[1] *Jin L, Deng Z, Bai Y, Ye P*. **Functions of Monocytes and Macrophages and the Associated Effective Molecules and Mechanisms at the Early Stage of Atherosclerosis**. Acta Cardiologica Sinica 2021; 37:522-533.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34584385

ABSTRACT
OBJECTIVE: This study aimed to explore the functions and possible underlying regulatory molecules and mechanisms of monocytes and macrophages under early atherosclerotic conditions. METHODS: THP-1-derived monocytes or macrophages were induced by 50 μg/ml oxidized low density lipoprotein (ox-LDL) for 24 hours, and the degree of lipid metabolism and inflammation were determined. In addition, we identified differentially expressed genes, noncoding ribonucleic acids (RNAs), pathways and mechanisms by RNA sequencing, and performed further correlation analysis and molecular expression verification. RESULTS: Monocytes could not form foam cells with oil red O staining directly and had low levels of lipids as determined by total cholesterol and triglycerides assays, cholesterol uptake molecules CD36, the class A macrophage scavenger receptor and lectin-like oxidized low-density lipoprotein receptor-1 and cholesterol efflux molecules ATP binding cassette transporter A1, ATP binding cassette transporter G1 and liver X receptor α, and inflammatory factors, which were markedly different from those in macrophages. Additionally, sequencing data showed obviously differentially expressed genes, microRNAs and long noncoding RNAs in the atherosclerotic group. We identified 15 upregulated and downregulated genes, and 10 biological processes and pathways involved in atherosclerosis. Specifically, fatty acid desaturase 2 and apolipoprotein A1 in the peroxisome proliferator-activated receptor signaling pathway were differentially expressed in stimulated macrophages, whereas no changes were observed in the monocyte groups. Furthermore, correlation analysis showed differential expressed lncRNAs targeting miRNAs and mRNAs, and 24 competing endogenous RNA (ceRNA) networks of long noncoding RNA-microRNA-messenger RNA in early oxidative macrophages. CONCLUSIONS: Monocytes did not directly participate in lipid metabolism before differentiation into macrophages at the early stage in vitro. Furthermore, noncoding RNAs and ceRNA networks might play important roles in regulating the lipid metabolism of macrophages at the early stage of atherosclerosis.

[2] *Vural Keskinler M, Bozkurt I, Telci Caklili O et al.* **COMPARISON OF REAL WORLD LIPID PROFILE OF PATIENTS WITH TYPE 2 DIABETES AND GUIDELINE RECOMMENDATIONS**. Acta clinica Croatica 2021; 60:63-67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34588723

ABSTRACT
Diabetes is a major risk factor for cardiovascular disease. Despite recommendations and available therapeutic options, patients with diabetes do not always reach the recommended lipid levels. In this study, our aim was to compare the real world lipid profile of type 2 diabetes patients with guideline recommendations for dyslipidemia. Four hundred and sixty eight consecutive patients referred to Outpatient Diabetes Clinic of Istanbul Medeniyet University were recruited. Patient anthropometric measurements (height, weight, waist circumference), biochemical test results (LDL cholesterol (LDL-c), triglycerides, HDL cholesterol, HbA1c) and treatment modalities were recorded. Patients were stratified into cardiovascular risk categories according to the risk factors and their treatment dose was compared to the recommendations. Among 468 patients, 56 (12%) patients had coronary heart disease (CHD). Thirty-four percent of these patients were not on statin treatment (n=19) and their

mean LDL-c level was 114±29 mg/dL (2.9±0.75 mmol/L). Nineteen percent of these patients were on high intensity statin treatment (atorvastatin 40-80 mg, rosuvastatin 20 mg). Only four patients with CHD had LDL-c levels <70 mg/dL (1.8 mmol/L). Four hundred and twelve patients had no CHD. In these patients, the mean LDL-c level was 132±38 mg/dL (3.4±0.9 mmol/L). Eighty (19%) patients had LDL-c level lower than 100 mg/dL (2.5 mmol/L). Overall 82% (n=384) of the cohort had not achieved treatment goal. In conclusion, a more pronounced approach for statin treatment is needed in diabetes patients for both primary and secondary prevention of cardiovascular diseases.

[3] *Baumer Y, McCurdy SG, Boisvert WA*. **Formation and Cellular Impact of Cholesterol Crystals in Health and Disease**. Adv Biol (Weinh) 2021; 5:e2100638.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34590446

ABSTRACT

Cholesterol crystals (CCs) were first discovered in atherosclerotic plaque tissue in the early 1900 and have since been observed and implicated in many diseases and conditions, including myocardial infarction, abdominal aortic aneurism, kidney disease, ocular diseases, and even central nervous system anomalies. Despite the widespread involvement of CCs in many pathologies, the mechanisms involved in their formation and their role in various diseases are still not fully understood. Current knowledge concerning the formation of CCs, as well as the molecular pathways activated upon cellular exposure to CCs, will be explored in this review. As CC formation is tightly associated with lipid metabolism, the role of cellular lipid homeostasis in the formation of CCs is highlighted, including the role of lysosomes. In addition, cellular pathways and processes known to be affected by CCs are described. In particular, CC-induced activation of the inflammasome and production of reactive oxygen species, along with the role of CCs in complement-mediated inflammation is discussed. Moreover, the clinical manifestation of embolized CCs is described with a focus on renal and skin diseases associated with CC embolism. Lastly, potential therapeutic measures that target either the formation of CCs or their impact on different cell types and tissues are highlighted.

[4] *Sorda JA, González Ballerga E, Barreyro FJ et al.* **Bezafibrate therapy in primary biliary cholangitis refractory to ursodeoxycholic acid: a longitudinal study of paired liver biopsies at 5 years of follow up**. Alimentary pharmacology & therapeutics 2021; 54:1202-1212.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587309

ABSTRACT

BACKGROUND: Ursodeoxycholic acid (UDCA) is the first-line therapy for primary biliary cholangitis (PBC). However, nearly 40% of patients have an incomplete response to UDCA. The addition of bezafibrate has shown biochemical benefit in this group of patients. AIM: To evaluate the long-term effects of UDCA in combination with bezafibrate on histological outcomes in patients with UDCA-refractory PBC. METHODS: Fifty-nine patients refractory to UDCA were included. Clinical parameters were monitored and paired liver biopsy (PLB) was performed after 5 years of follow-up. RESULTS: Of the total cohort, 49 subjects were analysed and 31 had PLB at 5 years. Values for serum ALP, AST, ALT and GGT significantly improved with UDCA-bezafibrate. This beneficial effect was observed at 12 months where 86% achieved ALP at normal levels. Analyses of PLB showed a significant decrease in liver damage as reflected by Ludwig (baseline 2.29 ± 1.2, to 1.84 ± 1 at year 5, P = 0.0242) and Ishak (baseline 6.19 ± 2.2 to 4.77 ± 2.2 at year 5, P = 0.0008) scores. Overall, regression of fibrosis was attained in 48% of patients. Furthermore, we observed a significant

reduction in the proportion with cirrhosis from 19% at baseline to 3% at 5 years ($P < 0.001$). These beneficial effects were associated with better predictive risk scores using the GLOBE and UK-PBC prognosis models. CONCLUSIONS: Adding bezafibrate to UDCA in patients with UDCA-refractory PBC showed a significant decrease in fibrosis and inflammatory histological scores at 5 years. These beneficial effects warrant further evaluation in long-term cohort studies and controlled trials.

[5] *Yin Y, Fang C, Jiang S et al.* **In vivo evidence of atherosclerotic plaque erosion and healing in patients with acute coronary syndrome using serial optical coherence tomography imaging**. American heart journal 2022; 243:66-76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34582778
ABSTRACT
BACKGROUND: The EROSION study (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography-Based Management in Plaque Erosion) allowed us to observe the healing process of coronary plaque erosion in vivo. The present study aimed to investigate the incidence of newly formed healed plaque and different baseline characteristics of acute coronary syndrome (ACS) patients caused by plaque erosion with or without newly formed healed plaque using optical coherence tomography (OCT). METHODS: A total of 137 ACS patients with culprit plaque erosion who underwent pre-intervention OCT imaging and received no stent implantation were enrolled. Patients were stratified according to the presence or absence of newly formed healed phenotype at 1-month (137 patients) or 1-year OCT follow-up (52 patients). Patient's baseline clinical, angiographic, OCT characteristics and outcomes were compared. RESULTS: There were 55.5% (76/137) of patients developed healed plaque at 1 month, and 69.2% (36/52) of patients developed healed plaque at 1 year. Patients with newly formed healed plaque had larger thrombus burden, and lower degree of area stenosis (AS%) at baseline than those without, and thrombus burden and AS% were predictors of plaque healing. The healing process was accompanied by the significant increase of AS% and incidence of microchannels, and greater inflammatory response. The outcomes appeared to be similar between the two groups. CONCLUSIONS: Newly formed healed plaque was found in more than half of ACS patients with plaque erosion without stenting. Patients with newly formed healed plaque had lower luminal stenosis and larger thrombus burden. During healing process, luminal stenosis increased gradually.

[6] *Slade JM, Abela GS, Rozman M et al.* **The impact of statin therapy and aerobic exercise training on skeletal muscle and whole-body aerobic capacity**. Am Heart J Plus 2021; 5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34590057
ABSTRACT
BACKGROUND: Statin use is widely recognized for improving cardiovascular health, but questions remain on how statin use influences skeletal muscle, particularly mitochondrial function. STUDY OBJECTIVE DESIGN AND PARTICIPANTS: The influence of statin therapy and exercise (EX) on aerobic capacity was determined. In Study1, skeletal muscle aerobic capacity was measured before and after 80 mg atorvastatin therapy. In Study2, aerobic capacity (skeletal muscle and whole body) was measured before and after a 12-week exercise randomized control trial in older adults (age = 67 ± 5 yrs.), a subset of which were on chronic low-moderate intensity statin therapy. MAIN OUTCOME MEASURES: Muscle oxidative capacity was determined from the phosphocreatine recovery rate constant (kPCr) using (31)P Magnetic Resonance Spectroscopy. Whole body peak oxygen uptake

(VO(2) peak) was measured during a graded exercise test with indirect calorimetry. RESULTS: High dose statin therapy resulted in a 12% reduction in muscle oxidative capacity (pre = 1.34 ± 0.34 min(-1), post = 1.17 ± 0.25 min(-1), p = 0.004). Similarly, chronic low-moderate dose statin therapy was associated with lower muscle oxidative capacity at baseline (1.50 ± 0.35 min(-1)) compared to non-statin users (1.88 ± 0.047 min(-1), p = 0.019). Following EX, muscle oxidative capacity increased by 35-40% (statin: Pre: 1.39 ± 0.44 vs. Post: 1.88 ± 0.47 min(-1), no statin Pre: 1.86 ± 0.58 vs. Post: 2.58 ± 0.85 min(-1)) compared to control groups (Pre: 1.74 ± 0.27 vs Post: 1.75 ± 0.49 min(-1), p = 0.001). VO(2) peak increased by 11% for EX groups (Pre: 18.8 ± 2.8 vs. Post: 20.8 ± 3.0 ml·kg(-1)·min(-1)) following training compared to a small decline in controls (Pre: 21.8 ± 3.7 vs. Post: 20.8 ± 3.04 ml·kg(-1)·min(-1), p = 0.001). CONCLUSIONS: Statin therapy resulted in reduced muscle oxidative capacity. Aerobic exercise improved skeletal muscle oxidative capacity and whole-body aerobic capacity during statin therapy.

[7] *O'Keefe EL, Sturgess JE, O'Keefe JH et al.* **Prevention and Treatment of Atrial Fibrillation via Risk Factor Modification**. The American journal of cardiology 2021; 160:46-52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34583808

ABSTRACT

Atrial fibrillation (AF) is the most common clinically significant arrhythmia, and it increases stroke risk. A preventive approach to AF is needed because virtually all treatments such as cardioversion, antiarrhythmic drugs, ablation, and anticoagulation are associated with high cost and carry significant risk. A systematic review was performed to identify effective lifestyle-based strategies for reducing primary and secondary AF. A PubMed search was performed using articles up to March 1, 2021. Search terms included atrial fibrillation, atrial flutter, exercise, diet, metabolic syndrome, type 2 diabetes mellitus, obesity, hypertension, stress, tobacco smoking, alcohol, Mediterranean diet, sodium, and omega-3 fatty acids. Additional articles were identified from the bibliographies of retrieved articles. The control of hypertension, ideally with a renin-angiotensin-aldosterone system inhibitor, is effective for preventing primary AF and recurrence. Obstructive sleep apnea is a common cause of AF, and treating it effectively reduces AF episodes. Alcohol increases the risk of AF in a dose-dependent manner, and abstinence reduces risk of recurrence. Sedentary behavior and chronic high-intensity endurance exercise are both risk factors for AF; however, moderate physical activity is associated with lower risk of AF. Recently, sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists have been associated with reduced risk of AF. Among overweight/obese patients, weight loss of ≥10% is associated with reduced AF risk. Lifestyle changes and risk factor modification are highly effective for preventing AF.

[8] *Ebbeling CB, Knapp A, Johnson A et al.* **Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia-a randomized controlled feeding trial**. The American journal of clinical nutrition 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34582545

ABSTRACT

BACKGROUND: Carbohydrate restriction shows promise for diabetes, but concerns regarding high saturated fat content of low-carbohydrate diets limit widespread adoption. OBJECTIVES: This preplanned ancillary study aimed to determine how diets varying widely in carbohydrate and saturated fat affect cardiovascular disease (CVD) risk factors during weight-loss maintenance.

METHODS: After 10-14% weight loss on a run-in diet, 164 participants (70% female; BMI = 32.4 ± 4.8 kg/m2) were randomly assigned to 3 weight-loss maintenance diets for 20 wk. The prepared diets contained 20% protein and differed 3-fold in carbohydrate (Carb) and saturated fat as a proportion of energy (Low-Carb: 20% carbohydrate, 21% saturated fat; Moderate-Carb: 40%, 14%; High-Carb: 60%, 7%). Fasting plasma samples were collected prerandomization and at 20 wk. Lipoprotein insulin resistance (LPIR) score was calculated from triglyceride-rich, high-density, and low-density lipoprotein particle (TRL-P, HDL-P, LDL-P) sizes and subfraction concentrations (large/very large TRL-P, large HDL-P, small LDL-P). Other outcomes included lipoprotein(a), triglycerides, HDL cholesterol, LDL cholesterol, adiponectin, and inflammatory markers. Repeated measures ANOVA was used for intention-to-treat analysis. RESULTS: Retention was 90%. Mean change in LPIR (scale 0-100) differed by diet in a dose-dependent fashion: Low-Carb (-5.3; 95% CI: -9.2, -1.5), Moderate-Carb (-0.02; 95% CI: -4.1, 4.1), High-Carb (3.6; 95% CI: -0.6, 7.7), P = 0.009. Low-Carb also favorably affected lipoprotein(a) [-14.7% (95% CI: -19.5, -9.5), -2.1 (95% CI: -8.2, 4.3), and 0.2 (95% CI: -6.0, 6.8), respectively; P = 0.0005], triglycerides, HDL cholesterol, large/very large TRL-P, large HDL-P, and adiponectin. LDL cholesterol, LDL-P, and inflammatory markers did not differ by diet. CONCLUSIONS: A low-carbohydrate diet, high in saturated fat, improved insulin-resistant dyslipoproteinemia and lipoprotein(a), without adverse effect on LDL cholesterol. Carbohydrate restriction might lower CVD risk independently of body weight, a possibility that warrants study in major multicentered trials powered on hard outcomes.

[9] *Sanllorente A, Soria-Florido MT, Castañer O et al.* **A lifestyle intervention with an energy-restricted Mediterranean diet and physical activity enhances HDL function: a substudy of the PREDIMED-Plus randomized controlled trial**. The American journal of clinical nutrition 2021; 114:1666-1674.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34582548
ABSTRACT
BACKGROUND: Consumption of a Mediterranean diet, adequate levels of physical activity, and energy-restricted lifestyle interventions have been individually associated with improvements in HDL functions. Evidence of intensive interventions with calorie restriction and physical activity is, however, scarce. OBJECTIVES: To determine whether an intensive lifestyle intervention with an energy-restricted Mediterranean diet plus physical activity enhanced HDL function compared to a non-hypocaloric Mediterranean eating pattern without physical activity. METHODS: In 391 older adults with metabolic syndrome (mean age, 65 years; mean BMI, 33.3 kg/m2) from 1 of the Prevención con Dieta Mediterránea-Plus trial centers, we evaluated the impact of a 6-month intervention with an energy-restricted Mediterranean diet plus physical activity (intensive lifestyle; n = 190) relative to a nonrestrictive Mediterranean diet without physical activity (control; n = 201) on a set of HDL functional traits. These included cholesterol efflux capacity, HDL oxidative/inflammatory index, HDL oxidation, and levels of complement component 3, serum amyloid A, sphingosine-1-phosphate, triglycerides, and apolipoproteins A-I, A-IV, C-III, and E in apoB-depleted plasma. RESULTS: The intensive-lifestyle intervention participants displayed greater 6-month weight reductions (-3.83 kg; 95% CI: -4.57 to -3.09 kg) but no changes in HDL cholesterol compared with control-diet participants. Regarding HDL functional traits, the intensive lifestyle decreased triglyceride levels (-0.15 mg/g protein; 95% CI: -0.29 to -0.014 mg/g protein) and apoC-III (-0.11 mg/g protein; 95% CI: -0.18 to -0.026 mg/g protein) compared to the control diet, with weight loss being the essential mediator

(proportions of mediation were 77.4% and 72.1% for triglycerides and apoC-III levels in HDL, respectively). CONCLUSIONS: In older adults with metabolic syndrome, an energy-restricted Mediterranean diet plus physical activity improved the HDL triglyceride metabolism compared with a nonrestrictive Mediterranean diet without physical activity. This trial is registered at isrctn.com as ISRCTN89898870.

[10] *Ismail ZH, Asnake ZT, Salabei JK*. **Effects of Anticoagulation on Low-Density Lipoprotein-Cholesterol and Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation**. The American journal of medicine 2021; 134:e533.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34593209
ABSTRACT

[11] *Levin MG*. **Circulating Lipids and COVID-19: Insights From Mendelian Randomization**. Arteriosclerosis, thrombosis, and vascular biology 2021; 41:2811-2813.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587759
ABSTRACT

[12] *Lu C, Weng R, Wu W et al.* **Moderate alcohol consumption and carotid intima-media thickness in type 2 diabetes**. Asia Pacific journal of clinical nutrition 2021; 30:497-503.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587709
ABSTRACT
BACKGROUND AND OBJECTIVES: Carotid intima-media thickness (IMT) is a risk predictor for myocardial infarction and stroke. Patients with type 2 diabetes mellitus are at higher risk for such conditions. The association of alcohol consumption with IMT is still controversial. METHODS AND STUDY DESIGN: We undertook a cross-sectional study of patients hospitalized in the Department of Endocrinology at Zhoushan Hospital from January 1st, 2013 to December 31st, 2015. Patients with a past medical history of cerebrovascular events, acute myocardial ischemia or unable to provide a detailed alcohol consumption history were excluded. Carotid IMT, together with blood biochemical examinations were collected. Data were analyzed using least significant difference t test, Tamhane's T2 test, Levene test, $\chi 2$-test and binary logistic regression model. RESULTS: 281 patients were enrolled in the study. The number of patients with elevated carotid IMT in moderate alcohol consumers was apparently less than alcohol non/heavy-consumers. In addition, the number of participants with elevated carotid IMT in liqueur consumers was higher than alcohol non-consumers and rice wine/beer consumers. Systolic blood pressure, C-reactive protein, glycosylated hemoglobin, low density lipoprotein cholesterol, triglyceride, gamma glutamyl transpeptidase, uric acid, cholesterol and creatinine levels were higher in elevated IMT patients, while high density lipoprotein cholesterol level was levels were significantly lower (p value<0.05). CONCLUSIONS: Moderate alcohol consumption has a protective effect on atherosclerosis in patients with type 2 diabetes mellitus, requiring consideration to dietary intake and physical activity, among other influences. Inflammation theory and lipid metabolism could be involved in such prophylaxis effects.

[13] *Fiorentino R, Chiarelli F*. **Treatment of Dyslipidaemia in Children**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34572264
ABSTRACT

Childhood dyslipidaemia is one of the main traditional cardiovascular risk factors that initiate and exacerbate the atherosclerotic process. Healthcare providers may play a key role in the management of children with lipid abnormalities; however, they have to properly evaluate the normal lipid values and know the available treatment options in children and adolescents. Current guidelines recommend healthy behaviours as the first-line treatment for childhood dyslipidaemia. The therapeutic lifestyle changes should focus on dietary modifications, daily physical activity, reduction in body weight and tobacco smoking cessation. Parents play a key role in promoting their children's healthy habits. In children with more severe forms of lipid abnormalities and in those who do not benefit from healthy behaviours, pharmacological therapy should be considered. Safe and effective medications are already available for children and adolescents. Statins represent the first-line pharmacological option, while ezetimibe and bile acid sequestrants are usually used as second-line drugs. Despite their limited use in children, other lipid-lowering agents (already approved for adults) are currently available or under study for certain categories of paediatric patients (e.g., familial hypercholesterolemia). Further studies are needed to evaluate the long-term efficacy, safety and tolerability of novel lipid-lowering drugs, especially in children.

[14] *Korneva VA, Kuznetsova TY, Julius U*. **Modern Approaches to Lower Lipoprotein(a) Concentrations and Consequences for Cardiovascular Diseases**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34572458

ABSTRACT

Lipoprotein(a) (Lp(a)) is a low density lipoprotein particle that is associated with poor cardiovascular prognosis due to pro-atherogenic, pro-thrombotic, pro-inflammatory and pro-oxidative properties. Traditional lipid-lowering therapy does not provide a sufficient Lp(a) reduction. For PCSK9 inhibitors a small reduction of Lp(a) levels could be shown, which was associated with a reduction in cardiovascular events, independently of the effect on LDL cholesterol. Another option is inclisiran, for which no outcome data are available yet. Lipoprotein apheresis acutely and in the long run decreases Lp(a) levels and effectively improves cardiovascular prognosis in high-risk patients who cannot be satisfactorily treated with drugs. New drugs inhibiting the synthesis of apolipoprotein(a) (an antisense oligonucleotide (Pelacarsen) and two siRNA drugs) are studied. Unlike LDL-cholesterol, for Lp(a) no target value has been defined up to now. This overview presents data of modern capabilities of cardiovascular risk reduction by lowering Lp(a) level.

[15] *Geng Q, Li X, Sun Q, Wang Z*. **Efficacy and safety of PCSK9 inhibition in cardiovascular disease: a meta-analysis of 45 randomized controlled trials**. Cardiology journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34581425

ABSTRACT

BACKGROUND: Safety concerns about proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors make physicians reluctant to prescribe agents for patients. The present aim was to assess the efficacy and safety of alirocumab, evolocumab and bococizumab in patients with atherosclerotic cardiovascular disease (ASCVD). METHODS: Medline, the Cochrane Library and Clinicaltrials.gov were searched for 45 randomized controlled trials, involving 97,297 patients. RESULTS: Compared with the control group, PCSK9 inhibitors could significantly reduce low-density lipoprotein cholesterol, total cholesterol, triglycerides and increase high-density lipoprotein cholesterol. Alirocumab was associated with lower incidence of unstable angina ($p < 0.05$) and myocardial infarction ($p < 0.05$),

compared with the control group. Alirocumab (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.60-0.97, p < 0.05), evolocumab (OR 0.79, 95% CI 0.66-0.95, p < 0.05) and bococizumab (OR 0.60, 95% CI 0.42-0.84, p < 0.05) were associated with lower incidence of stroke, compared with control group. The incidence of injection-site reactions was significantly higher in alirocumab (OR 1.68, 95% CI 1.45-1.93, p < 0.05), evolocumab (OR 1.64, 95% CI 1.41-1.91, p < 0.05) and bococizumab (OR 8.03, 95% CI 6.85-9.41, p < 0.05) group than in the control group. CONCLUSIONS: Alirocumab and evolocumab could ameliorate lipid profile and reduce the risk of cardiac disorders and stroke with satisfactory safety and tolerability. However, injection-site reactions should be paid attention to.

[16] *Tsioufis K, Castellano Vázquez JM, Sykara G et al.* **Real-world Evidence for Adherence and Persistence with Atorvastatin Therapy**. Cardiology and therapy 2021; 10:445-464.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34586613
ABSTRACT
Atorvastatin, which has been approved by regulatory agencies for primary- and secondary-prevention patients with dyslipidemia, has historically been the most commonly prescribed statin and is now widely available in generic formulations. Despite widespread statin usage, many patients fail to attain recommended (LDL-C) targets. While several factors impact the successful treatment of dyslipidemia, suboptimal patient adherence is a major limiting factor to medication effectiveness. In this narrative review we sought to investigate patient adherence and persistence with atorvastatin in a real-world setting and to identify barriers to LDL-C goal attainment and therapy outcomes beyond the realm of clinical trials. Moreover, in light of growing generic usage, we carried out targeted literature searches to investigate the impact of generic atorvastatin availability on patient adherence/persistence, and on lipid and efficacy outcomes, compared with branded formulations. Unsurprisingly, real-world data suggest that patient adherence/persistence to atorvastatin is suboptimal, but few studies have attempted to address factors impacting adherence. Data from studies comparing adherence/persistence in patients prescribed branded or generic atorvastatin are limited and show no clear evidence that initiation of a specific preparation of atorvastatin impacts adherence/persistence. Furthermore, results from studies comparing adherence/persistence of patients who switched from the branded to the generic drug are conflicting, although they do suggest that switching may negatively impact adherence over the long term. Additional real-world studies are clearly required to understand potential differences in adherence and persistence between patients initiating treatment with branded versus generic atorvastatin and, moreover, the factors that influence adherence. Targeted education initiatives and additional research are needed to understand and improve patient adherence in a real-world setting.

[17] *McKinley EC, Bittner VA, Brown TM et al.* **The Projected Impact of Population-Wide Achievement of LDL Cholesterol <70 mg/dL on the Number of Recurrent Events Among US Adults with ASCVD**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34599698
ABSTRACT
PURPOSE: Adults with atherosclerotic cardiovascular disease (ASCVD) are recommended high-intensity statins, with those at very high risk for recurrent events recommended adding ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 inhibitor if their low-density lipoprotein

cholesterol (LDL-C) is ≥70 mg/dL. We estimated the number of recurrent ASCVD events potentially averted if all adults in the United States (US) ≥45 years of age with ASCVD achieved an LDL-C <70 mg/dL. METHODS: The number of US adults with ASCVD and LDL-C ≥70 mg/dL was estimated from the National Health and Nutrition Examination Survey 2009-2016 (n = 596). The 10-year cumulative incidence of recurrent ASCVD events was estimated from the REasons for Geographic And Racial Differences in Stroke study (n = 5390), weighted to the US population by age, race, and sex. The ASCVD risk reduction by achieving an LDL-C <70 mg/dL was estimated from meta-analyses of lipid-lowering treatment trials. RESULTS: Overall, 14.7 (95% CI, 13.7-15.8) million US adults had ASCVD, of whom 11.6 (95% CI, 10.6-12.5) million had LDL-C ≥70 mg/dL. The 10-year cumulative incidence of ASCVD events was 24.3% (95% CI, 23.2-25.6%). We projected that 2.823 (95% CI, 2.543-3.091) million ASCVD events would occur over 10 years among US adults with ASCVD and LDL-C ≥70 mg/dL. Overall, 0.634 (95% CI, 0.542-0.737) million ASCVD events could potentially be averted if all US adults with ASCVD achieved and maintained LDL-C <70 mg/dL. CONCLUSION: A substantial number of recurrent ASCVD events could be averted over 10 years if all US adults with ASCVD achieved, and maintained, an LDL-C <70 mg/dL.

[18] *Chen G, Farris MS, Cowling T et al.* **Prevalence of atherosclerotic cardiovascular disease and subsequent major adverse cardiovascular events in Alberta, Canada: A real-world evidence study**. Clinical cardiology 2021; 44:1613-1620.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34585767
ABSTRACT
BACKGROUND: Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality worldwide. Data from Canadian populations regarding the burden of ASCVD are limited. Therefore, we describe the 5-year period prevalence of ASCVD and subsequent major adverse cardiovascular event (MACE) outcomes among patients with ASCVD in Alberta, Canada. METHODS: A retrospective, observational study was conducted by linking provincial health services data, vital statistics, and pharmaceutical dispenses data. Five-year period prevalence of clinical ASCVD was captured between 2011 and 2016, and a cohort of adult patients with an initial clinical ASCVD event were identified between 2012 and 2016. One-year incidence rates (IRs) of subsequent MACE outcomes were calculated as composite and individual measures. A subgroup of patients with acute myocardial infarction (AMI) as their index event was examined. RESULTS: There were 198 573 patients (mean [standard deviation] age: 63.9 [15.6] years; 56.6% males) identified with clinical ASCVD between 2012 and 2016. Overall, the 5-year period prevalence of ASCVD in Alberta was 89.9 per 1000 persons and the 1-year IR for a primary MACE outcome was 6.15 (95% confidence interval [CI]: 6.03-6.26) per 100 person-years. Among the ASCVD cohort, 9465 had an AMI as their index event and the IR for a primary MACE outcome was 14.30 (95% CI: 13.45-15.20) per 100 person-years. CONCLUSIONS: This study found that the prevalence of ASCVD and the rate of subsequent MACE outcomes 1 year following the initial ASCVD event are substantial, particularly among patients with an AMI. Secondary prevention strategies aimed at lowering this risk are needed for patients with ASCVD.

[19] *Kersten S.* **ANGPTL3 as therapeutic target**. Current opinion in lipidology 2021; 32:335-341.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34581310
ABSTRACT

PURPOSE OF REVIEW: Elevated LDL-C and triglycerides are important risk factors for the development of atherosclerotic cardiovascular disease. Although effective therapies for lipid lowering exist, many people do not reach their treatment targets. In the last two decades, ANGPTL3 has emerged as a novel therapeutic target for lowering plasma LDL-C and triglycerides. Here, an overview of the recent literature on ANGPTL3 is provided, focusing on the therapeutic benefits of inactivation of ANGPTL3 via monoclonal antibodies, antisense oligonucleotides, and other more nascent approaches. In addition, the potential mechanisms by which ANGPTL3 inactivation lowers plasma LDL-C are discussed. RECENT FINDINGS: ANGPTL3 is a factor secreted by the liver that inhibits lipoprotein lipase and other lipases via the formation of a complex with the related protein ANGPTL8. Large-scale genetic studies in humans have shown that carriers of loss-of-function variants in ANGPTL3 have lower plasma LDL-C and triglyceride levels, and are at reduced risk of atherosclerotic cardiovascular disease. Clinical studies in patients with different forms of dyslipidemia have demonstrated that inactivation of ANGPTL3 using monoclonal antibodies or antisense oligonucleotides markedly lowers plasma LDL-C and triglyceride levels. SUMMARY: Anti-ANGPTL3 therapies hold considerable promise for reducing plasma LDL-C and triglycerides in selected patient groups.

[20] *Mohan V, Shanthi Rani CS, Saboo B et al.* **Clinical profile of long-term survivors and non-survivors with type 1 diabetes in India**. Diabetes technology & therapeutics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34569820

ABSTRACT

Objective To compare the clinical profile of long-term survivors and non-survivors with T1D(T1D) in India. Research design and methods This is a retrospective study of 76 individuals with T1D who had survived for at least 40 years ('survivors') and 51 individuals with T1D who had died with shorter duration of diabetes ('non-survivors'), from diabetes clinics in different cities of India. Prevalence of complications in both groups and causes of death of the non-survivors were analyzed. Retinopathy was diagnosed by retinal photography; chronic kidney disease (CKD) by urinary albumin excretion (micro- or macroalbuminuria) and estimated glomerular filtration rate; peripheral vascular disease (PVD) by Doppler measurement of ankle-brachial pressure index; coronary artery disease (CAD) based on history of myocardial infarction or coronary revascularization and neuropathy by biothesiometry. Results Mean glycated hemoglobin (8.4±1.5 vs 10.7±2.2%, p<0.001), serum low density lipoprotein-cholesterol (91±29 vs 107±22mg/dl, p=0.004) and systolic blood pressure (135±16 vs 153±37mmHg, p=0.003) were lower, and high density-lipoprotein cholesterol (51±11 vs 43±15mg/dl, p=0.002) higher, among survivors compared to non-survivors. Diabetic retinopathy, CKD, neuropathy, PVD and CAD were more frequent among non-survivors. CAD [25.5%] and renal failure [23.5%] were the most frequent causes of death. Conclusions In this first report of long-term survivors with T1DM from India, we report that survivors had better glycemic and blood pressure control, more favorable lipid profiles and lower prevalence of complications compared to non-survivors. However, there could be other protective factors as well, which merit further studies.

[21] *Garcia AR, Finch C, Gatz M et al.* **APOE4 is associated with elevated blood lipids and lower levels of innate immune biomarkers in a tropical Amerindian subsistence population**. eLife 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34586066

ABSTRACT
In post-industrial settings, apolipoprotein E4 (APOE4) is associated with increased cardiovascular and neurological disease risk. However, the majority of human evolutionary history occurred in environments with higher pathogenic diversity and low cardiovascular risk. We hypothesize that in high-pathogen and energy-limited contexts, the APOE4 allele confers benefits by reducing innate inflammation when uninfected, while maintaining higher lipid levels that buffer costs of immune activation during infection. Among Tsimane forager-farmers of Bolivia (N = 1266, 50% female), APOE4 is associated with 30% lower C-reactive protein, and higher total cholesterol and oxidized LDL. Blood lipids were either not associated, or negatively associated with inflammatory biomarkers, except for associations of oxidized LDL and inflammation which were limited to obese adults. Further, APOE4 carriers maintain higher levels of total and LDL cholesterol at low body mass indices (BMIs). These results suggest that the relationship between APOE4 and lipids may be beneficial for pathogen-driven immune responses and unlikely to increase cardiovascular risk in an active subsistence population.
Genes contain the instructions needed for a cell to make molecules called proteins, which perform various roles in the body. Different variants of a gene can affect how the protein works, and in some cases, can increase a person's risk to develop certain diseases. For example, people who carry a version of the apolipoprotein E gene called APOE4 have a greater risk of developing Alzheimer's disease or heart disease. Individuals with two copies of this genetic variant have a 45% higher risk of heart disease and 12 times higher risk of Alzheimer's disease. Studies in industrialized countries suggest this increased risk may be the result of higher cholesterol and inflammation in people with APOE4. But if APOE4 is harmful, why does it continue to be so common worldwide? One potential explanation is that APOE4, which has been around since before modern humans, may be beneficial in some contexts. Cholesterol is essential for many vital tasks in the body. In physically demanding environments where parasitic infections are common – conditions similar to those experienced by early humans – APOE4 might be beneficial. Under those circumstances, having more cholesterol might help fuel metabolic activities, fight infections, or reduce inflammation caused by infections.
Garcia et al. investigated the link between the APOE4 genetic variant, cholesterol and inflammation in 1,266 Indigenous Tsimane people from 80 villages in Bolivia. Tsimane people live an active lifestyle foraging and farming for food. Parasite infections are a common problem in their communities, but obesity rates are very low. Garcia et al. found that Tsimane people with at least one copy of the APOE4 have lower levels of inflammation and higher levels of cholesterol than those who have two copies of the APOE3 version of the gene. Very lean people with APOE4 had especially high levels of the so called "bad" low density lipoprotein (LDL) cholesterol compared to people with APOE3 only. However, in this situation, storing a little extra cholesterol may not be so bad. The findings contradict other studies that have linked obesity to higher LDL levels and APOE4 to higher levels of inflammation. For the majority of human history, humans lived in more physically strenuous and calorically restrictive environments, with less access to clean water. Garcia et al. suggest that the harmful effects of APOE4 seen in studies in more industrialized societies – where people tend to be more sedentary and have less exposure to pathogens – may reflect a mismatch between a person's environment and their genes. More studies that capture the diversity of environmental conditions under which people live will help clarify the role of APOE4 health and disease.
eng

[22] *Doshi R, Majmundar M, Kumar A et al.* **Association of new-onset atrial fibrillation in patients taking high-dose fish oil**. European journal of internal medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34593295
ABSTRACT

[23] *Banerjee Y, Pantea Stoian A, Cicero AFG et al.* **Inclisiran: a small interfering RNA strategy targeting PCSK9 to treat hypercholesterolemia**. Expert opinion on drug safety 2021:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34596005
ABSTRACT
INTRODUCTION: Inclisiran is a novel posttranscriptional gene silencing therapy that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis by RNA interference and has a potent, dose-dependent, durable effect in lowering LDL-C, and therefore is an effective drug to treat dyslipidemia, reducing the risk for acute cardiovascular (CV) events. It is safe and well-tolerated. AREAS COVERED: This paper aims to review the mechanism of action of inclisiran while evaluating its efficacy and safety in the treatment of dyslipidemia from data of the clinical trials in the ORION program. EXPERT OPINION: Data from the clinical trials in the ORION program demonstrated efficacy and safety of inclisiran in patients with dyslipidemia. Adverse events were similar in the inclisiran and placebo groups in the clinical trials, although injection-site reactions were more frequent with inclisiran than with placebo. Although the combination of efficacy and safety makes inclisiran a good option for the treatment of dyslipidemia compared to other PCSK9 targeting therapeutic strategies, however, further studies should exclude the possibility that inclisiran, through lower-affinity interactions, may influence other mRNAs in the physiological milieu.

[24] *Grandys M, Majerczak J, Zapart-Bukowska J et al.* **Lowered Serum Testosterone Concentration Is Associated With Enhanced Inflammation and Worsened Lipid Profile in Men**. Frontiers in endocrinology 2021; 12:735638.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34566895
ABSTRACT
The negative relationship between testosterone and inflammatory cytokines has been reported for decades, although the exact mechanisms of their interactions are still not clear. At the same time, little is known about the relation between androgens and acute phase proteins. Therefore, in this investigation, we aimed to study the relationship between androgen status and inflammatory acute phase reactants in a group of men using multi-linear regression analysis. Venous blood samples were taken from 149 men ranging in age from 18 to 77 years. Gonadal androgens [testosterone (T) and free testosterone (fT)], acute phase reactants [C-reactive protein (CRP), ferritin (FER), alpha-1-acid glycoprotein (AAG), and interleukin-6 (IL-6)], cortisol (C), and lipid profile concentrations were determined. It was demonstrated that the markers of T and fT were negatively correlated with all acute phase proteins (CRP, FER, and AAG; $p < 0.02$) and the blood lipid profile [total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG); $p < 0.03$]. Multivariate analysis showed that T, fT, and the fT/C ratio were inversely correlated with the CRP, AAG, and FER concentrations independently of age and blood lipids. When adjustment for BMI was made, T, fT, and the fT/C ratio were negatively correlated with the AAG concentrations only. In addition, it was demonstrated that gonadal androgens were positively correlated with physical activity level ($p < 0.01$). We have concluded that a lowered serum T concentration may promote inflammatory processes independently

of adipose tissue and age through a reduced inhibition of inflammatory cytokine synthesis, which leads to enhanced acute phase protein production. Therefore, a low serum T concentration appears to be an independent risk factor in the development of atherosclerosis and cardiovascular diseases. Moreover, the positive correlation between testosterone and physical activity level suggests that exercise training attenuates the age-related decrease in gonadal androgens and, in this way, may reduce the enhancement of systemic low-grade inflammation in aging men.

[25] *Wang Y, Zhang J, Li H et al.* **Prognostic Value of Leucocyte to High-Density Lipoprotein-Cholesterol Ratios in COVID-19 Patients and the Diabetes Subgroup**. Frontiers in endocrinology 2021; 12:727419.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34589058

ABSTRACT
BACKGROUND: Blood parameters, such as neutrophil-to-lymphocyte ratio, have been identified as reliable inflammatory markers with diagnostic and predictive value for the coronavirus disease 2019 (COVID-19). However, novel hematological parameters derived from high-density lipoprotein-cholesterol (HDL-C) have rarely been studied as indicators for the risk of poor outcomes in patients with severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection. Here, we aimed to assess the prognostic value of these novel biomarkers in COVID-19 patients and the diabetes subgroup. METHODS: We conducted a multicenter retrospective cohort study involving all hospitalized patients with COVID-19 from January to March 2020 in five hospitals in Wuhan, China. Demographics, clinical and laboratory findings, and outcomes were recorded. Neutrophil to HDL-C ratio (NHR), monocyte to HDL-C ratio (MHR), lymphocyte to HDL-C ratio (LHR), and platelet to HDL-C ratio (PHR) were investigated and compared in both the overall population and the subgroup with diabetes. The associations between blood parameters at admission with primary composite end-point events (including mechanical ventilation, admission to the intensive care unit, or death) were analyzed using Cox proportional hazards regression models. Receiver operating characteristic curves were used to compare the utility of different blood parameters. RESULTS: Of 440 patients with COVID-19, 67 (15.2%) were critically ill. On admission, HDL-C concentration was decreased while NHR was high in patients with critical compared with non-critical COVID-19, and were independently associated with poor outcome as continuous variables in the overall population (HR: 0.213, 95% CI 0.090-0.507; HR: 1.066, 95% CI 1.030-1.103, respectively) after adjusting for confounding factors. Additionally, when HDL-C and NHR were examined as categorical variables, the HRs and 95% CIs for tertile 3 vs. tertile 1 were 0.280 (0.128-0.612) and 4.458 (1.817-10.938), respectively. Similar results were observed in the diabetes subgroup. ROC curves showed that the NHR had good performance in predicting worse outcomes. The cutoff point of the NHR was 5.50. However, the data in our present study could not confirm the possible predictive effect of LHR, MHR, and PHR on COVID-19 severity. CONCLUSION: Lower HDL-C concentrations and higher NHR at admission were observed in patients with critical COVID-19 than in those with noncritical COVID-19, and were significantly associated with a poor prognosis in COVID-19 patients as well as in the diabetes subgroup.

[26] *Mascellanti M, Fulgenzi F, Carnesale R, De Caterina R*. **[The healed plaque: tale of a story with good ending - with practical implications]**. Giornale italiano di cardiologia (2006) 2021; 22:827-832.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34570116

ABSTRACT

Acute coronary syndromes have heterogeneous clinical presentations, features and prognosis. They can also occur without angiographic evidence of significant coronary artery stenosis, based on multiple causes. We report on the diagnostic and therapeutic management of a 56-year-old man with an acute coronary syndrome and angiographic evidence of non-obstructive coronary artery disease. In addition to the basic angiographic evaluation, intracoronary imaging was here helpful to understand the underlying mechanism, prompting a tailored therapeutic strategy and avoiding inappropriate treatment with percutaneous coronary intervention and stenting. This clinical case here described offers the opportunity to briefly recapitulate the most meaningful milestones in the progress in the pathophysiology of acute coronary syndromes, also focusing on myocardial infarction non-obstructive coronary artery, and to appreciate the occurrence of rare cases and consequent lessons.

[27] *Jalali-Farahani S, Amiri P, Fakhredin H et al.* **Health-related quality of life in men and women who experienced cardiovascular diseases: Tehran Lipid and Glucose Study**. Health Qual Life Outcomes 2021; 19:225.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34565411

ABSTRACT

BACKGROUND: Cardiovascular diseases (CVDs) are among the most common causes of death worldwide, including in Iran. Considering the adverse effects of CVDs on physical and psychosocial health; this study aims to investigate the association between experience of CVDs and health-related quality of life (HRQoL) in adult participants of the Tehran Lipid and Glucose Study (TLGS). METHODS: The participants of this cross-sectional study were 7009 adults (≥20 years) who participated in the TLGS during 2014-2017. Demographic information and HRQoL data was collected through validated questionnaires by trained interviewers. HRQoL was assessed by the Iranian version of the SF-12 questionnaire. Data was analyzed using the SPSS software. RESULTS: The mean age of participants was 46.8 ± 14.6 years and 46.1% of them were men. A total of 9.0% of men and 4.4% of women had CVDs. In men, the mean physical HRQoL summary score was significantly lower in those with CVDs compared to those without CVDs (46.6 ± 0.8 vs. 48.5 ± 0.7, p > 0.001). In women, the mean mental HRQoL summary scores was significantly lower in those with CVDs compared to those without CVDs (42.8 ± 1.0 vs. 45.2 ± 0.5, p = 0.009). In adjusted models, men with CVDs were more likely to report poor physical HRQoL compared to men without CVDs (OR(95%CI): 1.93(1.32-2.84), p = 0.001); whereas for women, the chance of reporting poor mental HRQoL was 68% higher in those with CVDs than those without CVDs (OR(95%CI): 1.68(1.11-2.54), p = 0.015). CONCLUSION: The findings of the current study indicate poorer HRQoL in those who experienced CVDs compared to their healthy counterparts with a sex specific pattern. While for men, CVDs were associated with more significant impairment in the physical dimension of HRQoL, women experienced a similar impairment in the mental dimension of HRQoL.

[28] *Nirmala N, Avendano EE, Morin RA*. **Effectiveness of ezetimibe in human immunodeficiency virus patients treated for hyperlipidaemia: a systematic review and meta-analysis**. Infectious diseases (London, England) 2021:1-11.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34590982

ABSTRACT

OBJECTIVE: Systematic review and meta-analysis of lipid outcomes for human immunodeficiency virus (HIV)-positive or HIV-infected patients treated with ezetimibe. METHODS: We conducted a literature search from 1946 to 2021 for trials studying the effectiveness of ezetimibe in hyperlipidaemic HIV patients. We included trials of all designs in which HIV patients on highly active antiretroviral therapy (HAART)/non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy had hyperlipidaemia, were treated with ezetimibe, and reported lipid outcomes. RESULTS: Of thirteen eligible trials, five were randomized controlled trials (RCTs) and eight were single-arm trials. Two of the eligible RCTs were placebo-controlled; we performed a meta-analysis across those two trials for low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG). LDL-C was significantly lower in the ezetimibe arm (net change: -23.56 mg/dL, 95% CI: -40.22, -6.90 mg/dL). We then performed meta-analysis of the single-arm trials examining lipid outcomes after ezetimibe treatment which, like in the RCTs, revealed significant reductions of LDL-C (-23.89 mg/dL, 95% CI -29.94 to -17.83 mg/dL). In addition, significant reductions were seen for total cholesterol (TC) (-26.17 mg/dL, 95% CI -32.81 to -19.54 mg/dL) and TG (-18.57 mg/dL, 95% CI -34.01 to -3.14 mg/dL) but HDL-C did not show a change. CONCLUSIONS: Evidence for LDL-C reduction is limited in RCTs; single-arm trial LDL-C reductions are consistent with the RCTs. In addition, significant reductions in TC and TG were also seen in the meta-analysis of the single arm trials. The single-arm trials' meta-analysis corroborates evidence from RCTs to suggest that ezetimibe can be an option for hyperlipidaemia among HIV patients with mildly elevated TC and LDL-C levels, especially in cases where statins are contra-indicated due to drug-drug interactions with concomitant anti-retroviral therapy.

[29] *Yoshimura M, Umemoto S, Kawano R et al.* **Non-Fasting Hypertriglyceridemia as an Independent Risk Factor for Coronary In-Stent Restenosis after Primary Bare Metal Stent Implantation in Patients with Coronary Artery Disease**. Int Heart J 2021; 62:970-979.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34588411

ABSTRACT

After a percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD), in-stent neoatherosclerosis may pose a risk of in-stent restenosis (ISR). To clarify whether non-fasting hypertriglyceridemia contributes to ISR, we examined the relationship between non-fasting hypertriglyceridemia (i.e., triglyceride (TG) level ≥ 200 mg/dL) and ISR after stenting with a bare metal stent (BMS) post-primary PCI in patients with CAD by means of a single-site retrospective analysis. A total of 1,039 patients with CAD were enrolled, and 86 patients (112 lesions) were evaluated for BMS-ISR 3-6 months post-primary PCI. The percentage of patients with non-fasting hypertriglyceridemia was significantly higher in the ISR (+) group than in the ISR (-) group ($P < 0.009$). The follow-up period and number of patients in the ISR (+) group were significantly smaller than those in the ISR (-) group ($P < 0.001$). There were no significant between-group differences in the other baseline patient characteristics before the primary PCI or at the time of the follow-up coronary angiography. However, at the follow-up period, the ISR (+) group had significantly lower diastolic blood pressure and high-density lipoprotein cholesterol levels ($P = 0.015$) and significantly higher TG levels ($P = 0.012$) than the ISR (-) group. A multiple logistic regression analysis demonstrated that non-fasting hypertriglyceridemia and a follow-up period of ≥ 6 months were independent risk factors for ISR after primary PCI in patients with BMS implantation for stenotic CAD ($P = 0.006$), with an adjusted odds ratio of 8.232 (1.201-56.410) and 0.006 (95% confidence interval < 0.001-0.045), respectively. Non-

fasting hypertriglyceridemia may be an additional independent risk factor for BMS-ISR after primary PCI in patients with CAD.

[30] *Garg PK, Lima J, deFilippi CR et al.* **Associations of cardiac injury biomarkers with risk of peripheral artery disease: The Multi-Ethnic Study of Atherosclerosis**. International journal of cardiology 2021; 344:199-204.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34600979
ABSTRACT
INTRODUCTION: We investigated the associations of high-sensitivity cardiac Troponin T (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels with risk of developing clinical peripheral artery disease (PAD) or a low ankle-brachial index (ABI). METHODS: Hs-cTnT and NT-proBNP were measured in 6692 and 5458 participants respectively without baseline PAD between 2000 and 2002 in the Multi-ethnic Study of Atherosclerosis. A significant number also had repeat biomarker measurement between 2004 and 2005. Incident clinical PAD was ascertained through 2017. Incident low ABI, defined as ABI <0.9 and decline of ≥0.15 from baseline, was assessed among 5920 eligible individuals who had an ABI >0.9 at baseline and at least one follow-up ABI measurement 3-10 years later. Multivariable Cox proportional hazards and logistic regression modeling were used to determine the association of these biomarkers with clinical PAD and low ABI, respectively. RESULTS: Overall, 121 clinical PAD and 118 low ABI events occurred. Adjusting for demographic and clinical characteristics, each log unit increment in hs-cTnT and NT-proBNP was associated with a 30% (adjusted hazard ratio (HR) 1.3, 95% confidence interval (CI): 1.1, 1.6) and 50% (HR) 1.5, 95% CI: 1.2, 1.8) higher risk of clinical PAD respectively. No significant associations were observed for incident low ABI. Change in these biomarkers was not associated with either of the PAD outcomes. CONCLUSIONS: NT-proBNP and hs-cTnT are independently associated with the development of clinical PAD. Further study should determine whether these biomarkers can help to better identify those at higher risk for PAD.

[31] *Yu H, Su X, Lei T et al.* **Effect of Omega-3 Fatty Acids on Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. International journal of chronic obstructive pulmonary disease 2021; 16:2677-2686.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34588776
ABSTRACT
PURPOSE: Omega-3 fatty acid is an emerging hotspot on anti-inflammation and chronic obstructive pulmonary disease (COPD) is known as a chronic inflammatory disease. The effect of Omega-3 fatty acid supplement on patients with COPD remains mixed for insufficient evidence. This systematic review and meta-analysis is based on neat randomized controlled trials trying to give a clearer impression on the effect of Omega-3 on patients with COPD. METHODS: This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statements. Randomized clinical trials (RCTs) published in electronic databases including Medline, Embase, Cochrane Library, ClinicalTrials.gov and China National Knowledge Infrastructure (CNKI) by May 10, 2021 were searched. Data extracted from 6 predetermined domains (nutritional condition, lipid composition, inflammatory biomarker, lung function, physical endurance and quality of life [QoL]) were reviewed and analyzed. RESULTS: A total of 8 RCTs evaluating 418 patients (age, mean [SD] = 67.3 [10.2] years) were included. Statistical

differences were found in 3 parameters of 3 domains - weight (Wt) (0.25 [95% CI, 0.02 to 0.48], P = 0.03) in nutritional condition, low-density lipoprotein (LDL) (0.70 [95% CI, 0.30 to 1.10], P = 0.00) in lipid composition and interleukin-6 (IL-6) level (-0.32 [95% CI, -0.60 to -0.05], P = 0.02) in inflammatory biomarker - while no significant difference was found in lung function, physical endurance or QoL. CONCLUSION: Comparing with placebo, Omega-3 intake was associated with more weight-gaining, LDL increase and IL-6 reduction. These results should be interpreted cautiously for the quality and quantity of available evidence are limited.

[32] *Chen PY, Chao TY, Hsu HJ et al.* **The Lipid-Modulating Effect of Tangeretin on the Inhibition of Angiopoietin-like 3 (ANGPTL3) Gene Expression through Regulation of LXRα Activation in Hepatic Cells**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34576019

ABSTRACT

The excessive accumulation of TG-rich lipoproteins (TGRLs) in plasma is associated with dyslipidemia and atherosclerotic cardiovascular diseases (ASCVDs). Tangeretin is a bioactive pentamethoxyflavone mainly found in citrus peels, and it has been reported to protect against hyperlipidemia, diabetes, and obesity. The aim of this study was to investigate the lipid-modulating effects and the underlying mechanisms of tangeretin action in hepatic cells. Transcriptome and bioinformatics analyses with the Gene Ontology (GO) database showed that tangeretin significantly regulated a set of 13 differentially expressed genes (DEGs) associated with the regulation of lipoprotein lipase (LPL) activity. Among these DEGs, angiopoietin-like 3 (ANGPTL3), an essential inhibitor of LPL catalytic activity that regulates TGRL metabolism in plasma, was markedly downregulated by tangeretin. We demonstrated that tangeretin significantly inhibited the mRNA expression of ANGPTL3 in HepG2 and Huh-7 cells. Tangeretin treatment of hepatic cells also reduced the levels of both intracellular and secreted ANGPTL3 proteins. Moreover, we found that inhibition of ANGPTL3 production by tangeretin augmented LPL activity. We further demonstrated that the transcriptional activity of the ANGPTL3 promoter was significantly attenuated by tangeretin, and we identified a DNA element located between the -250 and -121 positions that responded to tangeretin. Furthermore, we found that tangeretin did not alter the levels of the nuclear liver X receptor α (LXRα) protein, an essential transcription factor that binds to the tangeretin-responsive element, but it can counteract LXRα-mediated ANGPTL3 transcription. On the basis of molecular docking analysis, tangeretin was predicted to bind to the ligand-binding domain of LXRα, which would result in suppression of LXRα activation. Our findings support the hypothesis that tangeretin exerts a lipid-lowering effect by modulating the LXRα-ANGPTL3-LPL pathway, and thus, it can be used as a potential phytochemical for the prevention or treatment of dyslipidemia.

[33] *Diaconu R, Schaaps N, Afify M et al.* **Apolipoprotein E4 Is Associated with Right Ventricular Dysfunction in Dilated Cardiomyopathy-An Animal and In-Human Comparative Study**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34575848

ABSTRACT

ApoE abnormality represents a well-known risk factor for cardiovascular diseases. Beyond its role in lipid metabolism, novel studies demonstrate a complex involvement of apoE in membrane homeostasis and signaling as well as in nuclear transcription. Due to the large spread of apoE

isoforms in the human population, there is a need to understand the apoE's role in pathological processes. Our study aims to dissect the involvement of apoE in heart failure. We showed that apoE-deficient rats present multiple organ damages (kidney, liver, lung and spleen) besides the known predisposition for obesity and affected lipid metabolism (two-fold increase in tissular damages in liver and one-fold increase in kidney, lung and spleen). Heart tissue also showed significant morphological changes in apoE(-/-) rats, mostly after a high-fat diet. Interestingly, the right ventricle of apoE(-/-) rats fed a high-fat diet showed more damage and affected collagen content (~60% less total collagen content and double increase in collagen1/collagen3 ratio) compared with the left ventricle (no significant differences in total collagen content or collagen1/collagen3 ratio). In patients, we were able to find a correlation between the presence of ε4 allele and cardiomyopathy ($\chi(2) = 10.244$; $p = 0.001$), but also with right ventricle dysfunction with decreased TAPSE (15.3 ± 2.63 mm in ε4-allele-presenting patients vs. 19.8 ± 3.58 mm if the ε4 allele is absent, $p < 0.0001$*) and increased in systolic pulmonary artery pressure (50.44 ± 16.47 mmHg in ε4-allele-presenting patients vs. 40.68 ± 15.94 mmHg if the ε4 allele is absent, $p = 0.0019$). Our results confirm that the presence of the ε4 allele is a lipid-metabolism-independent risk factor for heart failure. Moreover, we show for the first time that the presence of the ε4 allele is associated with right ventricle dysfunction, implying different regulatory mechanisms of fibroblasts and the extracellular matrix in both ventricles. This is essential to be considered and thoroughly investigated before the design of therapeutical strategies for patients with heart failure.

[34] *Goonewardena SN, Rosenson RS*. **The Enigma of PCSK9 Regulation: Leveraging Therapeutics Towards Mechanistic Understanding**. Journal of the American College of Cardiology 2021; 78:1450-1452.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34593127
ABSTRACT

[35] *Oleaga C, Shapiro MD, Hay J et al.* **Hepatic Sensing Loop Regulates PCSK9 Secretion in Response to Inhibitory Antibodies**. Journal of the American College of Cardiology 2021; 78:1437-1449.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34593126
ABSTRACT
BACKGROUND: Monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9i) lower LDL-C by up to 60% and increase plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) levels by 10-fold. OBJECTIVES: The authors studied the reasons behind the robust increase in plasma PCSK9 levels by testing the hypothesis that mechanisms beyond clearance via the low-density lipoprotein receptor (LDLR) contribute to the regulation of cholesterol homeostasis. METHODS: In clinical cohorts, animal models, and cell-based studies, we measured kinetic changes in PCSK9 production and clearance in response to PCSK9i. RESULTS: In a patient cohort receiving PCSK9i therapy, plasma PCSK9 levels rose 11-fold during the first 3 months and then plateaued for 15 months. In a cohort of healthy volunteers, a single injection of PCSK9i increased plasma PCSK9 levels within 12 hours; the rise continued for 9 days until it plateaued at 10-fold above baseline. We recapitulated the rapid rise in PCSK9 levels in a mouse model, but only in the presence of LDLR. In vivo turnover and in vitro pulse-chase studies identified 2 mechanisms contributing to the rapid increase in plasma PCSK9 levels in response to PCSK9i: 1) the expected delayed clearance of the

antibody-bound PCSK9; and 2) the unexpected post-translational increase in PCSK9 secretion. CONCLUSIONS: PCSK9 re-entry to the liver via LDLR triggers a sensing loop regulating PCSK9 secretion. PCSK9i therapy enhances the secretion of PCSK9, an effect that contributes to the increased plasma PCSK9 levels in treated subjects.

[36] *Block RC, Bang M, Peterson A et al.* **Awareness, diagnosis and treatment of heterozygous familial hypercholesterolemia (HeFH) - Results of a US national survey**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34593357
ABSTRACT
BACKGROUND: HeFH is a common inherited disorder that leads to markedly elevated LDL-cholesterol from birth and premature cardiovascular disease. HeFH is frequently underdiagnosed and undertreated. OBJECTIVE: To compare how well primary care physicians and cardiologists recognize and treat HeFH. METHODS: The National Lipid Association surveyed 500 primary care physicians and 500 cardiologists in the US who have patients with baseline LDL-cholesterol ≥ 190 mg/dL. The survey was conducted between August 29 and September 30, 2019. RESULTS: For a hypothetical case of HeFH, 57% of cardiologists versus 43% of primary care physicians made the correct diagnosis (P<0.001). Among respondents, 21% of cardiologists versus 29% of primary care physicians have never made a diagnosis of HeFH in a patient with an LDL-cholesterol ≥ 190 mg/dL (P<0.004). Only 7% of cardiologists versus 5% of primary care physicians would refer to a lipid specialist (P=0.05). For additional LDL-cholesterol lowering after statins, 58% of cardiologists versus 48% of primary care physicians would prescribe a PCSK9 inhibitor (P=0.004); however, 30% of cardiologists versus 53% of primary care physicians have never prescribed a PSCK9 inhibitor in an HeFH patient (P<0.001). CONCLUSION: Although cardiologists compared to primary care physicians are somewhat more likely to recognize and treat HeFH patients according to guidelines, both physician specialties do not adequately recognize or treat HeFH. There is a need for more education and training in recognizing and treating HeFH, greater access to lipid specialists, and fewer barriers for PCSK9 inhibitor use.

[37] *Vijayakanthi N, Felner EI, Romero R, Daley TC*. **Rhabdomyolysis due to rosuvastatin in a patient with ROHHAD syndrome**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34600840
ABSTRACT
We report a 13-year-old female with rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome, panhypopituitarism, dyslipidemia, type 2 diabetes mellitus, and nonalcoholic fatty liver disease, who developed rhabdomyolysis and acute kidney injury, two weeks after switching from lovastatin to rosuvastatin. She had been on lovastatin for eight years without any adverse effects.

[38] *Sun C, Zheng W, Liang L et al.* **Ezetimibe Improves Rosuvastatin Effects on Inflammation and Vascular Endothelial Function in Acute Coronary Syndrome Patients Undergoing PCI**. J Interv Cardiol 2021; 2021:2995602.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34566523
ABSTRACT

BACKGROUND: Little is known of the acute effects of ezetimibe in patients with acute coronary syndrome (ACS) undergoing PCI. We investigated whether ezetimibe improves inflammation and vascular endothelial function in patients with ACS undergoing PCI. METHODS: We randomized 171 patients with ACS undergoing PCI to receive ezetimibe 10 mg/day plus rosuvastatin 20 mg/day (combination group, n = 81) versus rosuvastatin 20 mg/day (rosuvastatin group, n = 90). Lipid profile, type II secretory phospholipase A2 (sPLA2-IIa), interleukin-1β (IL-1β), vascular cell adhesion molecule-1 (VCAM-1), and intercellular cell adhesion molecule-1 (ICAM-1) were measured at baseline and after 7 days. Three months after PCI, clinical outcomes were examined. RESULT: The levels of sPLA2-IIa and IL-1β reduced significantly in both groups, but more when ezetimibe and rosuvastatin were coadministered (sPLA2-IIa: 6.16 ± 2.67 vs. 7.42 ± 3.53 ng/ml, p=0.01; IL-1β: 37.39 ± 26.25 vs. 48.98 ± 32.26 pg/ml, p=0.01). A significant rise of VCAM-1 and ICAM-1 was observed on day 7 after PCI in the both groups, but was less in the combination group (VCAM-1: 918.28 ± 235.31 vs. 988.54 ± 194.41 ng/ml, p=0.03; ICAM-1: 213.01 ± 100.15 vs. 246.88 ± 105.71 ng/ml, p=0.03). Patients in the combination versus rosuvastatin group appeared to suffer from less major adverse events. Periprocedural therapy of ezetimibe improves rosuvastatin effects on proinflammatory responses and endothelial function associated with ACS patients undergoing PCI. This trial is registered with https://clinicaltrials.gov/ct2/show/ChiCTR-IPR-17012219 (Chinese Clinical Trial Registry, http://www.chictr.org.cn on 02/08/2017).

[39] *Yang L, Li N, Yang L et al.* **Atorvastatin-Induced Absorption of Chronic Subdural Hematoma Is Partially Attributed to the Polarization of Macrophages**. Journal of molecular neuroscience : MN 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34569007

ABSTRACT

As one of the main types of secondary craniocerebral injury, the onset, progression, and prognosis of chronic subdural hematoma (CSDH) are closely related to the local inflammation of intracranial hematoma. Atorvastatin is reported to be effective in the conservative treatment of CSDH. This study aimed to clarify whether atorvastatin regulated the inflammatory responses in CSDH by interfering with the function of macrophages. The rat CSDH model was prepared by repeated intracranial blood injection with velocity gradient, and MRI was applied to calculate the intracranial hematoma volume. Changes in rat nerve functions were evaluated by foot-fault and Morris water maze tests. Flow cytometry was applied to detect the number of total macrophages and the percentage of M1 or M2 macrophages. The expression of inflammatory factors was examined by ELISA and western blot. Western bolt was applied to detect the expression of proteins involved in the colony-stimulating factor 1 receptor (CSF-1R) signaling pathway. Our results showed that atorvastatin significantly accelerated the absorption of hematoma and improved the nerve functions of CSDH rats. In addition, atorvastatin treatment effectively suppressed the expression of TNF-α, IL-6, and IL-8 and promoted the expression of IL-10. The total number of macrophages was decreased, and the percentage of M2 macrophages was increased in the intracranial hematoma following atorvastatin treatment. Furthermore, atorvastatin increased the levels of M2-related genes and surface markers in BMDMs stimulated by lipopolysaccharides and IFNγ, and activated the CSF-1R signaling pathway. In conclusion, our study shows that atorvastatin could alleviate the symptoms of CSDH and promote hematoma ablation by polarizing macrophages to M2 type and regulating the inflammatory responses.

[40] *Hindi NN, Alenbawi J, Nemer G*. **Pharmacogenomics Variability of Lipid-Lowering Therapies in Familial Hypercholesterolemia**. Journal of personalized medicine 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34575654
ABSTRACT
The exponential expansion of genomic data coupled with the lack of appropriate clinical categorization of the variants is posing a major challenge to conventional medications for many common and rare diseases. To narrow this gap and achieve the goals of personalized medicine, a collaborative effort should be made to characterize the genomic variants functionally and clinically with a massive global genomic sequencing of "healthy" subjects from several ethnicities. Familial-based clustered diseases with homogenous genetic backgrounds are amongst the most beneficial tools to help address this challenge. This review will discuss the diagnosis, management, and clinical monitoring of familial hypercholesterolemia patients from a wide angle to cover both the genetic mutations underlying the phenotype, and the pharmacogenomic traits unveiled by the conventional and novel therapeutic approaches. Achieving a drug-related interactive genomic map will potentially benefit populations at risk across the globe who suffer from dyslipidemia.

[41] *Shim SY, Yoon HY, Yee J et al.* **Association between ABCA1 Gene Polymorphisms and Plasma Lipid Concentration: A Systematic Review and Meta-Analysis**. Journal of personalized medicine 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34575660
ABSTRACT
BACKGROUND: Although ABCA1 gene polymorphisms may be associated with the plasma lipid concentration, the literature has not shown a consistent pattern. In this study, we attempted to elucidate the association between the ABCA1 69C>T, 825V>I, and 230R>C polymorphisms and the plasma lipid concentration through a systematic review and meta-analysis. METHODS: We selected studies published up to October 2020 in the PubMed, Web of Science, and Embase databases according to inclusion and exclusion criteria. The mean difference (MD) and 95% confidence interval (CI) were used to assess the relationship between the presence of ABCA1 69C>T, 825V>I, and 230R>C and plasma lipid levels. Meta-analysis was performed using Review Manager (version 5.3). Both Begg's test and Egger's regression test of the funnel plot were performed using R Studio software (version 3.6.0) to identify publication bias. RESULTS: We analyzed the data on the ABCA1 69C>T polymorphism involving 14,843 subjects in 11 studies, 825V>I polymorphism involving 2580 subjects in 5 studies, and 230R>C polymorphism involving 4834 subjects in 4 studies. The T allele carriers in 69C>T, II carriers in 825V>I, and C carriers in 230R>C had lower high-density lipoprotein cholesterol levels; the MD (95% CI) was -0.05 mmol/L (95% CI: -0.09 to -0.01, $p = 0.02$), -0.05 mmol/L (95% CI: -0.09 to -0.00, $p = 0.03$), and -0.1 mmol/mL (95% CI: -0.12 to -0.07 mmol/L, $p < 0.00001$), respectively. In the case of 230R>C, the serum total cholesterol concentration of C carriers was significantly lower than that of RR carriers (-0.2 mmol/L, 95% CI: -0.3 to -0.11, $p < 0.0001$). CONCLUSION: This meta-analysis demonstrates that the ABCA1 69C>T, 825V>I, and 230R>C polymorphisms could affect the plasma lipid concentration. As the plasma lipid concentration may be related to various diseases, ABCA1 genotyping could be useful for the management of lipid levels.

[42] *Fokina VM, Patrikeeva S, Wang XM et al.* **Role of Uptake Transporters OAT4, OATP2A1, and OATP1A2 in Human Placental Bio-disposition of Pravastatin**. Journal of pharmaceutical sciences 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34597623
ABSTRACT
Pravastatin is currently under evaluation for prevention of preeclampsia. Factors contributing to placental disposition of pravastatin are important in assessment of potential undesirable fetal effects. The purpose of this study was to identify the uptake transporters that contribute to the placental disposition of pravastatin. Our data revealed the expression of organic anion transporting polypeptide 1A2 (OATP1A2) and OATP2A1 in the apical, and OATP2B1 and OATP5A1 in the basolateral membranes of the placenta, while organic anion transporter 4 (OAT4) exhibited higher expression in basolateral membrane but was detected in both membranes. Preloading placental membrane vesicles with glutarate increased the uptake of pravastatin suggesting involvement of glutarate-dependent transporters such as OAT4. In the HEK293 cells overexpressing individual uptake transporters, OATP2A1, OATP1A2 and OAT4 were determined to accept pravastatin as a substrate at physiological pH, while the uptake of pravastatin by OATP2B1 (known to interact with pravastatin at acidic pH) and OATP5A1 was not detected at pH 7.4. These findings led us to propose that OATP1A2 and OATP2A1 are responsible for the placental uptake of pravastatin from the maternal circulation, while OAT4 mediates the passage of the drug across placental basolateral membrane in the fetal-to-maternal direction.

[43] *Lu Y, Zhang H, Lu J et al.* **Prevalence of Dyslipidemia and Availability of Lipid-Lowering Medications Among Primary Health Care Settings in China**. JAMA network open 2021; 4:e2127573.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34586366
ABSTRACT
IMPORTANCE: Dyslipidemia, the prevalence of which historically has been low in China, is emerging as the second leading yet often unaddressed factor associated with the risk of cardiovascular diseases. However, recent national data on the prevalence, treatment, and control of dyslipidemia are lacking. OBJECTIVE: To assess the prevalence, treatment, and control of dyslipidemia in community residents and the availability of lipid-lowering medications in primary care institutions in China. DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional study used data from the China-PEACE (Patient-Centered Evaluative Assessment of Cardiac Events) Million Persons Project, which enrolled 2 660 666 community residents aged 35 to 75 years from all 31 provinces in China between December 2014 and May 2019, and the China-PEACE primary health care survey of 3041 primary care institutions. Data analysis was performed from June 2019 to March 2021. EXPOSURES: Study period. MAIN OUTCOMES AND MEASURES: The main outcome was the prevalence of dyslipidemia, which was defined as total cholesterol greater than or equal to 240 mg/dL, low-density lipoprotein cholesterol (LDL-C) greater than or equal to 160 mg/dL, high-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL, triglycerides greater than or equal to 200 mg/dL, or self-reported use of lipid-lowering medications, in accordance with the 2016 Chinese Adult Dyslipidemia Prevention Guideline. RESULTS: This study included 2 314 538 participants with lipid measurements (1 389 322 women [60.0%]; mean [SD] age, 55.8 [9.8] years). Among them, 781 865 participants (33.8%) had dyslipidemia. Of 71 785 participants (3.2%) who had established atherosclerotic

cardiovascular disease (ASCVD) and were recommended by guidelines for lipid-lowering medications regardless of LDL-C levels, 10 120 (14.1%) were treated. The overall control rate of LDL-C (≤70 mg/dL) among adults with established ASCVD was 26.6% (19 087 participants), with the control rate being 44.8% (4535 participants) among those who were treated and 23.6% (14 552 participants) among those not treated. Of 236 579 participants (10.2%) with high risk of ASCVD, 101 474 (42.9%) achieved LDL-C less than or equal to 100 mg/dL. Among participants with established ASCVD, advanced age (age 65-75 years, odds ratio [OR], 0.63; 95% CI, 0.56-0.70), female sex (OR, 0.56; 95% CI, 0.53-0.58), lower income (reference category), smoking (OR, 0.89; 95% CI, 0.85-0.94), alcohol consumption (OR, 0.87; 95% CI, 0.83-0.92), and not having diabetes (reference category) were associated with lower control of LDL-C. Among participants with high risk of ASCVD, younger age (reference category) and female sex (OR, 0.58; 95% CI, 0.56-0.59) were associated with lower control of LDL-C. Of 3041 primary care institutions surveyed, 1512 (49.7%) stocked statin and 584 (19.2%) stocked nonstatin lipid-lowering drugs. Village clinics in rural areas had the lowest statin availability. CONCLUSIONS AND RELEVANCE: These findings suggest that dyslipidemia has become a major public health problem in China and is often inadequately treated and uncontrolled. Statins were available in less than one-half of the primary care institutions. Strategies aimed at detection, prevention, and treatment are needed.

[44] *Lanzolla G, Sabini E, Leo M et al.* **Statins for Graves' orbitopathy (STAGO): a phase 2, open-label, adaptive, single centre, randomised clinical trial**. The lancet. Diabetes & endocrinology 2021; 9:733-742.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34592164

ABSTRACT

BACKGROUND: A protective action of statins on development of Graves' orbitopathy suggests that statins might be used for treatment of the disease. We aimed to assess the efficacy of the addition of a statin, atorvastatin, to intravenous glucocorticoids (ivGCs) on Graves' orbitopathy outcomes in patients with hypercholesterolaemia. METHODS: We did a randomised, open-label, phase 2, adaptive, clinical trial at a single, tertiary, referral hospital in Pisa, Italy. Patients with moderate-to-severe, active Graves' orbitopathy, with a low-density lipoprotein cholesterol concentration between 2·97 and 4·88 mmol/L were eligible for inclusion. Patients were randomly assigned (1:1) in 11 blocks of eight, using a computer-based system, to the ST group or the NST group. The ST group received ivGCs (methylprednisolone 500 mg once a week for 6 weeks followed by 250 mg once a week for an additional six weeks) for 12 weeks and oral atorvastatin (20 mg once a day) for 24 weeks. The NST group only received the ivGC regimen. Patients were unmasked to group allocation; however, the ophthalmological investigator was masked to randomisation. The primary endpoint was the Graves' orbitopathy outcome (composite evaluation of exophthalmos, clinical activity score, eyelid aperture, and diplopia) at 24 weeks in the modified intention-to-treat (ITT) population (patients who attended the week 12 visit). Patients were considered responders when at least two of the following criteria were fulfilled in the most affected eye, without worsening in any of the same measures in both eyes: (1) reduction in exophthalmos of 2 mm or more, with no increase by 2 mm or more in the other eye; (2) reduction of clinical activity score by two or more points; (3) reduction in eyelid aperture by 2 mm or more, with no increase by 2 mm or more in the other eye; and (4) disappearance or improvement (change from constant to inconstant, intermittent, or absent, or from inconstant to intermittent or absent) of diplopia, and (5) improvement in visual acuity by 0·2 decimals or more. The trial is

registered with EUDRACT, 2018-001317-33, and ClinicalTrials.gov, NCT03110848. FINDINGS: Between June 1, 2020, and Nov 30, 2020, 119 patients were screened for inclusion, of whom 88 (74%) patients were enrolled and randomly assigned to one of the two treatment groups (44 [50%] to the ST group and 44 [50%] to the NST group). Eight (9%) patients did not attend the 12 week visit; 80 (91%) patients (18 [23%] men and 62 [78%] women) were included in the modified ITT population (41 [51%] in the ST group and 39 [49%] in the NST group]. The proportion of Graves' orbitopathy composite evaluation responders at 24 weeks was higher in the ST group (21 [51%] of 41 patients) than the NST group (11 [28%] of 39 patients; attributable risk 0·23 [95% CI 0·02-0·44]; p=0·042). 26 adverse events occurred in 21 (24%) of 88 patients in the safety population. One (2%) of 44 patients in each group required treatment discontinuation, with no serious adverse events and no difference between groups. INTERPRETATION: Addition of oral atorvastatin to an ivGC regimen improved Graves' orbitopathy outcomes in patients with moderate-to-severe, active eye disease who were hypercholesterolaemic. Future phase 3 studies, which could potentially recruit patients regardless of low-density lipoprotein cholesterol concentration, are required to confirm this association. FUNDING: Associazione Allievi Endocrinologia Pisana.

[45] *Dong L, Wei W, Han M, Xu G*. **Utility of non-HDL-C in predicting proteinuria remission of idiopathic membranous nephropathy: a retrospective cohort study**. Lipids in health and disease 2021; 20:122.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587945
ABSTRACT
BACKGROUND: Idiopathic membranous nephropathy (IMN) may have various clinical outcomes. Hyperlipidemia is quite common in IMN. However, the utility of the lipid profile in predicting outcomes remains unknown. This study aimed to explore the correlation between hyperlipidemia and proteinuria remission in IMN. METHODS: 256 patients who diagnosed with IMN confirmed by renal biopsy in Wuhan Tongji Hospital from January 2016 to October 2020 were included in this study. The end point was defined as a combination of partial and complete remission. Cox proportional-hazards regression analysis and Kaplan-Meier curve were applied to assess the prognostic value of the lipid profile for proteinuria remission. RESULTS: A total of 153 (59.8%) patients achieved remission and 103 (40.2%) did not. The levels of total cholesterol, low-density lipoprotein, and non-high-density lipoprotein were significantly lower in the remission group than in the non-remission group. Non-high-density lipoprotein level revealed the strongest correlation with proteinuria (Spearman's rho = 0.42; P < 0.001). The multivariate analysis demonstrated that serum total cholesterol [hazard ratio (HR): 0.883; 95% confidence interval (CI): 0.813-0.958; P = 0.003] and non-high-density lipoprotein cholesterol (HR: 0.892; 95% CI: 0.820-0.970; P = 0.007) levels were independent markers to predict proteinuria remission in IMN. CONCLUSIONS: Among the lipid profile, the non-high-density lipoprotein level exhibited the strongest correlation with proteinuria in IMN. Moreover, elevated serum cholesterol and non-high-density lipoprotein cholesterol concentrations at baseline predicted probability of proteinuria non-remission in IMN.

[46] *Eden Friedman Y, Steinberg DM, Canetti M et al.* **An impact of lipid profile and lipid lowering drugs on ≥70 year olds of an upper socioeconomic class: a retrospective cohort study**. Lipids in health and disease 2021; 20:120.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587967

ABSTRACT
BACKGROUND: Life expectancy has greatly increased, generating an improvement in screening programs for disease prevention, lifesaving drugs and medical devices. The impact of lowering low-density lipoprotein cholesterol (LDL-C) in the very elderly is not well-established. Our aim was to explore the association of LDL-C, high density lipoprotein cholesterol (HDL-C) and lipid lowering drugs (LLDs) on cognitive decline, malignancies and overall survival. METHODS: This was a retrospective cohort study. Our study comprised 1498 (72.7%) males and 561 (27.3%) females, aged ≥70 who had attended the Institute for Medical Screening (IMS), Sheba Medical Center, Israel at least twice during 2013-2019. Data were obtained from the computerized database of the IMS. A manual quality control to identify potential discrepancies was performed. RESULTS: Overall, 6.3% of the subjects treated with LLDs (95/1421) versus 4.2% not treated (28/638), cognitively declined during the study years. No statistically significant effects of LDL-C, HDL-C and LLDs on cognitive decline were observed after correcting for age, prior stroke and other vascular risk factors. With regard to cancer, after adjusting for confounders and multiple inferences, no definite relationships were found. CONCLUSIONS: This analysis of an elderly, high socioeconomic status cohort suggests several relationships between the use of LLDs and health outcomes, some beneficial, especially, with regard to certain types of cancer, but with a higher risk of cognitive decline. Further studies are warranted to clarify the health effects of these medications in the elderly.

[47] *Li Y, Wang X, Jiang F et al.* **Serum lipid levels in relation to clinical outcomes in pregnant women with gestational diabetes mellitus: an observational cohort study**. Lipids in health and disease 2021; 20:125.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587947

ABSTRACT
BACKGROUND: Research on dyslipidemia during pregnancy in women with gestational diabetes mellitus (GDM) has rarely been conducted in Asia. The present study aimed to evaluate maternal mid-trimester lipid profile in relation to GDM and clinical outcomes in these high-risk populations. METHODS: The medical records of 632 pregnant women in the second trimester were retrospectively analyzed. Maternal fasting serum lipids were assayed for total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein A1 (Apo A1) and Apo B concentrations during the second trimester. The atherogenic index of plasma (AIP) was calculated as log (TG/HDL). The clinical outcomes were collected by evaluating delivery mode, postpartum hemorrhage, prematurity, macrosomia, birth weight, body length and neonatal Apgar 5 min score. RESULTS: Levels of TG and AIP were elevated while decreased HDL-C was observed in women with GDM compared with that of the control group. Significant differences were observed in gestational weeks at birth, cesarean section, postpartum hemorrhage, birth weight, body length, prematurity and macrosomia between the two groups. Compared with women with hyperlipidemia, the incidence of GDM and cesarean section was lower in normal lipid group. Women in the hyperlipidemia group had smaller gestational weeks at birth than those in the control group. According to the logistic regression analysis, each unit elevation in AIP increased the risk of GDM by 18.48 times (OR = 18.48, CI: 2.38-143.22). Besides, age (OR = 1.11, CI: 1.06-1.16) and pre-pregnancy BMI (OR = 1.15, CI: 1.07-1.24) were the risk factors of GDM. CONCLUSIONS: These findings suggested that reasonable lipid control in the second trimester might

reduce the incidence of GDM and be a potential strategy for improving clinical outcomes in these high-risk women.

[48] *Pinto LCS, Mello APQ, Izar MCO et al.* **Main differences between two highly effective lipid-lowering therapies in subclasses of lipoproteins in patients with acute myocardial infarction**. Lipids in health and disease 2021; 20:124.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587943
ABSTRACT
BACKGROUND: Large observational studies have shown that small, dense LDL subfractions are related to atherosclerotic cardiovascular disease. This study assessed the effects of two highly effective lipid-lowering therapies in the atherogenic subclasses of lipoproteins in subjects with ST-segment elevation myocardial infarction (STEMI). METHODS: Patients of both sexes admitted with their first myocardial infarction and submitted to pharmacoinvasive strategy (N = 101) were included and randomized using a central computerized system to receive a daily dose of simvastatin 40 mg plus ezetimibe 10 mg or rosuvastatin 20 mg for 30 days. Intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) subfractions were analysed by polyacrylamide gel electrophoresis (Lipoprint System) on the first (D1) and 30th days (D30) of lipid-lowering therapy. Changes in LDL and IDL subfractions between D1 and D30 were compared between the lipid-lowering therapies (Mann-Whitney U test). RESULTS: The classic lipid profile was similar in both therapy arms at D1 and D30. At D30, the achievement of lipid goals was comparable between lipid-lowering therapies. Cholesterol content in atherogenic subclasses of LDL ($p = 0.043$) and IDL ($p = 0.047$) decreased more efficiently with simvastatin plus ezetimibe than with rosuvastatin. CONCLUSIONS: Lipid-lowering therapy with simvastatin plus ezetimibe was associated with a better pattern of lipoprotein subfractions than rosuvastatin monotherapy. This finding was noted despite similar effects in the classic lipid profile and may contribute to residual cardiovascular risk. TRIAL REGISTRATION: ClinicalTrials.gov , NCT02428374, registered on 28/09/2014.

[49] *Urbanowicz TK, Olasińska-Wiśniewska A, Michalak M et al.* **Cardioprotective Effect of Low Level of LDL Cholesterol on Perioperative Myocardial Injury in Off-Pump Coronary Artery Bypass Grafting**. Medicina (Kaunas, Lithuania) 2021; 57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34577798
ABSTRACT
Background and Objectives: Coronary artery disease is still a major cause of death in developed countries. Low-density lipoprotein cholesterol (LDL-C) lowering with statin therapy is a key strategy in major acute coronary events' prevention. The aim of the study was to establish if there is a cardioprotective effect of pre-operative LDL lowering therapy on perioperative myocaridal injury in patients undergoing off-pump coronary artery bypass grafting (CABG). Moreover, the impact of pre-operative LDL level on long term outcome was analysed. Materials and Methods: The retrospective single center analysis included 662 consecutive patients (431 (65%) males and 231 (35%) female, mean age of 65 ± 8) referred for cardiac surgery due to stable chronic coronary syndrome between 2012-2018. The follow up was 9 years. Results: A statistically significant difference was found in postoperative serum Troponin-I for LDL thresholds of 1.8 mmol/L ($p = 0.009$), 2.6 mmol/L ($p = 0.03$) and 3.0 mmol/L ($p = 0.001$). The results indicate that cardioprotective role of LDL is achieved within LDL concentration rate below 1.8 mmol/L (<70 mg/dL). Five patients died perioperatively, whereas 1-

year and 9-year overall mortality rates were 4% (n = 28) and 18.6% (n = 123), respectively. Comparing the survival group with diseased, Mann-Whitney U test showed a statistically significant difference in HDL-C (p = 0.007), Troponin (p = 0.009), Castelli index (p = 0.001) and atherogenic index (p = 0.004). Preoperative levels of total cholesterol, LDL-C and HDL-C did not significantly differ between survivors and diseased. The 9-year mortality risk did not differ significantly between subgroups divided according to LDL-C thresholds of 1.4 mmol/L (55 mg/dL), 1.8 mmol/L (70 mg/dL), 2.6 mmol/L (100 mg/dL) and 3.0 mmol/L (116 mg/dL). Conclusions: Preoperative low level of LDL-C cholesterol (below 1.83 mmol/L, 70 mg/dL) has a cardioprotective effect on perioperative myocardial injury in off-pump coronary artery bypass grafting.

[50] *Dain CP, Ganapathi S, Geevar Z et al.* **The traditional and modifiable risk factors of coronary artery disease - a community-based cross-sectional study among 2 populations**. Medicine (Baltimore) 2021; 100:e27350.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34596141
ABSTRACT
A community-based cross-sectional study was undertaken by the Cardiology Society of India (Kerala Chapter) to determine the prevalence of coronary artery disease (CAD) and its risk factors. The periodontal health status of the rural and urban participants in the Thiruvananthapuram district of Kerala was evaluated to document any association between periodontal disease (PD) and CAD and to describe any shared risk factors.The participants were selected using a multistage cluster random sampling method. Socio-demographic data and personal histories were collected using a structured interview schedule and validated tools. Body mass index, blood pressure, electrocardiogram, and biochemical investigations were recorded and analyzed using standard protocols. A modification of the Ramfjord periodontal disease index was used to assess periodontal health.PD was more frequent among rural (61.4%) than in the urban population (35.5%). The frequencies of CAD associated with PD in the rural and urban populations were 82.6% and 40.5%, respectively. PD was not found to be a significant risk factor for CAD in the univariate regression analysis of urban populations. In the rural population, the odds of PD as a risk factor for CAD were found to be 3.08 (95% CI [1.38-8.38]) and significant (P=.043) in univariate regression analysis and 1.54 (95% CI: 0.44-5.4) and non-significant (P=.503) in the multivariate regression analysis.In rural areas, male sex and dyslipidemia demonstrated borderline significance as risk factors for CAD. PD was not found to be an independent risk factor after adjusting for age, sex, tobacco use, hypertension, sedentary lifestyle, and dyslipidemia. Male sex and dyslipidemia were identified as shared risk factors between PD and CAD, which could have confounded the significant association between the latter. In urban areas, age, male sex, and dyslipidemia demonstrated an independent association with CAD. This study could not establish an independent association between PD and CAD in either community. Future epidemiological studies should identify and recruit novel environmental factors to understand the interrelationships between PD and CAD and focus on the role of effect modifiers that may have a protective role against PD colluding with CAD.

[51] *Huang G, Lu H, Li M et al.* **Association of total cholesterol and atherosclerotic cardiovascular disease in patients with follicular thyroid cancer: A real-world study from Chinese populations**. Medicine (Baltimore) 2021; 100:e27310.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34596129

ABSTRACT
The association between serum total cholesterol (TC) level and incident atherosclerotic cardiovascular disease (ASCVD) in patients with follicular thyroid cancer postthyroidectomy is unknown.This was a retrospective study and patients (n=384) were divided into low and high TC groups according to the median TC level. Incidence of composite ASCVD (myocardial infarction, ischemic stroke, and cardiovascular death) was compared between these 2 groups and factors contributing to the association of TC and ASCVD were evaluated.Patients in the high TC group were older and more likely to have diabetes and have higher C-reactive protein level. After thyroidectomy, serum levels of free triiodothyronine and free thyroxine were lower while thyroid-stimulating hormone level was higher in the high TC group. 31.6% and 39.7% of patients developed hypothyroidism in the low and high TC groups (P<.05) postthyroidectomy. The incidence rate of composite ASCVD was higher in the high TC versus low TC groups, with incidence rate ratio of 1.69 (95% confidence interval [CI]: 1.07-2.69), which was mainly driven by a higher incidence rate of myocardial infarction in the high TC group (incidence rate ratio: 2.11 and 95% CI: 1.10-4.20). In unadjusted model, higher TC was associated with 73% higher risk of composite ASCVD. After adjustment for hypothyroidism, the association of higher TC and composite ASCVD was attenuated into insignificance, with hazard ratio of 0.92 and 95% CI: 0.81 to 1.34.Increased TC level was associated with composite ASCVD, which might be attributed to hypothyroidism postthyroidectomy. The use of levothyroxine might help to prevent hypercholestemia and reduce the incidence of ASCVD.

[52] *Benson JC, Nardi V, Hunt CH et al.* **Cardiovascular risk factors and cervical carotid plaque features on CT angiography**. Neuroradiol J 2021:19714009211047450.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34569868
ABSTRACT
BACKGROUND: Little is known about the impact that cardiovascular (CV) risk factors have on the formation of various carotid atherosclerotic plaque features. This study set out to assess the association between CV risk factors and plaque characteristics on computed tomography (CT) angiography (CTA). MATERIALS AND METHODS: A retrospective review was completed of consecutive patients that underwent a carotid endarterectomy and had CTA imaging of the head and neck vasculature. Atherosclerotic plaques of both carotid arteries were evaluated for calcification(s), low-density plaque (LDP) components, ulceration(s), and degree of stenosis. Various clinical CV risk factors were assessed using medical records. Last recorded laboratory levels were dichotomized into categories: total cholesterol <200 or ≥200 mg/dL, low-density lipoprotein (LDL) <130 or ≥130 mg/dL, high-density lipoprotein <35 or ≥35 mg/dL, and triglyceride <200 or ≥200 mg/dL. RESULTS: Of 97 included patients, 62 were male (63.9%); the average age was 72.7 (standard deviation = 9.5). Calcifications were in 95/97 (97.9%) of patients (one or both carotid plaques); LDP components were in 73/97 (75.3%), and ulcerations were in 21/97 (21.6%). Elevated total cholesterol and elevated LDL levels were both associated with a higher likelihood of LDP components ($p = 0.004$ and $p = 0.02$, respectively). There were no other statistically significant associations between individual plaque features or severity of arterial stenosis and CV risk factors. CONCLUSION: In carotid atherosclerotic plaques, LDP components are more frequently present in one or both carotid arteries in patients with elevated total cholesterol and/or LDL levels. Such findings raise the possibility that cholesterol levels may be directly related to the formation of specific high-risk plaque features.

[53] *Klonizakis M, Bugg A, Hunt B et al.* **Assessing the Physiological Effects of Traditional Regional Diets Targeting the Prevention of Cardiovascular Disease: A Systematic Review of Randomized Controlled Trials Implementing Mediterranean, New Nordic, Japanese, Atlantic, Persian and Mexican Dietary Interventions**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34578911

ABSTRACT

Traditional regional diets are considered as sustainable dietary patterns, while many have been examined with regard to their health benefits. The aim of the present systematic review was to aggerate all evidence on the physiological effects of regional diets among adults at high risk for cardiovascular disease (CVD). Three databases were searched for randomized controlled trials (RCTs) implementing any regional diet (Mediterranean (MedD), Persian, Southern European Atlantic, Japanese, Chinese, new Nordic, or other) while examining cardiovascular risk factors among adults at increased risk. Primary outcomes included anthropometric indices and secondary outcomes involved blood lipid concentrations, glucose metabolism, inflammation and other markers of CVD progression. Twenty RCTs fulfilled the study's criteria and were included in the qualitative synthesis, with the majority implementing a MedD. Adherence to most of the regional diets induced a reduction in the BW and anthropometric indices of the participants. The majority of RCTs with blood pressure endpoints failed to note a significant reduction in the intervention compared to the comparator arm, with the exception of some new Nordic and MedD ones. Despite the interventions, inflammation markers remained unchanged except for CRP, which was reduced in the intervention groups of one new Nordic, the older Japanese, and the Atlantic diet RCTs. With regard to blood lipids, regional diet interventions either failed to induce significant differences or improved selective blood lipid markers of the participants adhering to the experimental regional diet arms. Finally, in the majority of RCTs glucose metabolism failed to improve. The body of evidence examining the effect of regional dietary patterns on CVD risk among high-risk populations, while employing an RCT design, appears to be limited, with the exception of the MedD. More research is required to advocate for the efficacy of most regional diets with regard to CVD.

[54] *Kochan Z, Szupryczynska N, Malgorzewicz S, Karbowska J.* **Dietary Lipids and Dyslipidemia in Chronic Kidney Disease**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34579015

ABSTRACT

The progression of chronic kidney disease (CKD) leads to altered lipid metabolism. CKD patients exhibit high blood triglyceride (TG) levels, reduced concentrations and functionality of high-density lipoproteins (HDL), and elevated levels of atherogenic small, dense, low-density lipoproteins (sdLDL). Disorders of lipid metabolism and other metabolic disturbances place CKD patients at high risk for cardiovascular disease (CVD). Extensive evidence supports the cardioprotective effects of unsaturated fatty acids, including their beneficial effect on serum cholesterol and TG levels. Dietary lipids might therefore be especially important in the nutritional management of CKD. We review current dietary recommendations for fat intake by CKD patients and suggest potential nutritional interventions by emphasizing dietary lipids that might improve the blood lipid profile and reduce cardiovascular risk in CKD.

[55] *Kwon YJ, Lee S, Lee HS, Lee JW*. **Differing Nutrient Intake and Dietary Patterns According to the Presence of Hyper-Low-Density Lipoprotein Cholesterolemia or Hypertriglyceridemia**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34578886
ABSTRACT
Dietary choices may have differing effects on low-density lipoprotein cholesterol or triglyceride levels. The aim of this study was to investigate daily nutrient intake and dietary patterns of individuals with hyper-low-density lipoprotein cholesterolemia (hLDL) and hypertriglyceridemia (hTG) in a large Korean population-based study using propensity score (PS) matching. This study used data from the Korea National Health and Nutrition Examination Survey. Propensity score values for the predicted probability of patients with hLDL or hTG were estimated using logistic regression analysis, with age, sex, body mass index, alcohol consumption, smoking status, physical activity status, hypertension, and diabetes. After PS matching, intake of carbohydrates (%) was significantly lower ($p = 0.021$), and intake of fats (%) and saturated fatty acids (%) was significantly higher in the hLDL group than in the non-hLDL group ($p = 0.025$ and $p = 0.013$, respectively). The percentage of individuals with a high score for the Korean Healthy Eating Index (KHEI) "whole grains" or "saturated fatty acids" components was higher in the non-hLDL group than in the hLDL group ($p < 0.05$ for both). Dietary sodium/potassium ratio was significantly higher in the hTG than in the non-hTG ($p = 0.049$). Our results suggest that individualized dietary information and counseling require consideration of a person's specific lipid levels.

[56] *López-Espinoza M, Chacón-Moscoso S, Sanduvete-Chaves S et al.* **Effect of a Ketogenic Diet on the Nutritional Parameters of Obese Patients: A Systematic Review and Meta-Analysis**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34578824
ABSTRACT
The effect of a ketogenic diet (KD) on biochemical parameters and nutritional status has been the subject of debate over the years, as several randomized clinical trials (RCTs) obtained different results. METHOD: A systematic review and random-effects meta-analysis of RCTs comparing KD with a balanced diet was performed by means of a search of PubMed, Cochrane Library, Scopus, and Web of Science. Trials where the method for measuring the response variables was unclear, those that considered pathologies other than chronic non-communicable diseases and those with participants receiving pharmacological treatment for obesity were excluded from the comparison. RESULTS: Of the studies included in the meta-analysis, no statistically significant standardized mean differences were observed for body mass index (BMI) ($d = -0.457$, $p = 0.359$), total cholesterol, COL-T ($d = 0.230$, $p = 0.591$), high-density lipoprotein, HDL ($d = -0.028$, $p = 0.934$), low-density lipoprotein, LDL ($d = 0.528$, $p = 0.173$), or triglycerides, TG ($d = -0.283$, $p = 0.222$), with high values of heterogeneity. The percentage of women included in the studies is a significant moderating variable in terms of BMI ratio ($z = -6.68$, $p < 0.001$) and TG ($z = -2.27$, $p = 0.023$). CONCLUSION: A KD shows no more benefits on nutritional parameters than a balanced diet, and adverse effects of being on the diet are sometimes reported.

[57] *Penson PE, Banach M*. **Nutraceuticals for the Control of Dyslipidaemias in Clinical Practice**. Nutrients 2021; 13.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34578834

ABSTRACT

Dyslipidaemias result in the deposition of cholesterol and lipids in the walls of blood vessels, chronic inflammation and the formation of atherosclerotic plaques, which impede blood flow and (when they rupture) result in acute ischaemic episodes. Whilst recent years have seen enormous success in the reduction of cardiovascular risk using conventional pharmaceuticals, there is increasing interest amongst patients and practitioners in the use of nutraceuticals to combat dyslipidaemias and inflammation in cardiovascular disease. Nutraceutical is a portmanteau term: 'ceutical' indicate pharmaceutical-grade preparations, and 'nutra' indicates that the products contain nutrients from food. Until relatively recently, little high-quality evidence relating to the safety and efficacy of nutraceuticals has been available to prescribers and policymakers. However, as a result of recent randomised-controlled trials, cohort studies and meta-analyses, this situation is changing, and nutraceuticals are now recommended in several mainstream guidelines relating to dyslipidaemias and atherosclerosis. This article will summarise recent clinical-practice guidance relating to the use of nutraceuticals in this context and the evidence which underlies them. Particular attention is given to position papers and recommendations from the International Lipid Expert Panel (ILEP), which has produced several practical and helpful recommendations in this field.

[58] *Protic O, Bonfigli AR, Antonicelli R*. **Nutraceutical Combinations in Hypercholesterolemia: Evidence from Randomized, Placebo-Controlled Clinical Trials**. Nutrients 2021; 13.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34579005

ABSTRACT

There is an increasing number of nutraceutical combinations (NCs) on the market for hypercholesterolemia, although clinical trials to verify their safety and efficacy are scarce. We selected fourteen randomized, placebo-controlled clinical trials (RCTs) on different lipid-lowering NCs in hypercholesterolemic subjects. We described each compound's mechanism of action and efficacy in the mixtures and summarized the clinical trials settings and NCs safety and efficacy results. Almost all NCs resulted efficient against hypercholesterolemia; only one reported no changes. Interestingly, red yeast rice (RYR) was present in eleven mixtures. It is not clear whether the lipid-lowering efficacy of these combinations derives mainly from the RYR component monacolin K "natural statin" single effect. Up to now, few RCTs have verified the efficacy of every single compound vs. NCs to evaluate possible additive or synergistic effects, probably due to the complexity and the high resources request. In conclusion, to manage the arising nutraceutical tide against hypercholesterolemia, it could be helpful to increase the number and robustness of clinical studies to verify the efficacy and safety of the new NCs.

[59] *Ros E, Singh A, O'Keefe JH*. **Nuts: Natural Pleiotropic Nutraceuticals**. Nutrients 2021; 13.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34579146

ABSTRACT

Common nuts (tree nuts and peanuts) are energy-dense foods that nature has gifted with a complex matrix of beneficial nutrients and bioactives, including monounsaturated and polyunsaturated fatty acids, high-quality protein, fiber, non-sodium minerals, tocopherols, phytosterols, and antioxidant phenolics. These nut components synergize to favorably influence metabolic and vascular physiology pathways, ameliorate cardiovascular risk factors and improve cardiovascular prognosis. There is

increasing evidence that nuts positively impact myriad other health outcomes as well. Nut consumption is correlated with lower cancer incidence and cancer mortality, and decreased all-cause mortality. Favorable effects on cognitive function and depression have also been reported. Randomized controlled trials consistently show nuts have a cholesterol-lowering effect. Nut consumption also confers modest improvements on glycemic control, blood pressure (BP), endothelial function, and inflammation. Although nuts are energy-dense foods, they do not predispose to obesity, and in fact may even help in weight loss. Tree nuts and peanuts, but not peanut butter, generally produce similar positive effects on outcomes. First level evidence from the PREDIMED trial shows that, in the context of a Mediterranean diet, consumption of 30 g/d of nuts (walnuts, almonds, and hazelnuts) significantly lowered the risk of a composite endpoint of major adverse cardiovascular events (myocardial infarction, stroke, and death from cardiovascular disease) by ≈30% after intervention for 5 y. Impressively, the nut-supplemented diet reduced stroke risk by 45%. As they are rich in salutary bioactive compounds and beneficially impact various health outcomes, nuts can be considered natural pleiotropic nutraceuticals.

[60] *Alghamdi A, Balkhi B, Altowaijri A et al.* **Cost-Effectiveness Analysis of Evolocumab for the Treatment of Dyslipidemia in the Kingdom of Saudi Arabia**. Pharmacoecon Open 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34582002
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitors, such as evolocumab, are cholesterol-lowering drugs effective in lowering lipid levels in high-risk patients with primary hypercholesterolemia or mixed dyslipidemia. OBJECTIVE: This study assessed the cost effectiveness of evolocumab in combination with lipid-lowering therapies (LLTs) compared with LLTs alone, from a public healthcare perspective in the Kingdom of Saudi Arabia (KSA). METHODS: A Markov cohort state transition model was used, incorporating efficacy estimates from the FOURIER clinical trial and baseline cardiovascular event rates observed in clinical practice. Other model inputs were extracted from the literature and Saudi sources. RESULTS: In patients with clinically evident atherosclerotic cardiovascular disease and baseline low-density lipoprotein cholesterol ≥ 70 or ≥ 100 mg/dL, adding evolocumab to a maximally tolerated statin, with or without ezetimibe, was associated with incremental cost-effectiveness ratios (ICERs) of Saudi Arabian riyal (SAR) 109,274 ($US60,708) per quality-adjusted life-year (QALY) gained and SAR75,163 ($US41,757) per QALY gained, respectively. The ICER was SAR22,391 ($US12,440) per QALY gained in patients with heterozygous familial hypercholesterolemia. Sensitivity analysis results were robust to changes in model parameters and fell below the willingness-to-pay threshold of up to three times gross domestic product per capita in 2019 (SAR264,813 [$US147,118]). CONCLUSION: Evolocumab can be considered a cost-effective treatment option for patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia in the KSA.

[61] *Döbert M, Wright A, Varouxaki AN et al.* **STATIN trial: predictive performance of competing-risk model in screening for pre-eclampsia at 35-37 weeks' gestation**. Ultrasound Obstet Gynecol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34580947
ABSTRACT

OBJECTIVE: To examine the predictive performance of the previously reported competing risks model of screening for preeclampsia (PE) at 35-37 weeks' gestation by combinations of maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1) in the validation dataset derived from the screened population of the STATIN study. METHODS: This was a prospective third-trimester multicenter study of screening for PE in 29,677 singleton pregnancies by means of a previously reported algorithm that combines maternal risk factors and biomarkers. Women in the high-risk group were invited to participate in a trial of pravastatin versus placebo but the trial showed no evidence of an effect of pravastatin in the prevention of PE. Patient-specific risks of delivery with PE were calculated using the competing risks model and the performance of screening for PE by maternal risk factors alone and various combinations of risk factors and MAP, UtA-PI, PLGF and sFLT-1 was assessed. We examined the predictive performance of the model by first, the ability of the model to discriminate between the PE and no PE groups using the area under the receiver operating characteristic (AUROC) curve and the detection rate (DR) at fixed false positive rate (FPR) of 10%, and second, calibration by measurements of calibration slope and calibration-in-the-large. RESULTS: The study population of 29,677 pregnancies contained 653 that developed PE. In screening for PE by a combination of maternal risk factors, MAP, PlGF and sFLT-1 (triple test), the DR at 10% FPR was 79% (95% CI 76, 82%) and the results were consistent with the data used for developing the algorithm. Addition of UtA-PI did not improve the prediction provided by the triple test. The AUROC curve was 0.923 (95% CI 0.913, 0.932) demonstrating a very high discrimination between affected and unaffected pregnancies. Similarly, the calibration slope was 0.875 (95% CI 0.831, 0.919) demonstrating a good agreement between the predicted risks and observed incidence of PE. CONCLUSION: The competing risks model provides an effective and reproducible method for third-trimester prediction of term PE.

[62] *Miura Y, Kanamaru H, Yasuda R et al.* **Nonfasting Triglyceride as an Independent Predictor of Carotid Restenosis After Carotid Endarterectomy or Carotid Artery Stenting**. World neurosurgery 2021; 156:e415-e425.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34587521

ABSTRACT

OBJECTIVE: Nonfasting serum triglyceride (TG) level is attracting more and more attention as an atherosclerosis-promoting factor. However, no study has investigated the relationships between nonfasting TG levels and carotid restenosis after carotid endarterectomy (CEA) or carotid artery stenting (CAS). This study was conducted to investigate if nonfasting TG levels can be used to assess a risk for carotid restenosis after CEA or CAS. METHODS: This was a single-center retrospective study. We reviewed 201 consecutive primary carotid artery revascularization procedures (39 CEAs and 162 CASs), which were performed from 2008 to 2018 for 179 patients (163 men and 16 women) with atherosclerotic carotid stenosis, and were followed up for at least 1 year. Clinical variables including nonfasting lipid profiles and findings of magnetic resonance plaque imaging were compared between groups with and without postprocedural carotid restenosis (≥50% stenosis on ultrasonography). RESULTS: During a mean follow-up period of 1413 days, 24 of 201 carotid stenosis procedures (11.9%) suffered restenosis after successful revascularization procedures. Multivariate analyses demonstrated that nonfasting TG level was the only independent risk factor of postprocedural restenosis. The receiver operating characteristic curve analyses revealed

that a cutoff value of nonfasting TG to discriminate postprocedural carotid restenosis was 127.5 mg/dL, which was much lower than the upper limit of normal. CONCLUSIONS: This study showed that nonfasting TG level may be a useful marker to predict carotid restenosis after CEA or CAS, and could be a new therapeutic target to prevent carotid restenosis after revascularization procedures.

[63] *Yang Y, Yang D, Zhao W et al.* **[Establishment of a nomogram prediction model for coronary artery disease risk in elderly patients with acute myocardial infarction]**. Zhonghua wei zhong bing ji jiu yi xue 2021; 33:967-972.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34590565

ABSTRACT

OBJECTIVE: To establish a nomogram model for predicting the risk of coronary artery disease in elderly patients with acute myocardial infarction (AMI). METHODS: The clinical data of elderly patients with AMI who underwent coronary angiography in the department of cardiology of Cangzhou Central Hospital from July 2015 to March 2020 were analyzed, including age, gender, smoking history, underlying diseases, family history, blood pressure, left ventricular ejection fraction (LVEF), and several biochemical indicators at admission, such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein [Lp(a)], apolipoproteins (ApoA, ApoB), ApoA/B ratio, total bilirubin (TBil), direct bilirubin (DBil), indirect bilirubin (IBil), fasting blood glucose (FBG) and uric acid (UA). Patients were divided into model group (2 484 cases) and validation group (683 cases) according to the ratio of 8:2. According to Gensini score, the model group and validation group were divided into mild lesion group (0-20 points) and severe lesion group (≥ 81 points). The differences of each index between different coronary lesion degree groups were compared. Lasso regression and Logistic regression were used to analyze the risk factors of aggravating coronary lesion risk in elderly patients with AMI, and then the nomogram prediction model was established for evaluation and external validation. RESULTS: (1) In the model group, there were significant differences in the family history of coronary heart disease, FBG and HDL-C between the mild lesion group (411 cases) and the severe lesion group (417 cases) [family history of coronary heart disease: 3.6% vs. 7.7%, FBG (mmol/L): 5.88±1.74 vs. 6.43±2.06, HDL-C (mmol/L): 1.48±0.69 vs. 1.28±0.28, all $P < 0.05$]. In the validation group, there were significant differences between the mild lesion group (153 cases) and the severe lesion group [132 cases; FBG (mmol/L): 5.58±0.88 vs. 6.85±0.79, HDL-C (mmol/L): 1.59±0.32 vs. 1.16±0.21, both $P < 0.05$]. (2) Lasso regression analysis showed that family history of coronary heart disease, FBG, and HDL-C were risk factors of coronary artery disease in elderly patients with AMI, with coefficients 0.118, 0.767, and -0.558, respectively. Logistic regression analysis showed that FBG [odds ratio (OR) = 1.479, 95% confidence interval (95%CI) was 1.051-2.082, $P = 0.025$] and HDL-C (OR = 0.386, 95%CI was 0.270-0.553, $P < 0.001$] were independent risk factors of coronary artery disease in elderly patients with AMI. (3) According to the rank score of FBG and HDL-C, the nomogram prediction risk model of aggravating coronary artery disease degree was established for each patient. It was concluded that the risk of coronary artery disease in elderly people with higher FBG level and (or) lower HDL-C level was significantly increased. (4) The nomogram model constructed with the model group data predicted the risk concordance index (C-index) was 0.689, and the C-index of the external validation group was 0.709. CONCLUSIONS: FBG and HDL-C are independent risk factors for aggravating coronary artery disease in elderly patients with AMI. The nomogram model of aggravating coronary artery disease in elderly patients with AMI has good predictive ability, which can

provide more intuitive research methods and clinical value for preventing the aggravation of coronary artery disease in elderly patients.