[1] *Sankaranarayanan A, Pratt R, Anoop A et al.* **Serum Lipids and Suicidal Risk among Patients with Schizophrenia Spectrum Disorders: Systematic Review and Meta-Analysis**. Acta Psychiatr Scand 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33834474

ABSTRACT
OBJECTIVE: A systematic review of literature was conducted to determine the association between serum lipids and suicidality in people with schizophrenia spectrum disorders. METHODS: We undertook a systematic search of multiple databases for studies that ascertained an association between serum lipids and suicidality in adult patients with schizophrenia spectrum disorders (18-65 years) from database inception to 2(nd) September 2020. Qualitative analysis was done using National Institute of Health (NIH) scales. The Standard Mean Difference (SMD) and 95% confidence intervals (CI) were calculated for each study and standardized relative to the study. Adjusted p-value, Z-test, and heterogeneity were calculated, as well as testing for publication bias. RESULTS: Of 1262 records identified, 17 studies (n= 3113) were included in our systematic review, while 11 studies were included in the meta-analysis. The majority of studies (11) rated fair on qualitative analysis. Data from seven studies (n= 1597) revealed a medium effect size for an association between low total cholesterol and suicide attempts (SMD -0.560; 95% CI - 0.949 - 0.170; p =0.005). People with history of suicide attempt had a mean cholesterol value 0.56 SD lower than the mean in those without suicide attempts. There were differences in how a suicide attempt was defined and there was high heterogeneity (I(2) = 83.3%). No significant association was found between any of the serum lipid parameters and suicide ideation. Funnel-plot analysis suggested small study effects with publication bias. CONCLUSIONS: Suicide attempts in people with schizophrenia spectrum disorders is associated with low mean total cholesterol levels.

[2] *Ahrens I, Khachatryan A, Monga B et al.* **Association of Treatment Intensity and Adherence to Lipid-Lowering Therapy with Major Adverse Cardiovascular Events Among Post-MI Patients in Germany**. Adv Ther 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33830461

ABSTRACT
INTRODUCTION: Patients with a history of myocardial infarction (MI) are at very high risk of subsequent cardiovascular events. This study evaluated the association of treatment intensity and adherence to lipid-lowering therapies (LLT) with major adverse cardiovascular events (MACE) among post-MI patients in Germany. METHODS: We carried out a retrospective cohort study using German health claims data (2010-2015). We included patients ≥ 18 years, with a history of MI and who started an LLT (statin and/or ezetimibe), between 2011 and 2013. The follow-up period started 1 year after the second LLT prescription and continued until MACE, all-cause death or December 31, 2015, whichever occurred first. Treatment intensity was classified based on expected low-density lipoprotein cholesterol reduction; adherence was measured by the proportion of days covered using prescription data. A combined adherence-adjusted intensity variable was created by multiplying intensity and adherence. We used Cox proportional hazards models to control for age, sex, Charlson Comorbidity Index and other cardiovascular risk factors at baseline. RESULTS: A total of 14,944 patients were included. Mean age was 66.7 (SD = 13.0) years; 68.7% of patients were men. Each 10% increase in treatment intensity, adherence, or adherence-adjusted intensity was associated with a decrease in the risk of MACE of 17% (HR = 0.83, 95% CI 0.79-0.87), 5% (HR = 0.95, 95% CI 0.94-0.97), and

14% (HR = 0.86, 95% CI 0.83-0.90), respectively. CONCLUSIONS: Higher treatment intensity and/or adherence of LLT was associated with significantly lower risk of MACE in post-MI patients. Strategies to tailor intensity to patient profiles and improve adherence could reduce the risk of cardiovascular events.

[3] *Fleming JA, Kris-Etherton PM, Petersen KS, Baer DJ*. **Effect of varying quantities of lean beef as part of a Mediterranean-style dietary pattern on lipids and lipoproteins: a randomized crossover controlled feeding trial**. The American journal of clinical nutrition 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33826691

ABSTRACT

BACKGROUND: It remains unclear whether red meat consumption is causatively associated with cardiovascular disease (CVD) risk, and few randomized controlled studies have examined the effect of incorporating lean beef into a healthy dietary pattern. OBJECTIVES: To evaluate the effects of a Mediterranean (MED) diet (carbohydrate 42%, protein 17%, fat 41%, SFAs 8%, MUFAs 26%, PUFAs 8%) with 14 (MED0.5; 0.5 oz), 71 (MED2.5; 2.5 oz), and 156 (MED5.5; 5.5 oz) g/d/2000 kcal lean beef compared with an average American diet (AAD; carbohydrate 52%, protein 15%, fat 33%, SFAs 12%, MUFAs 13%, PUFAs 8%) on lipid and lipoprotein concentrations, particle number, and size. METHODS: This was a multicenter, 4-period controlled feeding, randomized crossover study. Fifty-nine generally healthy males and females (BMI 20-38 kg/m2; age 30-65 y) consumed each diet for 4 wk with a ≥1-wk washout between the diets. Fasting blood samples were collected at baseline and at the end of each 4-wk period. Lipid subfractions were measured by NMR. RESULTS: Compared with the AAD, all 3 MED diets decreased LDL cholesterol (MED0.5: -10.3 mg/dL; 95% CI: -5.4, -15.7 mg/dL; MED2.5: -9.1 mg/dL; 95% CI: -3.9, -14.3 mg/dL; MED5.5: -6.9 mg/dL; 95% CI: -1.7, -12.1 mg/dL; $P < 0.0001$). All MED diets elicited similar reductions in total LDL particle number compared with baseline ($P < 0.005$); however, significant decreases only occurred with MED0.5 (-91.2 nmol/L; 95% CI: -31.4, -151.0 nmol/L) and MED2.5 (-85.3 nmol/L; 95% CI: -25.4, -145.2 nmol/L) compared with AAD ($P < 0.003$). Compared with the AAD, non-HDL cholesterol ($P < 0.01$) and apoB ($P < 0.01$) were lower following the 3 MED diets; there were no differences between the MED diets. All diets reduced HDL-cholesterol and HDL particle number from baseline ($P < 0.01$). CONCLUSIONS: Lipid and lipoprotein lowering was not attenuated with the inclusion of lean beef in amounts ≤71 g (2.5 oz)/d as part of a healthy low-saturated-fat Mediterranean-style diet.This study is registered at clinicaltrials.gov as NCT02723617.

[4] *Arakelian VS*. **[Amputation as an anticipated consequence of peripheral artery disease and ways to improve the prognosis of limb salvage]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2021; 27:182-190.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33825747

ABSTRACT

Peripheral artery disease is a common and acute social burden worldwide. The main method of treatment of PAD consists in open surgical or endovascular revascularization. However, despite steady growth of the number and quality of interventions, the incidence of lower-limb amputation still remains at a high level. Lower-limb amputation is a severe psychological blow for the patient and leads to significant deterioration of his or her quality of life, as well as has an extremely negative prognosis concerning the frequency of subsequent complications and survival. Consequences of

amputations include not only severe disability but also an unfavourable prognosis of life, thus determining the necessity of adequate prevention of such events. Reconstructive and endovascular operations, as well as amputations are associated with a significant increase of the probability of the development of major adverse cardiovascular events, the frequency of repeat hospitalizations and, finally, the cost of treatment. Prescribing pathogenetically substantiated antithrombotic therapy is considered to be one of the methods to improve the results of surgical treatment and prognosis for the patient. Presented in the article is a literature review making it possible to assess the risks and consequences of amputations in patients with PAD, as well as to determine therapy capable of improving the prognosis.

[5] *Elgendy IY, Elshazly MB*. **LDL-C-lowering therapies reduce major vascular events in patients aged ≥75 y**. Annals of internal medicine 2021; 174:Jc38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33819068
ABSTRACT
Gencer B, Marston NA, Im K, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2020;396:1637-43. 33186535.

[6] *Georgakis MK, van der Laan SW, Asare Y et al.* **Monocyte-Chemoattractant Protein-1 Levels in Human Atherosclerotic Lesions Associate With Plaque Vulnerability**. Arteriosclerosis, thrombosis, and vascular biology 2021:Atvbaha121316091.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33827260
ABSTRACT
OBJECTIVE: To determine whether MCP-1 (monocyte chemoattractant protein 1) levels in human atherosclerotic plaques associate with plaque vulnerability features. Approach and Results: We measured MCP-1 levels in human atherosclerotic plaque samples from 1199 patients in the Athero-EXPRESS Biobank who underwent endarterectomy for treatment of carotid stenosis. We explored associations with histopathologic and molecular features of plaque vulnerability, clinical plaque manifestations, and vascular events up to 3 years after endarterectomy. Following adjustments for age, sex, and vascular risk factors, MCP-1 plaque levels were associated with histopathologic markers of plaque vulnerability (large lipid core, low collagen content, high macrophage burden, low smooth muscle cell burden, intraplaque hemorrhage) and with a composite vulnerability index (range 0-5, β per SD increment in MCP-1, 0.42 [95% CI, 0.30-0.53], P=5.4×10(-13)). We further found significant associations with higher plaque levels of other chemokines and proinflammatory molecules and markers of neovascularization and matrix turnover. When exploring clinical plaque instability, MCP-1 plaque levels were higher among individuals with symptomatic plaques as compared with those with asymptomatic plaques (odds ratio per SD increment in MCP-1, 1.36 [95% CI, 1.09-1.69]). MCP-1 levels were further associated with a higher risk of periprocedural major adverse vascular events and strokes occurring in the first 30 days after plaque removal. CONCLUSIONS: Higher MCP-1 plaque levels are associated with histopathologic, molecular, and clinical hallmarks of plaque vulnerability in individuals undergoing carotid endarterectomy. Our findings highlight a role of MCP-1 in clinical plaque instability in humans and complement previous epidemiological, genetic, and experimental studies supporting the translational perspective of targeting MCP-1 signaling in atherosclerosis.

[7] *Mashayekhi-Sardoo H, Atkin SL, Montecucco F, Sahebkar A*. **Potential Alteration of Statin-Related Pharmacological Features in Diabetes Mellitus**. BioMed research international 2021; 2021:6698743.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33834073

ABSTRACT

OBJECTIVE: Type 2 diabetes mellitus is a chronic metabolic disease caused by insulin resistance or insulin deficiency resulting in elevated blood glucose levels. Poorly controlled diabetes is associated with the development of cardiovascular disease and dyslipidemia. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statin) are an important class of therapeutic agents used to control hyperlipidemia and prevent cardiovascular disease in diabetic and nondiabetic patients. Since the effect of diabetes on the pharmacokinetics and pharmacodynamics of drugs and toxins has been shown, the aim was to review previous studies on the efficacy of statins such as atorvastatin, simvastatin, pravastatin, pitavastatin, fluvastatin, and rosuvastatin in clinical and preclinical studies in both diabetic and nondiabetic groups. METHOD: For this purpose, Web of Science, PubMed, Scopus, and Google Scholar databases were reviewed, and related English articles published until October 2020 were included in this review article. RESULTS: The findings revealed that diabetes affected statin effectiveness through changes in pharmacokinetic parameters such as clearance and biotransformation biomarkers at mRNA and protein levels. Plasma and serum concentrations of statins were accompanied by alteration in cellular activities including oxidative stress, Akt inhibition, and endothelial nitric oxide synthase (eNOS) and phosphorylation that were reflected in changes in the adverse drug reaction profile of the differing statins. CONCLUSION: Given that dyslipidemia frequently accompanies diabetes and statin therapy is common, more clinical studies are needed regarding the effects of diabetes on the effectiveness of these drugs.

[8] *Ryou IS, Chang J, Son JS et al.* **Association between CVDs and initiation and adherence to statin treatment in patients with newly diagnosed hypercholesterolaemia: a retrospective cohort study**. BMJ open 2021; 11:e045375.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33827840

ABSTRACT

OBJECTIVES: To evaluate the association between incident cardiovascular disease (CVD) and initiation and adherence to statin treatment for primary prevention of CVD in patients with newly diagnosed hypercholesterolaemia. DESIGN: A population-based retrospective cohort study. SETTING: This study used National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) from Republic of Korea. PARTICIPANTS: This study included 11 320 participants without previous history of CVD aged between 40 and 79 years who had elevated total cholesterol level (more than 240 mg/dL) and had initiated statin treatment within 24 months of the national health screening from 2004 to 2012 identified in the NHIS-HEALS. PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcome, CVD, was defined as first-ever admission or death due to ischaemic heart disease, acute myocardial infarction, revascularisation or stroke, or December 31 2013. The HRs of CVD according to statin adherence were calculated according to stratification by Systematic COronary Risk Evaluation. RESULTS: Early statin initiation significantly lowered risk of CVD outcomes compared with late initiation (HR of late statin user, 1.24; 95% CI 1.02 to 2.51). Among early initiators, statin discontinuers had a significantly higher risk for CVD compared with

persistent users (HR, 1.71; 95% CI 1.10 to 2.67), while statin reinitiators had an attenuated risk increase (HR 1.34, 95% CI 0.79 to 2.30). CONCLUSIONS: Among statin users with newly diagnosed hypercholesterolaemia, early statin initiation is associated with lower CVD risk compared with late initiation. Furthermore, statin discontinuation is associated with increased risk of CVD, but reinitiation attenuated the risk.

[9] *Helderman RC, Whitney DG, Duta-Mare M et al.* **Loss of function of lysosomal acid lipase (LAL) profoundly impacts osteoblastogenesis and increases fracture risk in humans**. Bone 2021; 148:115946.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33838322
ABSTRACT
Lysosomal acid lipase (LAL) is essential for cholesteryl ester (CE) and triacylglycerol (TAG) hydrolysis in the lysosome. Clinically, an autosomal recessive LIPA mutation causes LAL deficiency (LALD), previously described as Wolman Disease or Cholesteryl Ester Storage Disease (CESD). LAL-D is associated with ectopic lipid accumulation in the liver, small intestine, spleen, adrenal glands, and blood. Considering the importance of unesterified cholesterol and fatty acids in bone metabolism, we hypothesized that LAL is essential for bone formation, and ultimately, skeletal health. To investigate the role of LAL in skeletal homeostasis, we used LAL-deficient ((-/-)) mice, in vitro osteoblast cultures, and novel clinical data from LAL-D patients. Both male and female LAL(-/-) mice demonstarted lower trabecular and cortical bone parameters , which translated to reduced biomechanical properties. Further histological analyses revealed that LAL(-/-) mice had fewer osteoblasts, with no change in osteoclast or marrow adipocyte numbers. In studying the cell-autonomous role of LAL, we observed impaired differentiation of LAL(-/-) calvarial osteoblasts and in bone marrow stromal cells treated with the LAL inhibitor lalistat. Consistent with LAL's role in other tissues, lalistat resulted in profound lipid puncta accumulation and an altered intracellular lipid profile. Finally, we analyzed a large de-identified national insurance database (i.e. 2016/2017 Optum Clinformatics®) which revealed that adults (≥18 years) with CESD (n = 3076) had a higher odds ratio (OR = 1.21; 95% CI = 1.03-1.41) of all-cause fracture at any location compared to adults without CESD (n = 13.7 M) after adjusting for demographic variables and osteoporosis. These data demonstrate that alterations in LAL have significant clinical implications related to fracture risk and that LAL's modulation of lipid metabolism is a critical for osteoblast function.

[10] *Nienaber A, Ozturk M, Dolman RC et al.* **Omega-3 long-chain polyunsaturated fatty acids promote antibacterial and inflammation-resolving effects in Mycobacterium tuberculosis-infected C3HeB/FeJ mice, dependent on fatty acid status**. The British journal of nutrition 2021:1-35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33814018
ABSTRACT
Non-resolving inflammation is characteristic of tuberculosis (TB). Given their inflammation-resolving properties, omega-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA) may support TB treatment. This research aimed to investigate the effects of n-3 LCPUFA on clinical and inflammatory outcomes of Mycobacterium tuberculosis (Mtb)-infected C3HeB/FeJ mice with either normal or low n-3 PUFA status before infection. Using a two-by-two design, uninfected mice were conditioned on either an n-3 PUFA-sufficient (n-3FAS) or -deficient (n3FAD) diet for six weeks. One week post-infection, mice

were randomised to either n-3 LCPUFA supplemented (n-3FAS/n-3+ and n3FAD/n3+) or continued on n-3FAS or n3FAD diets for three weeks. Mice were euthanised and fatty acid status, lung bacterial load and pathology, cytokine, lipid mediator, and immune cell phenotype analysed. n-3 LCPUFA supplementation in n-3FAS mice lowered lung bacterial loads (P=0·003), T cells (P=0·019), CD4+ T cells (P=0·014), IFN-γ (P<0·001) and promoted a pro-resolving lung lipid mediator profile. Compared with n-3FAS mice, the n-3FAD group had lower bacterial loads (P=0·037), significantly higher immune cell recruitment and a more pro-inflammatory lipid mediator profile, however, significantly lower lung IFN-γ, IL-1α, IL-1β, and IL-17, and supplementation in the n-3FAD group provided no beneficial effect on lung bacterial load or inflammation. Our study provides the first evidence that n-3 LCPUFA supplementation has antibacterial and inflammation-resolving benefits in TB when provided one week after infection in the context of a sufficient n-3 PUFA status. Whilst a low n-3 PUFA status may promote better bacterial control and lower lung inflammation not benefiting from n-3 LCPUFA supplementation.

[11] *Tertsunen HM, Hantunen S, Tuomainen TP et al.* **A healthy Nordic diet score and risk of incident CHD among men: the Kuopio Ischaemic Heart Disease Risk Factor Study**. The British journal of nutrition 2021:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33823955
ABSTRACT
Healthy Nordic diet has been beneficially associated with CHD risk factors, but few studies have investigated risk of developing CHD. We investigated the associations of healthy Nordic diet with major CHD risk factors, carotid atherosclerosis and incident CHD in middle-aged and older men from eastern Finland. A total of 1981 men aged 42-60 years and free of CHD at baseline in 1984-1989 were investigated. Diet was assessed with 4-d food recording and the healthy Nordic diet score was calculated based on the Baltic Sea Diet Score. Carotid atherosclerosis was assessed by ultrasonography of the common carotid artery intima-media thickness in 1053 men. ANCOVA and Cox proportional hazards regression analyses were used for analyses. Healthy Nordic diet score was associated with lower serum C-reactive protein (CRP) concentrations (multivariable-adjusted extreme-quartile difference 0·66 mg/l, 95 % CI 0·11, 1·21 mg/l) but not with serum lipid concentrations, blood pressure or carotid atherosclerosis. During the average follow-up of 21·6 years (sd 8·3 years), 407 men had a CHD event, of which 277 were fatal. The multivariable-adjusted hazard ratios in the lowest v. the highest quartile of the healthy Nordic diet score were 1·15 (95 % CI 0·87, 1·51) for any CHD event (Ptrend 0·361) and 1·44 (95 % CI 0·99, 2·08) (Ptrend 0·087) for fatal CHD event. We did not find evidence that adherence to a healthy Nordic diet would be associated with a lower risk of CHD or with carotid atherosclerosis or major CHD risk factors, except for an inverse association with serum CRP concentrations.

[12] *Ballantyne CM, Bays H, Catapano AL et al.* **Role of Bempedoic Acid in Clinical Practice**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33818688
ABSTRACT
Many patients do not achieve optimal low-density lipoprotein cholesterol (LDL-C) levels with statins alone; others are unable to tolerate statin therapy. Additional non-statin treatment options including

ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, and bile acid sequestrants are often necessary to further reduce the risk of atherosclerotic cardiovascular disease. This review provides practical guidance as to the use of bempedoic acid to lower LDL-C and includes direction as to which patients may benefit and advice for safety monitoring during treatment. Bempedoic acid, a new class of agent, is a prodrug converted to bempedoyl-CoA by very long-chain acyl-CoA synthetase 1, an enzyme with high expression in the liver but that is undetectable in the skeletal muscle. Bempedoic acid inhibits the enzyme adenosine triphosphate (ATP)-citrate lyase, which lies two steps upstream from β-hydroxy β-methylglutaryl-CoA reductase in the cholesterol biosynthesis pathway. In clinical trials conducted in patients with or at risk for atherosclerotic cardiovascular disease or familial heterozygous hypercholesterolemia, bempedoic acid in combination with statins and/or ezetimibe significantly reduced LDL-C, apolipoprotein B, and high-sensitivity C-reactive protein compared with placebo. Bempedoic acid is generally well tolerated with no clinically meaningful increase in muscle-related symptoms relative to placebo, even in patients taking maximally tolerated statins. A small increase in serum uric acid (mean increase 0.8 mg/dL) is the most noteworthy adverse effect. Bempedoic acid provides an effective and generally well-tolerated medication to further reduce LDL-C in patients taking maximally tolerated statins or manage LDL-C levels in those who are unable to take statins. The potential for a reduced incidence of major cardiovascular events with bempedoic acid is being investigated in the CLEAR Outcomes trial, with results expected in 2023.

[13] *Qian S, You S, Sun Y et al.* **Remnant Cholesterol and Common Carotid Artery Intima-Media Thickness in Patients With Ischemic Stroke**. Circulation. Cardiovascular imaging 2021; 14:e010953.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33832329

ABSTRACT

BACKGROUND: Remnant cholesterol makes great contribution to residual risk of cardiovascular disease, but population-based evidence on the relationship between remnant cholesterol and atherosclerosis is rare. Common carotid artery intima-media thickness (cIMT) is an imaging marker of subclinical atherosclerosis. We aimed to explore the association between remnant cholesterol levels and cIMT in patients with ischemic stroke. METHODS: One thousand four hundred ninety-six ischemic stroke patients with baseline serum lipids and carotid artery imaging data were included in this analysis. Fasting remnant cholesterol was calculated as total cholesterol minus HDL (high-density lipoprotein) cholesterol minus LDL (low-density lipoprotein) cholesterol. Abnormal cIMT was defined as mean cIMT and maximum cIMT value ≥1 mm. Logistic regression and restricted cubic spline models were used to assess the relationships between remnant cholesterol levels and abnormal cIMT. RESULTS: The multivariable-adjusted odds ratios (95% CIs) for the highest versus lowest quartile of remnant cholesterol were 2.06 (1.46-2.91) for abnormal mean cIMT and 1.70 (1.23-2.35) for abnormal maximum cIMT. There were linear associations between remnant cholesterol levels and both abnormal mean cIMT (P for linearity, <0.001) and abnormal maximum cIMT (P for linearity, 0.003). Moreover, the remnant cholesterol-cIMT association remained significant in the subsample of patients with optimal LDL cholesterol levels (n=179). CONCLUSIONS: Elevated fasting remnant cholesterol levels were positively associated with mean cIMT and maximum cIMT in patients with ischemic stroke, even in patients with optimal LDL cholesterol levels. Future prospective studies are needed to verify our findings and to assess the effect of remnant cholesterol-lowering interventions in patients with ischemic stroke.

[14] *Sarak B, Savu A, Kaul P et al.* **Lipid Testing, Lipid-Modifying Therapy, and PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Eligibility in 27 979 Patients With Incident Acute Coronary Syndrome**. Circulation. Cardiovascular quality and outcomes 2021; 14:e006646.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33813856

ABSTRACT

BACKGROUND: While registry-based studies have shown that as many as 1 in 2 patients with stable atherosclerotic cardiovascular disease would be eligible for PCSK9i (proprotein convertase subtilisin-kexin type 9 inhibitor) therapy, this has not been studied in a large population-based postacute coronary syndrome (ACS) cohort. METHODS: We examined lipid testing performed in hospital or within 90 days of discharge and lipid-lowering therapies dispensed within 90 days of discharge in patients surviving for at least 1 year after their first ACS between 2012 and 2018 in the province of Alberta, Canada. We estimated the proportion of patients eligible for PCSK9i and the expected benefits of treatment. RESULTS: Of the 27 979 patients (median age 64.0 years, 29.3% female, 28.0% diabetic), 3750 (13.4%) did not have lipid testing in-hospital or within 90 days postdischarge. Untested patients were more likely to be older, female, from rural areas, to have more comorbidities, to already be on cardioprotective therapies, to present with unstable angina, and were less likely to have invasive interventions (all P<0.0001). Of the 24 229 tested, 18 767 (77.5%) had at least one lipid value above guideline-recommended threshold (LDL [low-density lipoprotein] ≥1.8 mmol/L [70 mg/dL] and non-HDL [high-density lipoprotein] ≥2.6 mmol/L [100 mg/dL]), of which 7284 (38.8%) did not have repeat testing within the year after discharge. Lipid testing in hospital was associated with higher rates of initiation or escalation of statin therapy within 90 days of their ACS (adjusted odds ratio, 2.13 [95% CI, 1.97-2.30). In total, 9592 patients (39.6% of the tested cohort) would be eligible for PCSK9i use, which could result in 184 fewer cardiovascular events over 3.4 years, including cardiovascular death, nonfatal ACS (myocardial infarction or unstable angina requiring hospitalization), and ischemic stroke. CONCLUSIONS: Within 90 days of incident ACS, ≈80% of patients did not meet guideline-recommended lipid thresholds and more than one-third would potentially be eligible for PCSK9i.

[15] *Inagaki Y, Arashi H, Yamaguchi J et al.* **Greater Change in the Eicosapentaenoic Acid to Arachidonic Acid Ratio Is Associated With Decreased Incidence of Cardiovascular Events in Acute Coronary Syndrome Patients With Elevated Triglyceride Levels**. Circulation journal : official journal of the Japanese Circulation Society 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33814529

ABSTRACT

BACKGROUND: This study investigated whether the percentage change (%Δ) in the eicosapentaenoic acid to arachidonic acid (EPA/AA) ratio is associated with cardiovascular event rates among acute coronary syndrome (ACS) patients receiving contemporary lipid-lowering therapy other than polyunsaturated fatty acids (PUFAs).Methods and Results:This post hoc subanalysis of the HIJ-PROPER study included PUFA-naïve patients for whom EPA/AA ratio data were available at baseline and after 3 months. Patients were categorized into 2 groups based on the median %ΔEPA/AA ratio: Group 1, change less than the median; and Group 2, change greater than or equal to the median. The 3-year rates of the primary endpoint, a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina pectoris, were compared between the 2

groups. The median %ΔEPA/AA ratio in Groups 1 and 2 was -26.2% (n=482 patients [49.9%]) and 42.2% (n=483 patients [50.1%]), respectively. At the 3-year follow-up, the occurrence of the primary endpoint was significantly lower in Group 2 than in Group 1 (29/483 [6.0%] vs. 53/482 [11.0%]; hazard ratio 0.53, 95% confidence interval 0.33-0.82; P=0.005). The same trend was observed after adjusting for patient factors (P=0.02). CONCLUSIONS: Among ACS patients receiving contemporary lipid-lowering therapy other than PUFAs, a greater change in the EPA/AA ratio was associated with a lower incidence of cardiovascular events.

[16] *Ghosh SS, Wang J, Yannie PJ et al.* **Over-Expression of Intestinal Alkaline Phosphatase Attenuates Atherosclerosis**. Circulation research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33834851
ABSTRACT
Rationale: Intestinal Alkaline Phosphatase (IAP) is secreted by enterocytes and is present on the apical surface. It not only detoxifies bacterial endotoxin lipopolysaccharide (LPS) in the gut lumen and limits intestinal inflammation but also restricts translocation of LPS into systemic circulation. Diet-induced intestinal barrier dysfunction and subsequent development of metabolic endotoxemia seen in diabetes and heart disease is associated with reduced IAP levels. To examine the direct effects of increased IAP expression on barrier function and development of metabolic diseases, we developed intestine-specific IAP transgenic mice (IAP(Tg)) over-expressing human chimeric IAP. Objective:The aim of this study was to evaluate the effects of intestine-specific IAP overexpression on Western-type diet (WD)-induced atherosclerosis in Ldlr(-/-) mice. Methods and Results: IAPTg mice crossed into Ldlr(-/-) background (Ldlr-/-IAP(Tg)) and Ldlr(-/-) littermates were fed WD for 16 weeks. Intestinal barrier dysfunction was assessed by monitoring plasma LPS levels and histological examination of colon. Over-expression of IAP attenuated WD-induced disruption of the colonic mucous layer, reducing intestinal barrier dysfunction and plasma LPS levels. Significant reduction in body, liver and adipose tissue weight was also seen in WD-fed Ldlr(-/-)IAP(Tg) mice. Plasma and hepatic lipids were also significantly reduced in WD-fed Ldlr(-/-)IAP(Tg) mice. Consistently, intestinal lipid absorption was attenuated in Ldlr(-/-)IAP(Tg) mice with reduced expression of apical lipid transporters (CD36, FATP4 and NPC1L1) and intracellular lipid transport proteins (FABP1/2, SCP2). Attenuation of WD-induced atherosclerosis in Ldlr(-/-)IAP(Tg) mice was demonstrated by significant reduction in arch and total aortic lesions as seen by enface analyses as well as significantly reduced atherosclerotic lesions in the ascending aorta of these mice.Conclusions: IAP overexpression improves intestinal barrier function by maintaining the integrity of the mucin layer in WD fed Ldlr(-/-)IAPTg mice and attenuates intestinal lipid absorption. Thus, by limiting translocation of gut-derived LPS and/or reducing plasma lipids, over-expression of IAP attenuates development of WD-induced atherosclerosis.

[17] *Yang J, Dong Y, Naugler CT, de Koning L*. **Serum 25-hydroxyvitamin D, cardiovascular risk markers, and incident cardiovascular disease in a high risk community population**. Clinical biochemistry 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33831385
ABSTRACT
BACKGROUND: It is unclear whether vitamin D status is related to cardiovascular risk beyond that explained by conventional risk markers. We examined the relationship between serum 25-hydroxy (OH) vitamin D and incident cardiovascular disease (CVD; heart attack/stroke) after adjusting for

individual- and community-level covariates from laboratory, administrative and survey data. METHODS: Patients receiving their first 25-OH vitamin D test in Calgary, Alberta from 2009 to 2013 without a past CVD diagnosis but an electrocardiogram and body mass index (BMI) +/- 3 months from testing were included. The following was merged to this data: first results for laboratory-measured CVD risk markers (lipid profile, fasting plasma glucose, and HbA1c) measured +/- 3 months from testing; Census Dissemination Area (CDA)-level indicators of socioeconomic status (SES) in 2011; and CVD diagnoses > 3 months from testing between 2009 and 2016. Linear and Poisson regression were used to examine associations between 25-OH vitamin D quartile and covariates, and Cox proportional hazard models were used to examine associations with incident CVD before and after adjusting for covariates. RESULTS: Among 72 348 patients, there were 1898 CVD events over a median of 6.0 years. Increasing quartile of 25-OH vitamin D was associated with improved lipid and glycemic profiles ($p < 0.01$), higher proportion of CDA-level indicators of high SES ($p < 0.01$), and a lower risk of CVD (Q4 vs Q1: HR: 0.72, 95% CI: 0.63-0.81, p for trend < 0.01) after adjusting for age, sex and average daily hours of sunlight during month of testing. The association with CVD was unchanged after adjusting for BMI, slightly attenuated after adjusting for SES but completely abolished after adjusting for laboratory-measured cardiovascular risk markers. CONCLUSIONS: Vitamin D status likely offers no additional information on CVD risk over conventional laboratory-measured risk markers.

[18] *Su X, Nie M, Zhang G, Wang B*. **MicroRNA in cardio-metabolic disorders**. Clinica chimica acta; international journal of clinical chemistry 2021; 518:134-141.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33823149
ABSTRACT
Hyperlipidemia is correlated with several health problems that contain the combination of hypertension, obesity, and diabetes mellitus, which are grouped as metabolic syndrome. Though the lipid-lowering agents, such as statins, which aims to reduce serum low-density lipoprotein cholesterol (LDL-C) has been considered as one of the most effective therapeutics in treating hyperlipidemia and coronary artery diseases, the persistent high risk of atherosclerosis after intensive lipid-lowering therapy could not be simply explained by hyperlipidemia. Therefore, it is necessary to identify novel factors to manage treatment and to predict risk of cardio-metabolic events. Endeavor over the past several decades has demonstrated the important functions of microRNAs in modulating macrophage activation, lipid metabolism, and hyperlipidemia. In the present review, we summarized the recent findings which highlighted the contributions of microRNAs in regulating serum lipid metabolism. Furthermore, we also provided the potential mechanisms whereby microRNAs controlled lipid metabolism and the risk of cardio-metabolic disorders, which could help us to identify microRNAs as a promising therapeutic target for hyperlipidemia and its related cardiovascular diseases.

[19] *Bhagavathula AS, Al Matrooshi NO, Clark CCT, Rahmani J*. **Authors' Reply to 'Comment on: Bempedoic Acid and Ezetimibe for the Treatment of Hypercholesterolemia: A Systematic Review and Meta-Analysis of Randomized Phase II/III Trials'**. Clinical drug investigation 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33840075
ABSTRACT

[20] *Suadoni MT*. **Comment on 'Bempedoic Acid and Ezetimibe for the Treatment of Hypercholesterolemia: A Systematic Review and Meta-Analysis of Randomized Phase II/III trials'**. Clinical drug investigation 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33826109
ABSTRACT

[21] *Sánchez-Hernández RM, González-Lleó AM, Tugores A et al.* **Familial hypercholesterolemia in Gran Canaria: Founder mutation effect and high frequency of diabetes**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33814196
ABSTRACT
INTRODUCTION: Gran Canaria is a region of genetic isolation of familial hypercholesterolemia due to a founder mutation, p. [Tyr400_Phe402del], in the LDL receptor (LDLR) gene. Initial data suggest that its carriers could have a high prevalence of diabetes. MATERIAL AND METHODS: Patients over 30 years of age with familial hypercholesterolemia and a confirmed mutation in LDLR were recruited from a tertiary hospital in Gran Canaria. The prevalence of diabetes and other clinical data were compared among carriers of p. [Tyr400_Phe402del] and those with other LDLR mutations. RESULTS: 76.4% of the 89 participants were carriers of p.[Tyr400_Phe402del]. The prevalence of diabetes in this group was significantly higher (25 vs. 4%, P=.045). These cases also had a higher prevalence of cardiovascular disease and higher levels of LDL cholesterol and triglycerides. There were no differences in age, weight, body mass index, waist, age of onset, and time of statin treatment. However, they required PCSK9 inhibitors more often (51.5 vs 24%, P=.027). CONCLUSIONS: The mutation p.[Tyr400_Phe402del] is associated with a high prevalence of diabetes, not explained by classic risk factors, such as age, obesity, or long-term use of statins.

[22] *Wendt FR, Koller D, Pathak GA et al.* **Biobank Scale Pharmacogenomics Informs the Genetic Underpinnings of Simvastatin Use**. Clinical pharmacology and therapeutics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33837531
ABSTRACT
Studying drug-metabolizing enzymes, encoded by pharmacogenes, may inform biological mechanisms underlying the diseases for which a medication is prescribed. Until recently, pharmacogenes could not be studied at biobank scale. In 7,649 unrelated African-ancestry (AFR) and 326,214 unrelated European-ancestry (EUR) participants from the UK Biobank, we associated pharmacogene haplotypes from 50 genes with 265 (EUR) and 17 (AFR) medication use phenotypes using generalized linear models. In EUR, N-acetyltransferase 2 (NAT2) metabolizer phenotype and activity score were associated with simvastatin use. The dose of NAT2*1 was associated with simvastatin use when compared with NAT2*5 (the most common haplotype). This association was robust to effects of low-density lipoprotein cholesterol (LDL-C) concentration (NAT2*1 odds ratio (OR) = 1.07, 95% CI: 1.05-1.09, P = 1.14 × 10(-8)) and polygenic risk for LDL-C concentration (NAT2*1 OR = 1.09, 95% CI: 1.04-1.14, P = 2.26 × 10(-4)). Interactive effects between NAT2*1 and simvastatin use on LDL-C concentration (OR = 0.957, 95% CI: 0.916-0.998, P = 0.045) were replicated in the electronic Medical Records and Genomics Pharmacogenetic Sequencing Pilot (eMERGE-PGx) cohort (OR = 0.987, 95% CI: 0.976-0.998, P = 0.029). We used biobank-scale data

to uncover and replicate an association between NAT2 locus variation and better response to statin therapy. Testing NAT2 alleles may be useful for making clinical decisions regarding the potential benefit (e.g., absolute risk reduction) in LDL-C concentration prior to statin treatment.

[23] *Chen LQ, Weber J, Christian T et al.* **Long-term all-cause mortality among asymptomatic individuals with 80th percentile of coronary calcium score based on age and gender in the St. Francis Heart Study**. Coronary artery disease 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33826539
ABSTRACT
OBJECTIVES: High coronary artery calcium score (CAC) is a significant risk factor for cardiovascular morbidity and mortality. We investigated the long-term outcome of subjects with elevated CAC. METHODS: We studied 1005 participants of The St. Francis Heart Study who were asymptomatic and apparently healthy and had CAC scores at 80th percentile or higher for age and gender. They were randomized to receive atorvastatin 20 mg daily or placebo for up to 5 years. We used an as-treated study design accounting for cross-overs at the end of the original trial. All-cause mortality risk was assessed using adjusted hazard ratios. RESULTS: Mean age was 59 ± 6 years and 26% (N = 263) were female. After 17 ± 3 years follow-up 176 subjects died. High CAC at baseline was associated with increased mortality risk with adjusted hazard ratio for logarithmic transformed CAC at 1.33 and 95% confidence interval 1.06-1.68. The mortality risk associated with CAC was similar between the group with high-sensitivity CRP ≥2 and <2 mg/dL. Those with a family history of premature coronary artery disease exhibited a higher mortality risk in association with high CAC with an adjusted hazard ratio 1.51 (1.09, 2.09). CONCLUSION: Elevated CAC is an independent risk for long-term all-cause mortality. The screening of CAC score in addition to identifying conventional risk factors can differentiate asymptomatic individuals with and without increased long-term mortality risk.

[24] *Krysiak R, Kowalcze K, Okopień B*. **The impact of hypotestosteronemia on cardiometabolic effects of atorvastatin in men with hypercholesterolemia: a pilot study**. Coronary artery disease 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33826536
ABSTRACT
BACKGROUND: Hypothyroidism, hyperprolactinemia, macroprolactinemia and low vitamin D status were found to impair pleiotropic effects of hypolipidemic agents. The aim of the current study was to investigate whether cardiometabolic effects of atorvastatin in men are determined by endogenous testosterone. METHODS: We studied three groups of men matched for age, BMI, plasma lipids and blood pressure: 19 untreated subjects with low testosterone levels (group A), 19 normotestosteronemic men receiving testosterone preparations (group B) and 21 untreated men with testosterone levels within the reference range (group C). Because of coexistent hypercholesterolemia, all subjects were managed with atorvastatin (40 mg daily) for 6 months. Glucose homeostasis markers, plasma lipids, as well as circulating levels of testosterone, uric acid, high-sensitivity C-reactive protein (hsCRP), fibrinogen, homocysteine and 25-hydroxyvitamin D were determined at the beginning and at the end of the study. RESULTS: At baseline, group A was more insulin-resistant and was characterized by higher levels of hsCRP, fibrinogen and homocysteine, and lower levels of 25-hydroxyvitamin D than the remaining groups of patients. Despite reducing total and low-density lipoprotein cholesterol and hsCRP levels in all treatment groups, this effect was stronger

in groups B and C than in group A. In groups B and C, atorvastatin use was also associated with a decrease in uric acid, fibrinogen and homocysteine concentrations and with an increase in 25-hydroxyvitamin D levels. In group A, but not in the remaining groups, the drug decreased insulin sensitivity. CONCLUSION: The obtained results suggest that untreated hypotestosteronemia may attenuate cardiometabolic effects of atorvastatin in men.

[25] *Nemati M, Srai M, Rudrangi R*. **Statin-Induced Autoimmune Myopathy**. Cureus 2021; 13:e13576.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33815984
ABSTRACT
Statins are one of the most widely prescribed drugs in the world. One of the common side effects of statin use is myopathy. We report a case of statin-induced autoimmune myopathy, which is a variant of statin-induced myopathy. A 56-year-old female with a history of hypertension, hyperlipidemia, cerebral aneurysm status post clipping, and seizure disorder presented with progressive muscle weakness. Her initial laboratory results demonstrated an elevated creatine phosphokinase (CPK) of 17,144 IU/L. The patient's atorvastatin was discontinued and she was placed on high-rate intravenous fluids; however, despite this, her CPK remained elevated. Patient underwent further blood testing for specific autoimmune etiologies. As there was high concern for autoimmune myositis, she was started on high-dose steroids. Anti-3-hydroxy-3-methylglutaryl-coenzyme A (anti-HMG-CoA) reductase antibody returned strongly positive. While the patient was on steroids, her muscle weakness and CPK level gradually improved. She was discharged on oral steroids. Statin-induced autoimmune myopathy should be considered with high suspicion when there is a significantly elevated CPK level. Discontinuation of statin therapy does not lead to muscle recovery or improvement in the CPK level. Diagnosis is confirmed by positive anti-HMG-CoA reductase autoantibody and a muscle biopsy.

[26] *Sugimoto H, Takeuchi M, Taniguchi Y, Sato J*. **Sudden Cardiac Arrest in a Patient With Sarcoidosis and Familial Hypercholesterolemia**. Cureus 2021; 13:e13649.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33824802
ABSTRACT
A 32-year-old Japanese man experienced out-of-hospital cardiac arrest. On arrival, computed tomography (CT) showed ground-glass opacity in the right lung. Emergency coronary angiography revealed triple vessel disease, then he underwent percutaneous coronary intervention. We also diagnosed him with heterozygous familial hypercholesterolemia and administered rosuvastatin and evolocumab. His clinical course was uncomplicated, and he was discharged on the 21st day of admission. Follow-up CT performed two years later revealed multiple areas of consolidation with sarcoid galaxy sign and mediastinal lymphadenopathy. We diagnosed him with pulmonary sarcoidosis by histopathological evaluation of the biopsied specimen via endobronchial ultrasound-guided transbronchial fine-needle aspiration of enlarged subcarinal lymph nodes. After we administered oral prednisolone with a gradual taper, his CT findings improved.

[27] *Bailey AL, Al-Adwan S, Sneij E et al.* **Atherosclerotic Cardiovascular Disease in Individuals with Hepatitis C Viral Infection**. Current cardiology reports 2021; 23:52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33822282
ABSTRACT

PURPOSE OF REVIEW: Hepatitis C virus (HCV) and atherosclerotic cardiovascular disease (ASCVD) are two diseases that affect millions around the globe. Hepatitis C affects more than 70 million individuals globally. ASCVD is commonly encountered and remains the top cause of death worldwide. A link has been identified between HCV and atherosclerosis. RECENT FINDINGS: A review of recent studies which define the association between HCV infection and an increased risk of subclinical ASCVD and experiencing cardiovascular (CV) events. It is now recognized that there is an increased burden of atherosclerosis in individuals infected with HCV that translates into increased cardiovascular events. An increase in the number of diagnosed cases of HCV is expected as screening recommendations for the virus have expanded. Strategies to educate healthcare professionals about this increased CV risk will need to be considered as well as the optimal strategy to lower CV risk in this growing population.

[28] *Makshood M, Post WS, Kanaya AM*. **Lipids in South Asians: Epidemiology and Management**. Current cardiovascular risk reports 2019; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33833849

ABSTRACT

PURPOSE OF REVIEW: This review focuses on lipoprotein abnormalities in South Asians (SA) and addresses risk stratification and management strategies to lower atherosclerotic cardiovascular disease (ASCVD) in this high-risk population. RECENT FINDINGS: South Asians (SAs) are the fastest growing ethnic group in the United States (U.S) and have an increased risk of premature coronary artery disease (CAD). While the etiology may be multifactorial, lipoprotein abnormalities play a key role. SAs have lower low-density lipoprotein cholesterol (LDL-C) compared with Whites and at any given LDL-C level, SA ethnicity poses a higher risk of myocardial infarction (MI) and coronary artery disease (CAD) compared with other non-Asian groups. SAs have lower high-density lipoprotein cholesterol (HDL-C) with smaller particle sizes of HDL-C compared with Whites. SAs also have higher triglycerides than Whites which is strongly related to the high prevalence of metabolic syndrome in SAs. Lipoprotein a (Lp(a)) levels are also higher in SAs compared with many other ethnic groups. This unique lipoprotein profile plays a vital role in the elevated ASCVD risk in SAs. Studies evaluating dietary patterns of SAs in the U.S show high consumption of carbohydrates and saturated fats. SUMMARY: SAs have a high-risk lipoprotein profile compared with other ethnicities. Lipid abnormalities play a central role in the pathogenesis of CAD in SAs. More studies are needed to understand the true impact of the various lipoproteins and their contribution to increasing ASCVD in SAs. Aggressive lowering of LDL-C in high-risk groups using medications, such as statins, and lifestyle modification including dietary changes is essential in overall CAD risk reduction.

[29] *Ceci FM, Ceccanti M, Petrella C et al.* **Alcohol Drinking, Apolipoprotein Polymorphisms and the Risk of Cardiovascular Diseases**. Current neurovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33823779

ABSTRACT

Lipoprotein disorders are a major risk factor for atherosclerotic neuro-cardiovascular disease (ACVD) and are heavily influenced by lifestyle, including alcohol drinking. Moderate drinkers have a lower ACVD risk than abstainers because of their higher levels of high-density lipoprotein (HDL) cholesterol, an important protective factor against ACVD. On the contrary, heavy drinking increases ACVD risk. According to a large literature body, ethanol intoxication modifies lipid serum profile and

induces endothelial dysfunction. Single nucleotide polymorphisms may influence the relationship between alcohol drinking, HDL cholesterol level, and atherosclerotic risk. The risk of ACVD in heavy drinkers seems enhanced in patients with apolipoprotein E4 allele, interleukin-6-174 polymorphism, and cholesteryl ester transfer protein TaqIB polymorphism. Apolipoprotein E4 is a known risk factor for ACVD, while apolipoprotein E2 has mixed effects. Therefore, even if a "protective role" may be attributed to moderate drinking, this effect cannot be extended to everyone.

[30] *Gill PK, Dron JS, Hegele RA*. **Genetics of hypertriglyceridemia and atherosclerosis**. Current opinion in cardiology 2021; 36:264-271.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33818545
ABSTRACT
PURPOSE OF REVIEW: The relationship between elevated triglyceride levels (i.e. hypertriglyceridemia) and risk of atherosclerotic cardiovascular disease (ASCVD) has been investigated for decades. Recent genetic studies have sought to resolve the decades-old question of a causal relationship. RECENT FINDINGS: Genetic studies seem to demonstrate associations between elevated triglyceride levels and ASCVD risk. Mendelian randomization studies suggest this association may be causal. However, simultaneous pleiotropic effects of metabolically linked lipid variables - such as non-HDL cholesterol, apolipoprotein B and HDL cholesterol -- often go unaccounted for in these studies. Complex underlying pleiotropic interactions of triglycerides with these lipid fractions together with unmeasured intercalated nonlipid-related mechanisms, such as inflammation and coagulation, impair the ability of genetic studies to implicate a direct role for triglycerides on ASCVD risk. One potential mechanism seems largely driven by the cholesterol carried within triglyceride-rich lipoproteins and their remnants, rather than their triglyceride content. SUMMARY: Although the exact mechanisms linking elevated triglyceride levels to ASCVD remain to be determined, new therapeutics that reduce triglyceride levels might be advantageous in certain patients. Newer investigational triglyceride-lowering therapies derived from human genetics target key proteins, such as apo C-III and ANGPTL3. Although these treatments clearly lower triglyceride levels, their efficacy in atherosclerotic risk reduction remains unproven.

[31] *Dutta D, Agarwal A, Maisnam I et al.* **Efficacy and Safety of the Novel Dipeptidyl Peptidase-4 Inhibitor Gemigliptin in the Management of Type 2 Diabetes: A Meta-Analysis**. Endocrinol Metab (Seoul) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33820392
ABSTRACT
BACKGROUND: No meta-analysis has holistically analysed and summarised the efficacy and safety of gemigliptin in type 2 diabetes. The meta-analysis addresses this knowledge gap. METHODS: Electronic databases were searched for randomised controlled trials (RCTs) involving diabetes patients receiving gemigliptin in the intervention arm and placebo/active comparator in the control arm. The primary outcome was change in haemoglobin A1c (HbA1c). The secondary outcomes were alterations in glucose, glycaemic targets, lipids, insulin resistance, and adverse events. RESULTS: Data from 10 RCTs involving 1,792 patients were analysed. Four had an active control group (ACG), with metformin/dapagliflozin/sitagliptin/glimepiride as the active comparator; six had a passive control group (PCG), with placebo/rosuvastatin as controls. HbA1c reduction by gemigliptin at 24 weeks was comparable to ACG (mean difference [MD], 0.09%; 95% confidence interval [CI], -0.06 to 0.23;

P=0.24; I2=0%; moderate certainty of evidence [MCE]), but superior to PCG (MD, -0.91%; 95% CI, -1.18 to -0.63); P<0.01; I2=89%; high certainty of evidence [HCE]). Gemigliptin was superior to PCG regarding achieving HbA1c <7% (12 weeks: odds ratio [OR], 5.91; 95% CI, 1.34 to 26.08; P=0.02; I2=74%; 24 weeks: OR, 4.48; 95% CI, 2.09 to 9.60; P<0.01; I2=69%; HCE). Gemigliptin was comparable to ACG regarding achieving HbA1c <7% after 24 weeks (OR, 0.92; 95% CI, 0.52 to 1.63; P=0.77; I2=66%; MCE). Adverse events were similar between the gemigliptin and control groups (risk ratio [RR], 1.06; 95% CI, 0.82 to 1.36; P=0.66; I2=35%; HCE). The gemigliptin group did not have increased hypoglycaemia (RR, 1.19; 95% CI, 0.62 to 2.28; P=0.61; I2=19%; HCE). CONCLUSION: Gemigliptin has good glycaemic efficacy and is well-tolerated over 6 months of use.

[32] *Rath AA, Lam HS, Schooling CM*. **Effects of selenium on coronary artery disease, type 2 diabetes and their risk factors: a Mendelian randomization study**. European journal of clinical nutrition 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33828238
ABSTRACT
BACKGROUND: The impact of selenium on coronary artery disease (CAD) and type 2 diabetes (T2D) remains unclear with inconsistent results from observational studies and randomized controlled trials. We used Mendelian randomization to obtain unconfounded estimates of the effect of selenium on CAD, T2D, lipids and glycemic traits. METHODS: We applied genetic variants strongly ($P<5\times10(-8)$) associated with blood and toenail selenium to publicly available summary statistics from large consortia genome-wide association studies of CAD (76,014 cases and 264,785 non-cases), T2D (74,124 cases and 824,006 controls), lipids and glycemic traits. Variant specific Wald estimates were combined using inverse variance weighting, with several sensitivity analyses. RESULTS: Genetically predicted selenium was associated with higher T2D (OR 1.27, 95% CI 1.07-1.50, $P=0.006$). There was little evidence of an association with CAD. Genetically predicted selenium was associated with lower low-density lipoprotein (LDL) cholesterol, lower high-density lipoprotein (HDL) cholesterol, higher fasting insulin and higher homeostasis model assessment of insulin resistance. These results were not robust to all sensitivity analyses. No associations with triglycerides, fasting glucose or homeostasis model assessment of β-cell function were evident. CONCLUSIONS: Our study suggests selenium may increase the risk of T2D, possibly through insulin resistance rather than pancreatic beta cell function, but may reduce lipids. We found little evidence of an association with CAD, although an inverse association cannot be definitively excluded. The effect of selenium on these outcomes warrants further investigation.

[33] *Blaum C, Brunner FJ, Kröger F et al.* **Modifiable lifestyle risk factors and C-reactive protein in patients with coronary artery disease: Implications for an anti-inflammatory treatment target population**. European journal of preventive cardiology 2021; 28:152-158.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33838040
ABSTRACT
BACKGROUND: Modifiable lifestyle risk factors (modRF) of coronary artery disease (CAD) are associated with increased inflammation represented by elevated C-reactive protein (CRP) levels. Lifestyle changes may influence the inflammatory burden in patients with CAD, relevantly modifying the target population for emerging anti-inflammatory compounds. AIMS: The aims of this study were to analyse the association of modRF and CRP levels in CAD patients, and to define a potential target

population for anti-inflammatory treatment with and without the optimisation of modRF. METHODS: We included all patients with angiographically documented CAD from the observational cohort study INTERCATH. Patients with recent myocardial infarction, malignancy, infectious disease, and pre-existing immunosuppressive medication including a history of solid organ transplantation were excluded. Overweight (body mass index (BMI) ≥ 25 kg/m2), smoking, lack of physical activity (PA; <1.5 h/week), and poor diet (≤12 points of an established Mediterranean diet score (MDS), range 0-28 points) were considered as modRF. CRP was measured by a high-sensitivity assay (hsCRP) at baseline. We performed multivariable linear regressions with log-transformed hsCRP as the dependent variable. Based on these associations, we calculated potential hsCRP levels for each patient, assuming optimisation of the individual modRF. RESULTS: Of 1014 patients, 737 (73%) were male, the mean age was 69 years, and 483 (48%) had an hsCRP ≥ 2 mg/l. ModRF were significantly overrepresented in patients with hsCRP ≥ 2 mg/l compared to patients with an hsCRP < 2 mg/l (BMI ≥ 25 kg/m2: 76% vs 61%; PA < 1.5 h/week: 69% vs 57%; MDS ≤ 12: 46% vs 37%; smoking: 61% vs 54%; $p < 0.05$ for all). hsCRP increased with the incremental number of modRF present (median hsCRP values for N = 0, 1, 2, 3, and 4 modRF: 1.1, 1.0, 1.6, 2.4, 2.8 mg/l, $p < 0.001$). Multivariable linear regression adjusting for age, sex, intake of lipid-lowering medication, and diabetes mellitus revealed independent associations between log-transformed hsCRP and all modRF (BMI ≥ 25 kg/m2: exp(ß) = 1.55, $p < 0.001$; PA < 1.5 h/week: exp(ß) = 1.33, $p < 0.001$; MDS ≤ 12: exp(ß) = 1.18, $p = 0.018$; smoking: exp(ß) = 1.18, $p = 0.019$). Individual recalculation of hsCRP levels assuming optimisation of modRF identified 183 out of 483 (38%) patients with hsCRP ≥ 2 mg/l who could achieve an hsCRP < 2 mg/l via lifestyle changes. CONCLUSION: modRF are strongly and independently associated with CRP levels in patients with CAD. A relevant portion of CAD patients with high inflammatory burden could achieve an hsCRP < 2 mg/l by lifestyle changes alone. This should be considered both in view of the cost and side-effects of pharmacological anti-inflammatory treatment and for the design of future clinical trials in this field.

[34] *Tomlinson B, Patil NG, Fok M, Lam CWK*. **Managing dyslipidemia in patients with type 2 diabetes**. Expert opinion on pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33823719

ABSTRACT

INTRODUCTION: Type 2 diabetes mellitus (T2DM) is associated with increased risk for atherosclerotic cardiovascular disease (ASCVD) which is partly related to the atherogenic dyslipidemia with raised triglycerides, reduced high-density lipoprotein cholesterol levels and accompanying lipid changes. Treatment of this dyslipidemia is regarded as a priority to reduce the ASCVD risk in T2DM. AREAS COVERED: In this article, the authors review the relevant studies and guidelines from the publications related to this area. EXPERT OPINION: Lifestyle modification should always be encouraged, and statin treatment is indicated in most patients with T2DM based on the outcome of randomized controlled trials. If LDL-C goals are not achieved, firstly ezetimibe and subsequently proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors should be added. Patients with T2DM derive greater benefits from ezetimibe and PCSK9 inhibitors due to their higher absolute ASCVD risk compared to patients without T2DM. If triglyceride levels remain elevated, high dose eicosapentaenoic acid ethyl ester should be added. Fibrates should be used for severe hypertriglyceridemia to prevent acute pancreatitis. Novel treatments including pemafibrate and inclisiran are undergoing cardiovascular outcome trials and RNA-based therapies may help to target

residual hypertriglyceridemia and high lipoprotein(a) with the long acting treatments offering potential improved adherence to therapy.

[35] *Luquero A, Badimon L, Borrell-Pages M*. **PCSK9 Functions in Atherosclerosis Are Not Limited to Plasmatic LDL-Cholesterol Regulation**. Frontiers in cardiovascular medicine 2021; 8:639727.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33834043
ABSTRACT
The relevance of PCSK9 in atherosclerosis progression is demonstrated by the benefits observed in patients that have followed PCSK9-targeted therapies. The impact of these therapies is attributed to the plasma lipid-lowering effect induced when LDLR hepatic expression levels are recovered after the suppression of soluble PCSK9. Different studies show that PCSK9 is involved in other mechanisms that take place at different stages during atherosclerosis development. Indeed, PCSK9 regulates the expression of key receptors expressed in macrophages that contribute to lipid-loading, foam cell formation and atherosclerotic plaque formation. PCSK9 is also a regulator of vascular inflammation and its expression correlates with pro-inflammatory cytokines release, inflammatory cell recruitment and plaque destabilization. Furthermore, anti-PCSK9 approaches have demonstrated that by inhibiting PCSK9 activity, the progression of atherosclerotic disease is diminished. PCSK9 also modulates thrombosis by modifying platelets steady-state, leukocyte recruitment and clot formation. In this review we evaluate recent findings on PCSK9 functions in cardiovascular diseases beyond LDL-cholesterol plasma levels regulation.

[36] *Wolf A, Kutsche HS, Atmanspacher F et al.* **Untypical Metabolic Adaptations in Spontaneously Hypertensive Rats to Free Running Wheel Activity Includes Uncoupling Protein-3 (UCP-3) and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Expression**. Front Physiol 2021; 12:598723.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33833685
ABSTRACT
Obesity and hypertension are common risk factors for cardiovascular disease whereas an active lifestyle is considered as protective. However, the interaction between high physical activity and hypertension is less clear. Therefore, this study investigates the impact of high physical activity on the muscular and hepatic expression of glucose transporters (Glut), uncoupling proteins (UCPs), and proprotein convertase subtilisin/kexin type 9 (PCSK9) in spontaneously hypertensive rats (SHRs). Twenty-four female rats (12 normotensive rats and 12 SHRs) were divided into a sedentary control and an exercising group that had free access to running wheels at night for 10 months. Blood samples were taken and blood pressure was determined. The amount of visceral fat was semi-quantitatively analyzed and Musculus gastrocnemius, Musculus soleus, and the liver were excised. Acute effects of free running wheel activity were analyzed in 15 female SHRs that were sacrificed after 2 days of free running wheel activity. M. gastrocnemius and M. soleus differed in their mRNA expression of UCP-2, UCP-3, GLUT-4, and PCSK9. Hypertension was associated with lower levels of UCP-2 and PCSK9 mRNA in the M. gastrocnemius, but increased expression of GLUT-1 and GLUT-4 in the M. soleus. Exercise down-regulated UCP-3 in the M. soleus in both strains, in the M. gastrocnemius only in normotensives. In SHRs exercise downregulated the expression of UCP-2 in the M. soleus. Exercise increased the expression of GLUT-1 in the M. gastrocnemius in both strains,

and that of GLUT-4 protein in the M. soleus, whereas it increased the muscle-specific expression of PCSK9 only in normotensive rats. Effects of exercise on the hepatic expression of cholesterol transporters were seen only in SHRs. As an acute response to exercise increased expressions of the myokine IL-6 and that of GLUT-1 were found in the muscles. This study, based on transcriptional adaptations in striated muscles and livers, shows that rats perform long-term metabolic adaptations when kept with increased physical activity. These adaptations are at least in part required to stabilize normal protein expression as protein turnover seems to be modified by exercise. However, normotensive and hypertensive rats differed in their responsiveness. Based on these results, a direct translation from normotensive to hypertensive rats is not possible. As genetic differences between normotensive humans and patients with essential hypertension are likely to be present as well, we would expect similar differences in humans that may impact recommendations for non-pharmacological interventions.

[37] *Kanagasundaram P, Lee J, Prasad F et al.* **Pharmacological Interventions to Treat Antipsychotic-Induced Dyslipidemia in Schizophrenia Patients: A Systematic Review and Meta Analysis**. Frontiers in psychiatry 2021; 12:642403.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33815174

ABSTRACT
Introduction: Antipsychotic-induced dyslipidemia represents a common adverse effect faced by patients with schizophrenia that increases risk for developing further metabolic complications and cardiovascular disease. Despite its burden, antipsychotic-induced dyslipidemia is often left untreated, and the effectiveness of pharmacological interventions for mitigating dyslipidemia has not been well-addressed. This review aims to assess the effectiveness of pharmacological interventions in alleviating dyslipidemia in patients with schizophrenia. Methods: Medline, PsychInfo, and EMBASE were searched for all relevant English articles from 1950 to November 2020. Randomized placebo-controlled trials were included. Differences in changes in triglycerides, HDL cholesterol, LDL cholesterol, and VLDL cholesterol levels between treatment and placebo groups were meta-analyzed as primary outcomes. Results: Our review identified 48 randomized controlled trials that comprised a total of 3,128 patients and investigated 29 pharmacological interventions. Overall, pharmacological interventions were effective in lowering LDL cholesterol, triglycerides, and total cholesterol levels while increasing the levels of HDL cholesterol. Within the intervention subgroups, approved lipid-lowering agents did not reduce lipid parameters other than total cholesterol level, while antipsychotic switching and antipsychotic add-on interventions improved multiple lipid parameters, including triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol. Off label lipid lowering agents improved triglycerides and total cholesterol levels, with statistically significant changes seen with metformin. Conclusion: Currently available lipid lowering agents may not work as well in patients with schizophrenia who are being treated with antipsychotics. Additionally, antipsychotic switching, antipsychotic add-ons, and certain off label interventions might be more effective in improving some but not all associated lipid parameters. Future studies should explore novel interventions for effectively managing antipsychotic-induced dyslipidemia. Registration: PROSPERO 2020 CRD42020219982; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020219982.

[38] *Santi RL, Márquez MF, Piskorz D et al.* **Ambulatory Patients with Cardiometabolic Disease and Without Evidence of COVID-19 During the Pandemic. The CorCOVID LATAM Study**. Global heart 2021; 16:15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33833939
ABSTRACT
BACKGROUND: SARS-CoV-2 pandemic has modified the cardiovascular care of ambulatory patients. The aim of this survey was to study changes in lifestyle habits, treatment adherence, and mental health status in patients with cardiometabolic disease, but no clinical evidence of COVID-19. METHODS: A cross-sectional survey was conducted in ambulatory patients with cardiometabolic disease using paper/digital surveys. Variables investigated included socioeconomic status, physical activity, diet, tobacco use, alcohol intake, treatment discontinuation, and psychological symptoms. RESULTS: A total of 4,216 patients (50.9% males, mean age 60.3 ± 15.3 years old) from 13 Spanish-speaking Latin American countries were enrolled. Among the study population, 46.4% of patients did not have contact with a healthcare provider, 31.5% reported access barriers to treatments and 17% discontinued some medication. Multivariate analysis showed that non-adherence to treatment was more prevalent in the secondary prevention group: peripheral vascular disease (OR 1.55, CI 1.08-2.24; p = 0.018), heart failure (OR 1.36, CI 1.05-1.75; p = 0.017), and coronary artery disease (OR 1.29 CI 1.04-1.60; p = 0.018). No physical activity was reported by 38% of patients. Only 15% of patients met minimum recommendations of physical activity (more than 150 minutes/week) and vegetable and fruit intake. Low/very low income (45.5%) was associated with a lower level of physical activity ($p < 0.0001$), less fruit and vegetables intake ($p < 0.0001$), more tobacco use ($p < 0.001$) and perception of depression ($p < 0.001$). Low educational level was also associated with the perception of depression (OR 1.46, CI 1.26-1.70; $p < 0.01$). CONCLUSIONS: Patients with cardiometabolic disease but without clinical evidence of COVID-19 showed significant medication non-adherence, especially in secondary prevention patients. Deterioration in lifestyle habits and appearance of depressive symptoms during the pandemic were frequent and related to socioeconomic status.

[39] *Vijayan A, Chithra V, Sandhya C*. **The relationship of lipid peroxidation and antioxidant status to selected modifiable risk factors in coronary artery disease patients**. Int J Cardiol Hypertens 2021; 8:100077.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33817621
ABSTRACT
BACKGROUND: Coronary artery disease (CAD) is found to be associated with a wide range of modifiable and non-modifiable risk factors. AIM OF THE STUDY: To evaluate the relationship of lipid peroxidation and antioxidant status to selected modifiable risk factors in angiographically proven CAD patients. METHODS: 150 angiographically proven CAD patients were categorized into three, based on selected risk factors. Data was collected using proforma and from hospital records. Peroxidation and antioxidant levels in blood samples were assessed using standard procedures. RESULTS: In category, I, significantly higher level of lipid peroxidation and the lower enzymatic antioxidant level were observed in patients with diabetes, hypertension, and with both diabetes and hypertension, when compared with patients without these clinical characteristics ($p < 0.01$). Similar results obtained for patients following a non-vegetarian diet when compared with patients following a vegetarian diet (category II). In BMI based group (category III), patients with BMI>25kg/m2 showed a significant increase in peroxidation and low enzymatic and non-enzymatic antioxidant levels than those with

normal BMI. CONCLUSION: The study confirmed a strong association between selected modifiable risk factors, higher lipid peroxidation, and lower antioxidant levels in angiographically proven CAD patients. This provides leads in the management of cardiovascular events in CAD patients.

[40] *Derington CG, Colantonio LD, Herrick JS et al.* **Factors Associated With PCSK9 Inhibitor Initiation Among US Veterans**. Journal of the American Heart Association 2021; 10:e019254.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33821686

ABSTRACT

Background Few adults at high risk for atherosclerotic cardiovascular disease events use a PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor). Methods and Results Using data from the US Veterans Health Administration, we identified veterans who initiated a PCSK9i between January 2018 and December 2019, matched 1:4 to veterans who did not initiate this medication over this time period (case-cohort study). Two cohorts of veterans were analyzed: (1) atherosclerotic cardiovascular disease, with a most recent low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL; and (2) severe hypercholesterolemia (ie, familial hypercholesterolemia or any prior LDL-C ≥190 mg/dL, with most recent LDL-C ≥100 mg/dL). Conditional logistic regression was used to analyze factors associated with PCSK9i initiation, adjusting for all factors, simultaneously. There were 2394 initiators and 9576 noninitiators in the atherosclerotic cardiovascular disease cohort (median LDL-C, 141 and 96 mg/dL, respectively; P<0.001). Factors associated with a higher likelihood of PCSK9i initiation included age 65 to <75 versus <65 years, highest versus lowest quartile of median area-level income, familial hypercholesterolemia, former statin use, and current ezetimibe use. PCSK9i initiation was lower among veterans of a race/ethnicity other than non-Hispanic White. There were 245 initiators and 980 noninitiators in the severe hypercholesterolemia cohort (median LDL-C, 183 and 151 mg/dL, respectively; P<0.001). Age ≥75 versus <65 years, history of chronic kidney disease, former statin use, and current ezetimibe use were associated with a higher likelihood of PCSK9i initiation. Conclusions Several patient-level factors, including age, sex, and race/ethnicity, were significantly associated with PCSK9i initiation, suggesting an unmet treatment need in several patient groups.

[41] *Beshir SA, Hussain N, Elnor AA, Said ASA*. **Umbrella Review on Non-Statin Lipid-Lowering Therapy**. Journal of cardiovascular pharmacology and therapeutics 2021:10742484211002943.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33836639

ABSTRACT

OBJECTIVES: The main aim of this review was to summarize current evidence on approved and emerging non-statin lipid-lowering therapies. METHODS AND MATERIALS: Recent literature on U.S. FDA approved non-statin lipid-lowering therapies and evolving lipid-lowering drugs currently under development was reviewed. RESULTS AND DISCUSSION: In the past 20 years, the emergence of non-statin cholesterol-lowering drugs has changed the landscape of dyslipidemia management. Food and Drug Administration approval of non-statin lipid-lowering therapies such as ezetimibe, proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors (evolocumab, alirocumab), bempedoic acid and combination of bempedoic acid and ezetimibe, evinacumab and other triglyceride-lowering agents (eg, icosapent ethyl) has emerged. The European Commission has also recently approved inclisiran for treatment of hypercholesterolemia and mixed hypercholesterolemia even though FDA has put the approval of this drug on hold. Recent guidelines have incorporated PCSK9 inhibitors to treat patients with primary hyperlipidemia and patients with very high-risk ASCVD, who could not achieve adequate

lipid-lowering with combination therapy of maximally tolerated statin and ezetimibe. Icosapent ethyl use as an adjunct therapy to statins is also recommended to reduce the risk of ASCVD in patients with hypertriglyceridemia. CONCLUSION: Despite cost limitations, the uptake of PCSK9 inhibitors is increasing. Approval of bempedoic acid alone or in combination with ezetimibe has provided additional oral lipid-lowering drug alternatives to ezetimibe. Various lipid-lowering drug targets are under investigation.

[42] *Shao S, Zhou K, Liu X et al.* **Predictive value of serum lipid for intravenous immunoglobulin resistance and coronary artery lesion in Kawasaki disease**. The Journal of clinical endocrinology and metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33837779
ABSTRACT
CONTEXT: Intravenous immunoglobulin (IVIG) resistance and coronary artery lesions (CALs) prediction are pivotal topic of interests in Kawasaki disease (KD). However, data on the predictive value of lipid profile for both IVIG resistance and CALs are limited. PURPOSE: To investigate the predictive validity of lipid profile for IVIG resistance and CALs in KD. DESIGN: Prospective cohort study. SETTING: West China Second University Hospital. PATIENTS: 363 KD patients were divided into the initial IVIG-resistant group and initial IVIG-responsive group; repeated IVIG-resistant group and repeated IVIG-responsive group; CAL+ group and CAL- group. MAIN OUTCOME MEASURES: Validity of lipid profile in predicting IVIG resistance and CALs. RESULTS: TG was significantly higher whereas TC, HDL-C, LDL-C as well as Apo A were significantly lower in initial IVIG-resistant subjects, with cut-off values of 1.625 mmol/L, 3.255 mmol/L, 0.475 mmol/L, and 1.965 mmol/L and 0.665 g/L, yielding sensitivities of 52%, 70%, 52%, 61%, 50%, and specificities of 68%, 53%, 78%, 71%, 81%, respectively. TC, LDL-C, and Apo A levels were significantly lower in repeated IVIG-resistant subjects, with cut-off values of 3.20 mmol/L, 1.78 mmol/L, 0.605 g/L, producing sensitivities of 91%, 70%, 57% and specificities of 55%, 67%, 70%, respectively. Apo-A level was significantly lower in the CAL group, with cut-off value of 0.805g/L, yielding sensitivity of 66% and specificity of 54%. CONCLUSIONS: Lipid profiles were significantly dysregulated in KD patients suffering IVIG resistance and CALs. Some of them, such as LDL-c and Apo-A, could serve as complementary laboratory markers for predicting both IVIG resistance and CALs.

[43] *Mariamenatu AH, Abdu EM*. **Overconsumption of Omega-6 Polyunsaturated Fatty Acids (PUFAs) versus Deficiency of Omega-3 PUFAs in Modern-Day Diets: The Disturbing Factor for Their "Balanced Antagonistic Metabolic Functions" in the Human Body**. Journal of lipids 2021; 2021:8848161.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33815845
ABSTRACT
Polyunsaturated fatty acids (PUFAs) contain ≥2 double-bond desaturations within the acyl chain. Omega-3 (n-3) and Omega-6 (n-6) PUFAs are the two known important families in human health and nutrition. In both Omega families, many forms of PUFAs exist: α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from the n-3 family and linoleic acid (LA), dihomo-γ-linolenic acid (DGLA), and arachidonic acid (AA) from the n-6 family are the important PUFAs for human health. Omega-3 and Omega-6 PUFAs are competitively metabolized by the same set of desaturation, elongation, and oxygenase enzymes. The lipid mediators produced from their

oxidative metabolism perform opposing (antagonistic) functions in the human body. Except for DGLA, n-6 PUFA-derived lipid mediators enhance inflammation, platelet aggregation, and vasoconstriction, while those of n-3 inhibit inflammation and platelet aggregation and enhance vasodilation. Overconsumption of n-6 PUFAs with low intake of n-3 PUFAs is highly associated with the pathogenesis of many modern diet-related chronic diseases. The volume of n-6 PUFAs is largely exceeding the volume of n-3PUFAs. The current n-6/n-3 ratio is 20-50/1. Due to higher ratios of n-6/n-3 in modern diets, larger quantities of LA- and AA-derived lipid mediators are produced, becoming the main causes of the formation of thrombus and atheroma, the allergic and inflammatory disorders, and the proliferation of cells, as well as the hyperactive endocannabinoid system. Therefore, in order to reduce all of these risks which are due to overconsumption of n-6 PUFAs, individuals are required to take both PUFAs in the highly recommended n-6/n-3 ratio which is 4-5/1.

[44] *Maratni NPT, Saraswati MR, Dewi NNA et al.* **Association of Apolipoprotein E Gene Polymorphism with Lipid Profile and Ischemic Stroke Risk in Type 2 Diabetes Mellitus Patients**. J Nutr Metab 2021; 2021:5527736.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33833872

ABSTRACT

BACKGROUND: Altered lipid profiles have consistently been linked to cerebrovascular events. Ischemic stroke (IS) was a common comorbid condition established in type 2 diabetes mellitus (T2DM). The apolipoprotein E (ApoE) gene which has a notably critical function in lipoprotein metabolism is believed as one of the potential candidate genes susceptible to IS complications in T2DM. This research aimed to determine the association of apolipoprotein E gene polymorphism with lipid profile and IS risk in T2DM patients. METHODS: This case-control study involved a total of 60 diabetic participants divided into two groups with and without IS. ApoE was genotyped using PCR and sequencing analysis. RESULTS: The most predominant genotype observed in 27 participants (45%) was E3/E3. Lower levels of high-density lipoprotein cholesterol (HDL-C) were found in ε2 carriers (p=0.003; 95% CI -23.35--4.89) and ε4 carriers (p=0.019; 95% CI 1.38-14.55) compared to ε3 homozygotes. Total cholesterol (TC), triglyceride, and low-density lipoprotein cholesterol (LDL-C) levels had no association with ApoE gene polymorphism in this study. ApoE gene polymorphism was not related to IS in T2DM (p=0.06; adjusted OR: 4.71; 95% CI 0.93-23.79). CONCLUSIONS: ApoE ε2 and ε4 carriers were associated with lower levels of HDL-C. No association was identified between ApoE gene polymorphism and IS in T2DM patients.

[45] *McDermott MM, Spring B, Tian L et al.* **Effect of Low-Intensity vs High-Intensity Home-Based Walking Exercise on Walk Distance in Patients With Peripheral Artery Disease: The LITE Randomized Clinical Trial**. Jama 2021; 325:1266-1276.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33821898

ABSTRACT

IMPORTANCE: Supervised high-intensity walking exercise that induces ischemic leg symptoms is the first-line therapy for people with lower-extremity peripheral artery disease (PAD), but adherence is poor. OBJECTIVE: To determine whether low-intensity home-based walking exercise at a comfortable pace significantly improves walking ability in people with PAD vs high-intensity home-based walking exercise that induces ischemic leg symptoms and vs a nonexercise control. DESIGN, SETTING, AND PARTICIPANTS: Multicenter randomized clinical trial conducted at 4 US centers and

including 305 participants. Enrollment occurred between September 25, 2015, and December 11, 2019; final follow-up was October 7, 2020. INTERVENTIONS: Participants with PAD were randomized to low-intensity walking exercise (n = 116), high-intensity walking exercise (n = 124), or nonexercise control (n = 65) for 12 months. Both exercise groups were asked to walk for exercise in an unsupervised setting 5 times per week for up to 50 minutes per session wearing an accelerometer to document exercise intensity and time. The low-intensity group walked at a pace without ischemic leg symptoms. The high-intensity group walked at a pace eliciting moderate to severe ischemic leg symptoms. Accelerometer data were viewable to a coach who telephoned participants weekly for 12 months and helped them adhere to their prescribed exercise. The nonexercise control group received weekly educational telephone calls for 12 months. MAIN OUTCOMES AND MEASURES: The primary outcome was mean change in 6-minute walk distance at 12 months (minimum clinically important difference, 8-20 m). RESULTS: Among 305 randomized patients (mean age, 69.3 [SD, 9.5] years, 146 [47.9%] women, 181 [59.3%] Black patients), 250 (82%) completed 12-month follow-up. The 6-minute walk distance changed from 332.1 m at baseline to 327.5 m at 12-month follow-up in the low-intensity exercise group (within-group mean change, -6.4 m [95% CI, -21.5 to 8.8 m]; P = .34) and from 338.1 m to 371.2 m in the high-intensity exercise group (within-group mean change, 34.5 m [95% CI, 20.1 to 48.9 m]; P < .001) and the mean change for the between-group comparison was -40.9 m (97.5% CI, -61.7 to -20.0 m; P < .001). The 6-minute walk distance changed from 328.1 m at baseline to 317.5 m at 12-month follow-up in the nonexercise control group (within-group mean change, -15.1 m [95% CI, -35.8 to 5.7 m]; P = .10), which was not significantly different from the change in the low-intensity exercise group (between-group mean change, 8.7 m [97.5% CI, -17.0 to 34.4 m]; P = .44). Of 184 serious adverse events, the event rate per participant was 0.64 in the low-intensity group, 0.65 in the high-intensity group, and 0.46 in the nonexercise control group. One serious adverse event in each exercise group was related to study participation. CONCLUSIONS AND RELEVANCE: Among patients with PAD, low-intensity home-based exercise was significantly less effective than high-intensity home-based exercise and was not significantly different from the nonexercise control for improving 6-minute walk distance. These results do not support the use of low-intensity home-based walking exercise for improving objectively measured walking performance in patients with PAD. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02538900.

[46] *Chen Z, Chen L, Sun B et al.* **LDLR inhibition promotes hepatocellular carcinoma proliferation and metastasis by elevating intracellular cholesterol synthesis through the MEK/ERK signaling pathway**. Molecular metabolism 2021; 51:101230.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33823318

ABSTRACT

OBJECTIVE: Adaptive rewiring of cancer energy metabolism has received increasing attention. By binding with LDLs, LDLRs make most of the circulating cholesterol available for cells to utilize. However, it remains unclear how LDLR works in HCC development by affecting cholesterol metabolism. METHODS: Database analyses and immunohistochemical staining were used to identify the clinical significance of LDLR in HCC. A transcriptome analysis was used to reveal the mechanism of LDLR aberration in HCC progression. A liver orthotopic transplantation model was used to evaluate the role of LDLR in HCC progression in vivo. RESULTS: Downregulation of LDLR was identified as a negative prognostic factor in human HCC. Reduced expression of LDLR in HCC cell lines impaired LDL uptake but promoted proliferation and metastasis in vitro and in vivo. Mechanistically, increasing

intracellular de novo cholesterol biosynthesis was the chief contributor to malignant behaviors caused by LDLR inhibition, which could be rescued by simvastatin. Activation of the MEK/ERK pathway by LDLR downregulation partially contributed to intracellular cholesterol synthesis in HCC. CONCLUSIONS: Downregulation of LDLR may elevate intracellular cholesterol synthesis to accelerate proliferation and motility through a mechanism partially attributed to stimulation of the MEK/ERK signaling pathway. Repression of intracellular cholesterol synthesis with statins may constitute a targetable liability in the context of lower LDLR expression in HCC.

[47] *Mansour A, Mohajeri-Tehrani MR, Samadi M et al.* **Effects of supplementation with main coffee components including caffeine and/or chlorogenic acid on hepatic, metabolic, and inflammatory indices in patients with non-alcoholic fatty liver disease and type 2 diabetes: a randomized, double-blind, placebo-controlled, clinical trial**. Nutrition journal 2021; 20:35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33838673

ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is much more frequent and more severe, including cirrhosis, hepatocellular carcinoma in patients with type 2 diabetes. Coffee is a complex beverage with hundreds of compounds whereas caffeine and chlorogenic acid are the most abundant bioactive compounds. The published epidemiological data demonstrating beneficial associations between all categories of coffee exposure and ranges of liver outcomes are rapidly growing; however, the main contributors and cause-effect relationships have not yet been elucidated. To address existing knowledge gaps, we sought to determine the efficacy and safety of 6 months chlorogenic acid and/or caffeine supplementation in patients with type 2 diabetes affected by NAFLD. METHODS: This trial was carried out at two Diabetes Centers to assess the effects of supplementation with daily doses of 200 mg chlorogenic acid, 200 mg caffeine, 200 mg chlorogenic acid plus 200 mg caffeine or placebo (starch) in patients with type 2 diabetes and NAFLD. The primary endpoint was reduction of hepatic fat and stiffness measured by FibroScan, and changes in serum hepatic enzymes and cytokeratin - 18 (CK-18) levels. Secondary endpoints were improvements in metabolic (including fasting glucose, homeostasis model assessment-estimated insulin resistance (HOMA-IR), hemoglobin A1c (HBA1C), C-peptide, insulin and lipid profiles) and inflammatory (including nuclear factor k-B (NF-KB), tumor necrosis factor (TNF-α), high sensitive- C reactive protein(hs-CRP)) parameters from baseline to the end of treatment. RESULTS: Neither chlorogenic acid nor caffeine was superior to placebo in attenuation of the hepatic fat and stiffness and other hepatic outcomes in patients with diabetes and NAFLD. Except for the lower level of total cholesterol in caffeine group ($p = 0.04$), and higher level of insulin in chlorogenic acid plus caffeine group ($p = 0.01$) compared with placebo, there were no significant differences among the treatment groups. CONCLUSION: These findings do not recommend caffeine and/or chlorogenic acid to treat NAFLD in type 2 diabetes patients. TRIAL REGISTRATION: IRCT201707024010N21 . Registered 14 September 2017.

[48] *Becerra-Tomás N, Paz-Graniel I, Tresserra-Rimbau A et al.* **Fruit consumption and cardiometabolic risk in the PREDIMED-plus study: A cross-sectional analysis**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33838995

ABSTRACT

BACKGROUND AND AIMS: Total fruit consumption is important for cardiovascular disease prevention, but also the variety and form in which is consumed. The aim of the study was to assess the associations between total fruit, subgroups of fruits based on their color and fruit juices consumption with different cardiometabolic parameters. METHODS AND RESULTS: A total of 6633 elderly participants (aged 55-75 years) with metabolic syndrome from the PREDIMED-Plus study were included in this analysis. Fruit and fruit juice consumption was assessed using a food frequency questionnaire. Linear regression models were fitted to evaluate the association between exposure variables (total fruit, subgroups based on the color, and fruit juices) and different cardiometabolic risk factors. Individuals in the highest category of total fruit consumption (≥3 servings/d) had lower waist circumference (WC) (β = -1.04 cm; 95%CI:-1.81, -0.26), fasting glucose levels (β = -2.41 mg/dL; 95%CI(-4.19, -0.63) and LDL-cholesterol (β = -4.11 mg/dL; 95%CI:-6.93, -1.36), but, unexpectedly, higher systolic blood pressure (BP) (β = 1.84 mmHg; 95%CI: 0.37, 3.30) and diastolic BP (β = 1.69 mmHg; 95%CI:0.83, 2.56) when compared to those in the lowest category of consumption (<1 servings/d). Participants consuming ≥1 serving/day of total fruit juice had lower WC (β = -0.92 cm; 95%CI:-1.56, -0.27) and glucose levels (β = -1.59 mg/dL; 95%CI:-2.95, -0.23) than those consuming <1 serving/month. The associations with cardiometabolic risk factors differed according to the color of fruits. CONCLUSION: Fruit consumption is associated with several cardiometabolic risk factors in Mediterranean elders with metabolic syndrome. The associations regarding BP levels could be attributed, at least partially, to reverse causality bias inherent to the cross-sectional design of the study.

[49] *Yang Z, Mi J, Wang Y et al.* **Effects of low-carbohydrate diet and ketogenic diet on glucose and lipid metabolism in type 2 diabetic mice**. Nutrition 2021; 89:111230.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33838492

ABSTRACT

OBJECTIVE: With the prevalence of diabetes worldwide, it is urgent to find a suitable treatment. Recently, the ketogenic diet has shown beneficial effects in reducing blood glucose, but some concerns have been raised about its probable side effects, such as hyperlipidemia and hepatic steatosis. Because a low-carbohydrate diet replaces part of the fat with carbohydrates on the basis of the ketogenic diet, we would like to know whether it does better in treating type 2 diabetes. The aim of this study was to explore the possibility of a low-carbohydrate diet as a substitute for a ketogenic diet intervention in mice with type 2 diabetes. METHODS: C57 BL/6 J mice with type 2 diabetes, constructed by a high-fat diet combined with streptozotocin, were fed a standard diet, a high-fat diet, a low-carbohydrate diet, or a ketogenic diet for 14 wk, respectively. Then glucose and insulin tolerance tests were conducted. At the end of the study, blood and liver samples were collected and analyzed for serum biochemical indicators, histopathologic evaluation, hepatic lipid and glycogen content, and expression levels of mRNA and protein. RESULTS: Reduced blood glucose could be observed in both low-carbohydrate and ketogenic diets, as well as improvement in glucose tolerance and insulin sensitivity. However, the ketogenic diet decreased liver glycogen content and promoted gluconeogenesis. Mechanistically, this effect was due to inhibition of phosphorylated AMP-activated protein kinase, which could be improved by a low-carbohydrate diet. Regarding lipid metabolism, the ketogenic diet increased lipid oxidation and reduced de novo lipogenesis, but the hepatic lipid content still inevitably increased. On the contrary, the low-carbohydrate diet reduced triacylglycerols and markers of liver damage. CONCLUSIONS: Collectively, these findings suggest that both diets are

effective in lowering blood glucose, improving glucose tolerance, and raising insulin sensitivity. Moreover, the low-carbohydrate diet plays a role in inhibiting hepatic gluconeogenesis and improving lipid metabolism. The results suggest that the two diets have different effects on glucose and lipid metabolism, and that the low-carbohydrate diet might have more benefits in the treatment of type 2 diabetes mellitus.

[50] *Jin T, Wang L, Li D et al.* **Testosterone aggravates cerebral vascular injury by reducing plasma HDL levels**. Open Life Sci 2020; 15:1042-1048.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33817290

ABSTRACT

Testosterone is often used to improve the physiological function. But increased testosterone levels affect blood lipids and cause inflammation and oxidative stress, which are risk factors for vascular diseases. This study aimed at investigating the effects of testosterone on cerebral vascular injury using an established intracranial aneurysm (IA) model. Sixteen-week-old female C57Bl/6 mice were subcutaneously infused with testosterone propionate (TP; 5 mg/kg day) or plain soybean oil (controls) for 6 weeks. After 2 weeks of treatment, mice were given angiotensin II-elastase for another 4 weeks. The results showed that TP significantly increased cell apoptosis and reactive oxygen species production in cerebral artery, together with increases in plasma tumor necrosis factor-α (TNF-α) levels and in urinary 8-isoprostane levels. Plasma assays showed that 2 weeks after TP or soybean oil administration, the high-density lipoprotein (HDL) level was higher in the TP group than in controls. In vitro studies showed that testosterone increased TNF-α and monocyte chemotactic protein-1 mRNA and protein expression levels in RAW 264.7 macrophages. In summary, by reducing the HDL level, TP aggravates cerebral artery injury by increasing cell apoptosis, inflammation, and oxidative stress.

[51] *Wang JR, Wang MZ, Zheng SH, Li ZY*. **Neural Remodeling of the Left Atrium in Rats by Rosuvastatin Following Acute Myocardial Infarction**. Open Life Sci 2019; 14:603-610.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33817198

ABSTRACT

OBJECTIVE: This study aims to investigate the effect of rosuvastatin on sympathetic neural remodeling of the left atrium (LA) in rats after myocardial infarction (MI). METHODS: Rats were randomly divided into a three groups: sham group, statin group, and MI group. The mRNA expression levels of the growth-associated protein-43 (GAP43) and nerve growth factor (NGF) were measured by RT-PCR. Immunohistochemistry was used to detect the distribution and density of GAP43- and NGF-positive nerves. The expression levels of these proteins were quantified by Western blot. RESULTS: Compared with the sham group, the average optical density (AOD) values of GAP43 and nerve growth factor (NGF)-positive substances in the LA in the statin and MI groups were significantly higher ($P<0.01$), but the AOD values in the statin group were lower than of those in the MI group ($P<0.01$). Furthermore, the AOD values of GAP43 and NGF positive nerves in the left stellate ganglion in the statin and MI groups were significantly higher ($P<0.01$), but the AOD values in the statin group were lower, when compared with the MI group ($P<0.01$). CONCLUSION: Rosuvastatin could effectively improve the sympathetic neural remodeling of LA in MI rats.

[52] *Fernandes Forte CP, Oliveira FAF, de Barros Lopes C et al.* **Streptococcus mutans in atherosclerotic plaque: molecular and immunohistochemical evaluations**. Oral diseases 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33825326

ABSTRACT

OBJECTIVES: To verify the presence of Streptococcus mutans (SM) in atherosclerotic plaque (AP) using techniques with different sensitivities, correlating with histological changes in plaque and immunoexpression of inflammatory markers. MATERIALS AND METHODS: Thirteen AP samples were subjected to real-time polymerase chain reaction (qRT-PCR), histopathological analyses, histochemical analysis by Giemsa staining (GS), and immunohistochemical analysis for SM, IL-1β, and TNF-α (streptavidin-biotin-peroxidase method). Ten necropsy samples of healthy vessels were used as controls. RESULTS: All AP samples showed histopathological characteristics of severe atherosclerosis and were positive for SM (100.0%) in qRT-PCR and immunohistochemical analyses. GS showed that Streptococcus sp. colonized the lipid-rich core regions and fibrous tissue, while the control group was negative for Streptococcus sp. IL-1β and TNF-α were expressed in 100% and 92.3% of the AP tested, respectively. The control samples were positive for SM in qRT-PCR analysis, but negative for SM, IL-1β, and TNF-α in immunohistochemical analyses. CONCLUSION: The detection of SM in AP and the visualization of Streptococcus sp. suggested a possible association between SM and atherosclerosis. The results obtained from the control samples suggested the presence of DNA fragments or innocuous bacteria that were not associated with tissue alteration. However, future studies are necessary to provide more information.

[53] *Strobescu-Ciobanu C, Giuşcă SE, Căruntu ID et al.* **Osteopontin and osteoprotegerin in atherosclerotic plaque - are they significant markers of plaque vulnerability?** Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie 2020; 61:793-801.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33817720

ABSTRACT

Atherosclerosis (ATS) is still considered as a major, global health problem. For a deeper understanding of its pathogenesis, in the last years the research was translated from tissue visible events to molecular mechanisms. Osteopontin (OPN) and osteoprotegerin (OPG) are two molecules that have been associated with the initiation and progression of ATS lesions. The aim of our study was to assess the OPN and OPG expression in advanced stages of carotid ATS, to analyze the correlation between these markers and the ultrasonographic plaque properties, pointing out the identification of possible patterns that can predict plaque vulnerability and risks of restenosis. The study group comprised 49 consecutive patients (38 males and 11 females) diagnosed with carotid stenotic lesions by using ultrasonography. The carotid endarterectomy specimens were standardly processed for histopathological and immunohistochemical exams. The OPN and OPG expression was semi-quantitatively assessed. Our results sustained the relationship between histological American Heart Association (AHA) type and ultrasonographic classification (echogenic versus echolucent) ($p<0.001$). The semi-quantitative analysis showed that in most cases (31 plaques) OPG and OPN had opposite expressions, whereas in the remaining cases (18 plaques) the expression was similar. There were no correlations between low versus high expression of intra-plaque OPN and OPG ($p=0.335$). We found significant correlation for OPN and plaque echogenicity ($p=0.011$), but not for OPG ($p=0.079$). OPN expression (low versus high) was correlated with plaque type (stable versus unstable) ($p=0.036$), plaque ulceration ($p=0.009$) and inflammation ($p<0.001$). OPG expression (low

versus high) did not reveal statistically significant differences with plaque type (stable versus unstable) and vulnerability plaque parameters, respectively. OPG and OPN co-exist in carotid atherosclerotic plaque demonstrating a modulatory role in inflammatory and calcification processes. OPG is strongly expressed in stable, calcified plaques, while OPN is poorly expressed in calcified plaques and in plaques without hemorrhage, ulceration, inflammation, or necrosis. Starting from the molecular mechanisms, further studies of biomarkers are important to identify new therapeutic resources meant to prevent and treat vascular calcification.

[54] *Im J, Kawada-Watanabe E, Yamaguchi J et al.* **Baseline low-density lipoprotein cholesterol predicts the benefit of adding ezetimibe on statin in statin-naïve acute coronary syndrome**. Scientific reports 2021; 11:7480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33820931

ABSTRACT

We aimed to evaluate the effect of baseline low-density lipoprotein cholesterol (LDL-C) on the outcomes of patients with the acute coronary syndrome (ACS) receiving pitavastatin monotherapy or the combination of pitavastatin + ezetimibe. In the HIJ-PROPER study, 1734 ACS patients with dyslipidemia were randomly assigned to receive pitavastatin or pitavastatin + ezetimibe therapy. Statin-naïve participants (n = 1429) were divided into two groups based on the median LDL-C level (131 mg/dL) at enrollment. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and ischemia-driven coronary revascularization. The median follow-up was 3.2 years. In the < 131 mg/dL group (n = 686), LDL-C changes were - 34.0% and - 49.8% in the pitavastatin monotherapy and pitavastatin + ezetimibe-treated groups (P < 0.0001), respectively; in the ≥ 131 mg/dL group (n = 743), LDL-C changes were - 42.9% and - 56.4% (P < 0.0001, respectively. Kaplan-Meier analyses revealed that the primary endpoint was not significantly different between the treatment groups for the < 131 mg/dL group, however, it was significantly lower in patients treated with pitavastatin + ezetimibe in the ≥ 131 mg/dL group (Hazard ratio = 0.72, 95% confidence interval = 0.56-0.91, P = 0.007, P value for interaction = 0.012). Statin-naïve ACS patients with baseline LDL-C < 131 mg/dL did not clinically benefit from pitavastatin + ezetimibe, while patients with baseline LDL-C ≥ 131 mg/dL treated with pitavastatin + ezetimibe showed better clinical results than those treated with pitavastatin monotherapy.Clinical Trial Registration: Original HIJ PROPER study; URL: http://www.umin.ac.jp/ctr . Unique Identifier; UMIN000002742, registered as an International Standard Randomized Controlled Trial.