmented this effect. CONCLUSION: These results suggest that Sim may alleviate intestinal ischemia/reperfusion injury by modulating Omi/HtrA2 signaling pathways.

[48] *Chen YH, Zhan Z, Hu P et al.* **[A new attempt with lipoprotein lipase agonists in the treatment of nonalcoholic steatohepatitis]**. Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese journal of hepatology 2019; 27:533-540.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31357780
ABSTRACT
Objective: To analyze non-alcoholic steatohepatitis (NASH)-related differentially expressed genes (DEGs) by bioinformatics methods to find key pathways and potential therapeutic targets for NASH. Methods: GSE61260 chip was downloaded from the public microarray database and liver biopsy samples from 24 NASH cases and 38 healthy controls were included. The Limma software package in R language was used to screen DEGs under the condition of difference multiple > 1.5 and adj. P < 0.05. The clusterProfiler software package was used for GO analysis and KEGG analysis. The STRING online database was used for protein-protein interaction analysis, and the L1000 and DrugBank databases were used for drug prediction. Results: Compared with healthy control group, 857 DEGs were screened out in NASH group including 167 up-regulated genes and 690 down-regulated genes. GO analysis showed that DEGs were mainly involved in inflammation and cholesterol metabolism. KEGG analysis showed that DEGs were mainly enriched in PPAR, non-alcoholic fatty liver disease, oxidative phosphorylation and other signaling pathways. Among them, eight genes of ACSL4, CYP7A1, FABP4, FABP5, lipoprotein lipase, ME1, OLR1 and PLIN1 were enriched in PPAR signaling pathway, and 165 interaction nodes were formed with 47 DEGs-encoded proteins. Lipoprotein lipase interacted

with 21 DEGs, and its up-regulated expression had improved lipid metabolism, insulin resistance and anti-inflammatory effects. Four drugs (gemfibrozil, bezafibrate, omega-3 carboxylic acid and glycyrrhizic acid) were screened by L1000 and DrugBank to activate lipoprotein lipase. Presently, these four drugs are clinically used to treat hypertriglyceridemia or to improve inflammation. In this regard, we speculated that the pharmacological effects of these four drugs had improved NASH by activating lipoprotein lipase to promote liver lipid metabolism and alleviate inflammation. Conclusion: PPAR signaling pathway is closely associated to the occurrence and development of NASH, and thereby lipoprotein lipase agonist is a new attempt to treat NASH.