[1] *Hardy J, Niman S, Goldfaden RF et al.* **A Review of the Clinical Pharmacology of Pelacarsen: A Lipoprotein(a)-Lowering Agent**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34490591
ABSTRACT
Patients with genetically associated elevated lipoprotein(a) [Lp(a)] levels are at greater risk for coronary artery disease, heart attack, stroke, and peripheral arterial disease. To date, there are no US FDA-approved drug therapies that are designed to target Lp(a) with the goal of lowering the Lp(a) level in patients who have increased risk. The American College of Cardiology (ACC) has provided guidelines on how to use traditional lipid profiles to assess the risk of atherosclerotic cardiovascular disease (ASCVD); however, even with the emergence of statin add-on therapies such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, some populations with elevated Lp(a) biomarkers remain at an increased risk for cardiovascular (CV) disease. Residual CV risk has led researchers to inquire about how lowering Lp(a) can be used as a potential preventative therapy in reducing CV events. This review aims to present and discuss the current clinical and scientific evidence pertaining to pelacarsen.

[2] *Cao RY, Zheng Y, Zhang Y et al.* **Berberine on the Prevention and Management of Cardiometabolic Disease: Clinical Applications and Mechanisms of Action**. The American journal of Chinese medicine 2021:1-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34488551
ABSTRACT
Berberine is an alkaloid from several medicinal plants originally used to treat diarrhea and dysentery as a traditional Chinese herbal medicine. In recent years, berberine has been discovered to exhibit a wide spectrum of biological activities in the treatment of diverse diseases ranging from cancer and neurological dysfunctions to metabolic disorders and heart diseases. This review article summarizes the clinical practice and laboratory exploration of berberine for the treatment of cardiometabolic and heart diseases, with a focus on the novel insights and recent advances of the underlying mechanisms recognized in the past decade. Berberine was found to display pleiotropic therapeutic effects against dyslipidemia, hyperglycemia, hypertension, arrhythmia, and heart failure. The mechanisms of berberine for the treatment of cardiometabolic disease involve combating inflammation and oxidative stress such as inhibiting proprotein convertase subtilisin/kexin 9 (PCSK9) activation, regulating electrical signals and ionic channels such as targeting human ether-a-go-go related gene (hERG) currents, promoting energy metabolism such as activating adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, modifying gut microbiota to promote transforming of berberine into its intestine-absorbable form, and interacting with non-coding RNAs via targeting multiple signaling pathways such as AMPK, mechanistic target of rapamycin (mTOR), etc. Collectively, berberine appears to be safe and well-tolerated in clinical practice, especially for those who are intolerant to statins. Knowledge from this field may pave the way for future development of more effective pharmaceutical approaches for managing cardiometabolic risk factors and preventing heart diseases.

[3] *Lu Y, Jia Z, Su S et al.* **Establishment of trimester-specific reference intervals of serum lipids and the associations with pregnancy complications and adverse perinatal outcomes: a population-based prospective study**. Annals of medicine 2021; 53:1632-1641.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34498500
ABSTRACT
BACKGROUND: Disturbances in maternal lipid metabolism may increase the risk of developing pregnancy complications and adverse perinatal outcomes. However, there is no consensus as to what constitutes normal serum lipid ranges during pregnancy. Our study was aimed to establish trimester-specific serum lipid reference intervals (RIs) and investigate the associations between maternal dyslipidaemia and adverse outcomes in a population-based study. METHODS: The first- and third-trimester lipid profiles were derived from 16,489 singlet pregnant women for regular antenatal check-ups between 2017 and 2019. The serum samples were assayed for total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) in the institutional clinical laboratory. The trimester-specific lipid RIs were estimated with both of the direct observational and the indirect Hoffmann methods. The associations between maternal lipid profiling and pregnancy complications and perinatal outcomes were assessed statistically. RESULTS: Serum levels of TC, TG, LDL-C and HDL-C were all increased significantly in the third trimester of pregnancy. There was no significant difference between the observed RIs established with healthy pregnant women and the calculated RIs derived from the Hoffmann method. A trend towards increased risks of gestational complications and adverse perinatal outcomes was observed in the subjects with elevated levels of TC, TG, and LDL-C or decreased level of HDL-C. CONCLUSIONS: In pregnancy, increased serum levels of TC, TG and LDL-C, and a decreased level of HDL-C posed higher risks of developing pregnancy complications and adverse perinatal outcomes.Key messagesIt is necessary to establish trimester-specific reference intervals for serum lipids including TC, TG, LDL-C and HDL-C that were found significantly increased as the gestational age went up. More importantly, around the upper reference limits of TC, TG and LDL-C (or the lower reference limit of HDL-C), the higher the serum lipid levels were (or the lower the HDL-C level was), the higher risks of developing pregnancy complications and adverse perinatal outcomes were observed.

[4] *Manfredini E, Alves RJ*. **Unusual Finding of Rare Exuberant Xanthomatosis in Hyperlipidemia**. Arquivos brasileiros de cardiologia 2021; 117:407-410.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34495241
ABSTRACT

[5] *Souza P, Perfete C*. **The Paradox of Exercise Intensity in Preventing Cardiovascular Events in Peripheral Arterial Occlusive Disease**. Arquivos brasileiros de cardiologia 2021; 117:317-318.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34495226
ABSTRACT

[6] *Zago VHS, Scherrer DZ, Parra ES et al.* **Effects of SNVs in ABCA1, ABCG1, ABCG5, ABCG8, and SCARB1 Genes on Plasma Lipids, Lipoproteins, and Adiposity Markers in a Brazilian Population**. Biochem Genet 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34505223

ABSTRACT
Several proteins are involved in cholesterol homeostasis, as scavenger receptor class B type I and ATP-binding cassette (ABC) transporters including ABCA1, ABCG1, ABCG5, and ABCG8. This study aimed to determine the effects of single nucleotide variants (SNVs) rs2275543 (ABCA1), rs1893590 (ABCG1), rs6720173 (ABCG5), rs6544718 (ABCG8), and rs5888 (SCARB1) on plasma lipids, lipoproteins, and adiposity markers in an asymptomatic population and its sex-specific effects. Volunteers (n = 590) were selected and plasma lipids, lipoproteins, and adiposity markers (waist-to-hip and waist-to-height ratios, lipid accumulation product and body adiposity index) were measured. Genomic DNA was isolated from peripheral blood cells according to the method adapted from Gross-Bellard. SNVs were detected in the TaqMan® OpenArray® Real-Time polymerase chain reaction platform and data analyses were performed using the TaqMan® Genotyper Software. The rs2275543*C point to an increase of high-density lipoprotein size in females while in males very-low-density lipoprotein, cholesterol, and triglycerides were statistically lower (P value < 0.05). The rs1893590*C was statistically associated with lower apolipoprotein A-I levels and higher activities of paraoxonase-1 and cholesteryl ester transfer protein (P value < 0.05). The rs6720173 was statistically associated with an increase in cholesterol and low-density lipoprotein cholesterol in males; moreover, rs6544718*T reduced adiposity markers in females (P value < 0.05). Regarding the rs5888, a decreased adiposity marker in the total population and in females occurred (P value < 0.05). Multivariate analysis of variance showed that SNVs could influence components of high-density lipoprotein metabolism, mainly through ABCG1 (P value < 0.05). The ABCA1 and ABCG5 variants showed sex-specific effects on lipids and lipoproteins, while SCARB1 and ABCG8 variants might influence adiposity markers in females. Our data indicate a possible role of ABCG1 on HDL metabolism.

[7] *Li F, Du X, He L et al.* **Relationship between serum lipid levels and ischemic stroke in patients with atrial fibrillation: a nested case-control study based on the China Atrial Fibrillation Registry**. BMC cardiovascular disorders 2021; 21:424.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34496759

ABSTRACT
BACKGROUND: Atrial fibrillation (AF) is an important risk factor for acute ischemic stroke. METHODS: A nested case-control study was conducted among patients diagnosed with AF, whose information was acquired from the prospective China Atrial Fibrillation Registry (China-AF), from August 2011 to December 2018. RESULTS: This study compared patients with stroke group (n = 145) with a matched control group (n = 577). Demographic data were similar except for body mass index (BMI), diastolic blood pressure (DBP) which were higher, and new oral anticoagulant (NOAC) treatment rate which was lower in the stroke group (all P < 0.05). Baseline median [IQR] levels of including triglyceride (TG) were higher in the stroke group (21.96 [16.74, 21.52], mg/dL) than the control group (19.62 [14.76, 27.36], mg/dL) (P = 0.012), while the total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were similar between the two groups. Elevated TG and HDL-C were positively associated with ischemic stroke (OR 1.01, 95% CI 1.00-1.02, P = 0.032; OR 1.03, 95% CI 1.00-1.05, P = 0.025), after adjustment for BMI, systolic blood pressure, DBP, CHA(2)DS(2)-VASc score, HAS-BLED score, NOAC, LDL-C and HDL-C. However, NOAC (OR 0.20, 95% CI 0.05-0.84, P = 0.029) could decrease the likelihood of ischemic stroke in patients with AF. In subgroup analysis, higher TG level remained significantly associated

with ischemic stroke for AF patients without a history of smoking (OR 1.26, 95% CI 1.02-1.55, P = 0.028). CONCLUSION: Higher level of TG and HDL-C were positively associated with ischemic stroke in patients with AF.

[8] *Harshfield EL, Fauman EB, Stacey D et al.* **Genome-wide analysis of blood lipid metabolites in over 5000 South Asians reveals biological insights at cardiometabolic disease loci**. BMC medicine 2021; 19:232.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34503513
ABSTRACT
BACKGROUND: Genetic, lifestyle, and environmental factors can lead to perturbations in circulating lipid levels and increase the risk of cardiovascular and metabolic diseases. However, how changes in individual lipid species contribute to disease risk is often unclear. Moreover, little is known about the role of lipids on cardiovascular disease in Pakistan, a population historically underrepresented in cardiovascular studies. METHODS: We characterised the genetic architecture of the human blood lipidome in 5662 hospital controls from the Pakistan Risk of Myocardial Infarction Study (PROMIS) and 13,814 healthy British blood donors from the INTERVAL study. We applied a candidate causal gene prioritisation tool to link the genetic variants associated with each lipid to the most likely causal genes, and Gaussian Graphical Modelling network analysis to identify and illustrate relationships between lipids and genetic loci. RESULTS: We identified 253 genetic associations with 181 lipids measured using direct infusion high-resolution mass spectrometry in PROMIS, and 502 genetic associations with 244 lipids in INTERVAL. Our analyses revealed new biological insights at genetic loci associated with cardiometabolic diseases, including novel lipid associations at the LPL, MBOAT7, LIPC, APOE-C1-C2-C4, SGPP1, and SPTLC3 loci. CONCLUSIONS: Our findings, generated using a distinctive lipidomics platform in an understudied South Asian population, strengthen and expand the knowledge base of the genetic determinants of lipids and their association with cardiometabolic disease-related loci.

[9] *Uyagu OD, Ofoegbu C, Ikhidero J et al.* **Quality assessment and comparative analysis on the recommendations of current guidelines on the management of peripheral arterial disease: a systematic review protocol**. BMJ open 2021; 11:e047980.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34497080
ABSTRACT
INTRODUCTION: Peripheral arterial disease (PAD) is the third leading atherosclerotic arterial disease. There is evidence that there is a high variation in the quality and recommendations of clinical practice guidelines for PAD, leading to the possibility of confusion among clinicians and patients. This study aims to conduct a quality assessment and comparative analysis of the clinical practice guidelines on PAD written between 2010 and 2020. METHOD AND ANALYSIS: We aim to perform a systematic review of clinical practice guidelines written between 2010 and 2020. A search for guidelines will be conducted through medical databases Scope, Pubmed, TRIP, Guideline Clearinghouses and specialist international organisations' specific websites. Guidelines that meet the inclusion criteria will be extracted from the search result. The Appraisal of Guidelines for Research and Evaluation II (AGREE-II instrument) will assess the quality of the selected guidelines. The recommendations, level of evidence and other relevant information will be extracted in a datasheet for qualitative analysis. The score for each guideline's quality will be represented using charts and central

tendency measures for comparison. The summary of recommendations will also be represented in tables for easy comparison for similarities and variations across sections. Finally, the level of evidence on which the recommendations are based will also be noted along with other significant characteristics such as the authors' financial relationship to the biomedical community. We aim to point out deficiencies present in current guidelines and elucidate areas where recommendations are made with low-level evidence. The results will enable the scientific community to design future research to fill in PAD management knowledge gaps. ETHICS AND DISSEMINATION: No ethical approval was sought. Dissemination will be via journal articles and conference presentations. PROSPERO REGISTRATION NUMBER: CRD42020219176.

[10] *Yamada Y, Sugi K, Gatate Y et al.* **Premature Acute Myocardial Infarction in a Young Patient With Sitosterolemia**. CJC Open 2021; 3:1085-1088.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34505049
ABSTRACT
Sitosterolemia is a rare, inherited, autosomal recessive disorder of lipid metabolism characterized by increased levels of plant sterols, such as sitosterol and campesterol, xanthomas, and accelerated atherosclerosis. In a 15-year-old boy exhibiting ST-elevation acute myocardial infarction, lipid panels, including plant sterol, and genetic testing for the ATP-binding cassette sub-family G member 5 (ABCG5) gene mutation, confirmed the diagnosis of sitosterolemia. A comprehensive lipid panel and genetic testing should be considered in patients with premature coronary artery disease to prevent disease progression through dietary and pharmacologic interventions specific to sitosterolemia.

[11] *Afifi N, Khalifa MMM, Al Anany A, Hassan H.* **Cardiac calcium score in systemic sclerosis**. Clinical rheumatology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34495426
ABSTRACT
Cardiac coronary Ca score (CCS), and extra coronary Ca score (ECCS) estimation in asymptomatic systemic sclerosis (SSc) patients and their relation to different disease and patients' variables. The CCS and ECCS were estimated in asymptomatic 20 SSc patients compared to 20 age and sex-matched healthy control using non-contrast cardiac computed tomography. All were applied for cardiac history taking, examination, echocardiography, body mass index (BMI), complete blood picture, erythrocyte sedimentation rate, and lipid profile estimation. The SSc patients were 11 females and 9 males with a mean age of (42.55 ± 9.145) and mean disease duration (12.9 ± 6.774). CCS was reported in 9 (45%) SSc cases and 2 (10%) of the control; ($p = 0.013$) and was significantly greater in SSc patients (58.4 ± 175.443) than in the control group (0.7 ± 2.25); ($p = 0.01$). The ECCS was significantly higher in SSc cases (194.45 ± 586.511) than control group (2.8 ± 7.8); ($p = 0.001$) and reported in 16 (80%) SSc cases and 3 (15%) of controls; ($p = 0.000$). Limited scleroderma cases had higher scores than diffuse type. Patients with total ca score (>100) were older ($p = 0.016$), had longer disease duration ($p = 0.001$) and greater BMI ($p = 0.002$). Significant correlation was found between the log-transformed CCS and disease duration, age, BMI, left ventricular mass, and mass index. Systemic sclerosis patients are at increased risk of subclinical cardiovascular disease determined by cardiac Ca scoring as a noninvasive and reliable method. Extra coronary calcification may be an earlier indicator for this. Disease duration is a determinant risk factor for cardiac calcification in SSc. Key Points • Although the association between interleukin-6 (IL-6) promoter polymorphism and

rheumatic arthritis (RA) has been discussed in the previous meta-analysis, their conclusions are inconsistent. • Systemic sclerosis patients are at high risk of accelerated atherosclerosis and cardiovascular diseases. Coronary atherosclerosis was previously estimated in SSc patients through coronary angiography. A novel method of assessing coronary artery disease is the coronary calcium score, as determined by multidetector computed tomography, it measures coronary artery calcification that occurs in atherosclerotic plaque. In this study, the cardiac coronary and extra coronary Ca score were evaluated in relation to disease characteristics in asymptomatic SSC patients for early detection of coronary artery disease.

[12] *Balendiran GK, Verma M, Perry E*. **Chemistory of Fibrates**. Curr Chem Biol 2007; 1:311-316.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34485047

ABSTRACT

Since the description of the synthetic chemical clofibrate in 1962, various derivatives of fibrates with a diversity of chemical structures have been developed. Several of these are used clinically to treat dyslipidemia because they are generally effective in lowering elevated plasma triglycerides and cholesterol. Studies suggest that several biochemical mechanisms underlie fibrate-mediated modulation of lipoprotein and related metabolites. These mechanisms are: 1) induced lipoprotein lipolysis; 2) induced hepatic fatty acid uptake and reduced hepatic triglyceride formation; 3) amplified removal of low density lipoprotein (LDL) particles; 4) reduced neutral lipid (cholesteryl ester and triglyceride) exchange between very low density lipoprotein (VLDL) and high density lipoprotein (HDL) resulting from decreased plasma levels of triglyceride-rich lipoprotein (TRL); and 5) increased HDL production and stimulation of reverse cholesterol transport. Recent studies of structure-based inhibitor design strategy revealed that an independent enzyme, aldose reductase (AR), is a target of fibrate activity, an additional biochemical mechanism. AR has been implicated as a major player in the development of diabetes and diabetic complications because of its ability to catalyze the conversion of glucose to sorbitol. This article discusses various targets of fibrate action, biochemical pathways and commonalities in potential molecular interactions.

[13] *Nastasi DR, Norman R, Moxon JV et al.* **The Potential Benefits and Costs of an Intensified Approach to Low Density Lipoprotein Cholesterol Lowering in People with Abdominal Aortic Aneurysm**. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2021; 62:643-650.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34507892

ABSTRACT

OBJECTIVE: The aims of this study were to assess the incidence of major vascular events (MVE) and peripheral vascular events (PVE) in people with a small asymptomatic abdominal aortic aneurysm (AAA) and model the theoretical benefits and costs of an intensified low density lipoprotein cholesterol (LDL-C) lowering programme. METHODS: A total of 583 participants with AAAs measuring 30 - 54 mm were included in this study. The control of LDL-C and prescription of lipid lowering drugs were assessed by dividing participants into approximately equal tertiles depending on their year of recruitment into the study. The occurrence of MVE (myocardial infarction, stroke, cardiovascular death, and coronary or non-coronary revascularisation) and PVE (non-coronary revascularisation, AAA repair, and major amputation) were recorded prospectively, and the incidence of these events was calculated using Kaplan-Meier analysis. The relative risk reduction reported for

these events in a previous randomised control trial (RCT) was then applied to these figures to model the absolute risk reduction and numbers needed to treat (NTT) that could theoretically be achieved with a mean LDL-C lowering of 1 mmol/L. The maximum allowable expense for a cost effective intensive LDL-C lowering programme was estimated using a cost utility analysis. RESULTS: At entry, only 28.5% of participants had an LDL-C of < 1.8 mmol/L and only 18.5% were prescribed a high potency statin (atorvastatin 80 mg or rosuvastatin 40 mg). The five year incidences of MVE and PVE were 38.1% and 44.7%, respectively. It was estimated that if the mean LDL-C of the cohort had been reduced by 1 mmol/L, this could have reduced the absolute risk of MVE and PVE by 6.5% (95% CI 4.4 - 8.7; NNT 15) and 5.3% (95% CI 1.4 - 7.5; NNT 19), respectively. It was estimated that the maximum allowable expense for a cost effective LDL-C lowering programme would be between $1 239 AUD (€768) and $1 582 AUD (€981) per person per annum over a five year period. CONCLUSION: People with a small asymptomatic AAA are at high risk of MVE and PVE. This study provides evidence of the possible benefits and allowable expense for a cost effective intensive LDL-C lowering programme in this population.

[14] *Chen CN, Hsu KJ, Chien KY, Chen JJ*. **Effects of Combined High-Protein Diet and Exercise Intervention on Cardiometabolic Health in Middle-Aged Obese Adults: A Randomized Controlled Trial**. Frontiers in cardiovascular medicine 2021; 8:705282.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34485407

ABSTRACT

Background: Obesity is the main risk factor of cardiovascular diseases (CVD) and metabolic diseases. The middle-aged population is the age group with the highest prevalence of obesity. Thus, improving cardiometabolic health is important to prevent CVD and metabolic diseases in middle-aged obese adults. The aim of this study was to examine the effects of exercise alone or in combination with a high-protein diet on markers of cardiometabolic health in middle-aged adults with obesity. Methods: Sixty-nine middle-aged adults with obesity were assigned randomly to the control group (C; n = 23), exercise group (E; n = 23), or exercise combined with high-protein diet group (EP; n = 23). Individuals in the E and EP groups received supervised exercise training and individuals in the EP group received high-protein diet intervention. Body composition (assessed by dual-energy X-ray absorptiometry), oral glucose tolerance test (OGTT), lipid profiles, and inflammatory markers were determined before and after 12 weeks of intervention. Insulin sensitivity index (ISI(0,120)) was calculated from values of fasting and 2-h insulin and glucose concentration of OGTT. Insulin-peak-time during the OGTT was recorded to reflect β-cell function. Analysis of covariance with baseline values as covariates was used to examine the effects of the intervention. The significant level was set at 0.05. Results: After 12 weeks of intervention, the E group had a greater percentage of individuals with early insulin-peak-time during the OGTT than that in the C and EP groups (p = 0.031). EP group had lower total cholesterol and triglycerides than that in the C group (p = 0.046 and 0.014, respectively). Within-group comparisons showed that the 2-h glucose of OGTT and C-reactive protein decreased in the EP group (p = 0.013 and 0.008, respectively) but not in the E and C groups; insulin sensitivity improved in the EP group (p = 0.016) and had a trend to improve in the E group (p = 0.052); and abdominal fat mass and total body fat mass decreased in both intervention groups (p < 0.05). Conclusion: Combined high-protein diet and exercise intervention significantly decreased fat mass and improved lipid profiles, insulin sensitivity, glucose tolerance, and inflammation in middle-

aged adults with obesity. Clinical Trial Registration: Thai Clinical Trials Registry, TCTR20180913003, 13-09-2018.

[15] *Gong J, Chen Y, Jie Y et al.* **U-Shaped Relationship of Low-Density Lipoprotein Cholesterol With Risk of Severe COVID-19 From a Multicenter Pooled Analysis**. Frontiers in cardiovascular medicine 2021; 8:604736.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34504873
ABSTRACT
Low-density lipoprotein cholesterol (LDL-C) is a well-known risk factor for coronary heart disease but protects against infection and sepsis. We aimed to disclose the exact association between LDL-C and severe 2019 novel coronavirus disease (COVID-19). Baseline data were retrospectively collected for 601 non-severe COVID-19 patients from two centers in Guangzhou and one center in Shenzhen, and patients on admission were medically observed for at least 15 days to determine the final outcome, including the non-severe group (n = 460) and the severe group (severe and critical cases) (n = 141). Among 601 cases, 76 (12.65%) received lipid-lowering therapy; the proportion of patients taking lipid-lowering drugs in the severe group was higher than that in the non-severe group (22.7 vs. 9.6%). We found a U-shaped association between LDL-C level and risk of severe COVID-19 using restricted cubic splines. Using univariate logistic regression analysis, odds ratios for severe COVID-19 for patients with LDL-C ≤1.6 mmol/L (61.9 mg/dL) and above 3.4 mmol/L (131.4 mg/dL) were 2.29 (95% confidence interval 1.12-4.68; p = 0.023) and 2.02 (1.04-3.94; p = 0.039), respectively, compared to those with LDL-C of 2.81-3.40 mmol/L (108.6-131.4 mg/dL); following multifactorial adjustment, odds ratios were 2.61 (1.07-6.37; p = 0.035) and 2.36 (1.09-5.14; p = 0.030). Similar results were yielded using 0.3 and 0.5 mmol/L categories of LDL-C and sensitivity analyses. Both low and high LDL-C levels were significantly associated with higher risk of severe COVID-19. Although our findings do not necessarily imply causality, they suggest that clinicians should pay more attention to lipid-lowering therapy in COVID-19 patients to improve clinical prognosis.

[16] *Grigorian-Shamagian L, Edel K, Esteve-Pastor MA et al.* **Practical Decision Algorithms for the Use of the Cardiovascular Polypill in Secondary Prevention in Europe**. Frontiers in cardiovascular medicine 2021; 8:663361.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34504874
ABSTRACT
The main objective of cardiovascular disease (CVD) prevention is to reduce morbidity and mortality. Despite recommendations on evidence-based pharmacological treatment and lifestyle changes, the control of CV risk factors such as hypertension or dyslipidaemia is not optimal. The use of a CV polypill, including guideline-recommended drugs, as a baseline therapy, may contribute to improving risk factors control either by improving the treatment adherence or by the synergistic effect of its components. The CNIC-Polypill is the first CV polypill approved in Europe as an effective strategy for secondary prevention, which contains acetylsalicylic acid, atorvastatin (in two optional doses), and ramipril (in three optional doses) in a single pill. The present practical clinical document aims to provide a guide for patient management after an acute coronary syndrome (ACS) or with chronic CVD (CCVD) with a strategy based on the CNIC-Polypill, also considering the need to add other therapies for a personalized treatment. The most suitable clinical scenarios for the CNIC-Polypill use are discussed: (a) in patients after an ACS at discharge, (b) in patients with CCVD (chronic coronary

syndrome, stroke, or peripheral artery disease) with uncontrolled low-density lipoprotein cholesterol (LDL-c) and/or blood pressure levels and (c) in patients with CCVD with well-controlled risk factors to simplify treatment and reduce polypharmacy in the context of CCVD prevention.

[17] *Lin Y, Hidru TH, Fan R et al.* **The Relationship Between Serum Uric Acid at Different Concentrations of Lipid Indices and the Risk of Myocardial Revascularization in Patients With Acute Coronary Syndrome: A Retrospective Analysis**. Frontiers in cardiovascular medicine 2021; 8:732715.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34497839

ABSTRACT

Objective: Both serum uric acid (SUA) levels and lipid components, such as LDL, HDL, and Lp(a), have been reported to associate with CAD. However, the influence of SUA status at different concentrations of lipid indices for the risk of myocardial revascularization (MRT) in ACS patients is currently unknown. Methods: We retrospectively analyzed a hospital-based sample of 14,234 ACS patients with no previous history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. All patients went for coronary angiography. Binary logistic regression models were performed, and the odds ratios (OR) at 95% confidence interval (CIs) were used to approximate the associated risk of UA and lipid profile for myocardial revascularization, with the lowest quartile/tertile serving as the reference category. Results: Overall, 8,818 (61.9%) patients undergone MRT out of 14,234 patients. Elevated SUA and HDL were negatively associated with an increased likelihood of MRT during admission ($P < 0.001$). However, LDL and Lp(a) levels were positively associated with MRT among ACS patients. Furthermore, interaction analyses between SUA and lipid profiles, particularly LDL and Lp(a), compared with those in the lowest quartile of SUA levels, show that patients in higher SUA quartiles grouped by lipid components had a significantly lower chance of undergoing MRT, with the lowest OR (95%CI) for subjects being 0.222 (0.170-0.290), 0.478 (0.374-0.612), and 0.604 (0.468-0.780) in LDL tertiles, being 0.671(0.523-0.862), 0.316(0.242-0.413), and 0.410 (0.310-0.542) in Lp(a) tertiles, respectively. In the three tertiles of HDL levels, the incidence of MRT dropped steadily as SUA levels increased. Also, we further analyzed ACS patients without diabetes. Compared with the first quartile of SUA levels, the risks of MRT were significantly lower in different tertiles of lipids components [LDL, Lp(a), HDL]. Conclusion: An increase in SUA levels may decrease the chance of undergoing MRT in ACS patients, even in those with increased Lp(a) and LDL-c. Elevated serum uric acid may play a protective role during an acute stage of ACS.

[18] *Jia X, Xu W, Zhang L et al.* **Impact of Gut Microbiota and Microbiota-Related Metabolites on Hyperlipidemia**. Frontiers in cellular and infection microbiology 2021; 11:634780.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34490132

ABSTRACT

Hyperlipidemia, defined as the presence of excess fat or lipids in the blood, has been considered as a high-risk factor and key indicator of many metabolic diseases. The gut microbiota has been reported playing a vital role in regulating host lipid metabolism. The pathogenic role of gut microbiota in the development of hyperlipidemia has been revealed through fecal microbiota transplantation experiment to germ-free mice. The effector mechanism of microbiota-related metabolites such as bile acids, lipopolysaccharide, and short-chain fatty acids in the regulation of hyperlipidemia has been

partially unveiled. Moreover, studies on gut-microbiota-targeted hyperlipidemia interventions, including the use of prebiotics, probiotics, fecal microbiota transplantation, and natural herbal medicines, also have shown their efficacy in the treatment of hyperlipidemia. In this review, we summarize the relationship between gut microbiota and hyperlipidemia, the impact of gut microbiota and microbiota-related metabolites on the development and progression of hyperlipidemia, and the potential therapeutic management of hyperlipidemia targeted at gut microbiota.

[19] *Íñiguez M, Pérez-Matute P, Villoslada-Blanco P et al.* **ACE Gene Variants Rise the Risk of Severe COVID-19 in Patients With Hypertension, Dyslipidemia or Diabetes: A Spanish Pilot Study**. Frontiers in endocrinology 2021; 12:688071.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34489863
ABSTRACT
Coronavirus disease 19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continues to scale and threaten human health and public safety. It is essential to identify those risk factors that lead to a poor prognosis of the disease. A predisposing host genetic background could be one of these factors that explain the interindividual variability to COVID-19 severity. Thus, we have studied whether the rs4341 and rs4343 polymorphisms of the angiotensin converting enzyme (ACE) gene, key regulator of the renin-aldosterone-angiotensin system (RAAS), could explain the different outcomes of 128 COVID-19 patients with diverse degree of severity (33 asymptomatic or mildly symptomatic, 66 hospitalized in the general ward, and 29 admitted to the ICU). We found that G allele of rs4341 and rs4343 was associated with severe COVID-19 in hypertensive patients, independently of gender ($p<0.05$). G-carrier genotypes of both polymorphisms were also associated with higher mortality ($p< 0.05$) and higher severity of COVID-19 in dyslipidemic ($p<0.05$) and type 2 diabetic patients ($p< 0.01$). The association of G alleles with disease severity was adjusted for age, sex, BMI and number of comorbidities, suggesting that both the metabolic comorbidities and the G allele act synergistically on COVID-19 outcome. Although we did not find a direct association between serum ACE levels and COVID-19 severity, we found higher levels of ACE in the serum of patients with the GG genotype of rs4341 and rs4343 ($p<0.05$), what could explain the higher susceptibility to develop severe forms of the disease in patients with the GG genotype, in addition to hypertension and dyslipidemia. In conclusion, our preliminary study suggests that the G-containing genotypes of rs4341 and rs4343 confer an additional risk of adverse COVID-19 prognosis. Thus, rs4341 and rs4343 polymorphisms of ACE could be predictive markers of severity of COVID-19 in those patients with hypertension, dyslipidemia or diabetes. The knowledge of these genetic data could contribute to precision management of SARS-CoV-2 infected patients when admitted to hospital.

[20] *Ito M, Hiwasa T, Oshima Y et al.* **Association of Serum Anti-PCSK9 Antibody Levels with Favorable Postoperative Prognosis in Esophageal Cancer**. Frontiers in oncology 2021; 11:708039.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34504788
ABSTRACT
BACKGROUND: Esophageal cancer often appears as postoperative metastasis or recurrence after radical surgery. Although we had previously reported that serum programmed cell death ligand 1 (PD-L1) level correlated with the prognosis of esophageal cancer, further novel biomarkers are required

for more precise prediction of the prognosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is associated with the cholesterol metabolism. But there was no report of relationship between serum PCSK9 antibody and cancer. Therefore, we investigated whether anti-PCSK9 antibodies could be a novel biomarker for solid cancer. METHODS: Serum levels of anti-PCSK9 antibodies and antigens in patients with solid cancer were analyzed using amplified luminescence proximity homogeneous assay-linked immunosorbent assay (AlphaLISA). The reactivity of serum antibodies against recombinant PCSK9 protein was investigated by Western blotting, and the expression of PCSK9 antigens in esophageal cancer tissues was examined by immunohistochemical staining. RESULTS: AlphaLISA showed that serum anti-PCSK9 antibody (s-PCSK9-Ab) levels were significantly higher in patients with esophageal cancer, gastric cancer, colorectal cancer, lung cancer, and breast cancer than in healthy donors, and patients with esophageal cancer had the highest levels. The presence of serum antibody in patients was confirmed by Western blotting. There was no apparent correlation between s-PCSK9-Ab and PCSK9 antigen levels. Immunohistochemical staining demonstrated the expression of PCSK9 antigen in both the cytoplasm and nuclear compartments of esophageal squamous cell carcinoma tissue but not in normal tissue. Compared with patients with low s-PCSK9-Ab levels, those with high s-PCSK9-Ab levels had a favorable postoperative prognosis after radical surgery for esophageal cancer. In the multivariate analysis, tumor depth and s-PCSK9-Ab level were identified as independent prognostic factors. In the univariate analysis of clinicopathological features, high PCSK9 antibody levels were not associated with sex, age, location, tumor depth, lymph node status, squamous cell carcinoma antigen, or p53-Ab, whereas they correlated significantly with PD-L1 levels, which were associated with unfavorable prognosis. Correlation between s-PCSK9-Ab and PD-L1 levels was also confirmed in the logistic regression analysis; therefore, low s-PCSK9-Ab levels could discriminate another poor prognosis group other than high-PD-L1 group. CONCLUSIONS: Patients with solid cancer had higher s-PCSK9-Ab levels than healthy donors. High s-PCSK9-Ab levels indicated better prognosis for overall survival after surgery in patients with esophageal cancer.

[21] *Zinellu A, Paliogiannis P, Fois AG et al.* **Cholesterol and Triglyceride Concentrations, COVID-19 Severity, and Mortality: A Systematic Review and Meta-Analysis With Meta-Regression**. Frontiers in public health 2021; 9:705916.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34490188

ABSTRACT

Lipid profile alterations have been observed in patients with coronavirus disease 2019 (COVID-19) in relation to disease severity and mortality. We conducted a systematic review and meta-analysis with meta-regression of studies reporting total, HDL, and LDL-cholesterol, and triglyceride concentrations in hospitalized patients with COVID-19. We searched PubMed, Web of Science and Scopus, between January 2020 and January 2021, for studies describing lipid concentrations, COVID-19 severity, and survival status (PROSPERO registration number: CRD42021253401). Twenty-two studies in 10,122 COVID-19 patients were included in the meta-analysis. Pooled results showed that hospitalized patients with severe disease or non-survivor status had significantly lower total cholesterol (standardized mean difference, SMD = -0.29, 95% CI -0.41 to -0.16, $p < 0.001$), LDL-cholesterol (SMD = -0.30, 95% CI -0.41 to -0.18, $p < 0.001$), and HDL-cholesterol (SMD = -0.44, 95% CI -0.62 to -0.26, $p < 0.001$), but not triglyceride (SMD = 0.04, 95% CI -0.10 to -0.19, $p = 0.57$), concentrations compared to patients with milder disease or survivor status during follow up. Between-study heterogeneity was large-to-extreme. In sensitivity analysis, the effect size of different lipid fractions

was not affected when each study was in turn removed. The Begg's and Egger's t-tests did not show evidence of publication bias, except for studies investigating LDL-cholesterol. In meta-regression, significant associations were observed between the SMD of LDL-cholesterol and age and hypertension, and between the SMD of triglycerides and study endpoint and aspartate aminotransferase. In our systematic review and meta-analysis, lower total, HDL, and LDL-cholesterol, but not triglyceride, concentrations were significantly associated with COVID-19 severity and mortality. Cholesterol concentrations might be useful, in combination with other clinical and demographic variables, for risk stratification and monitoring in this group. Systematic Review Registration: PROSPERO registration number: CRD42021253401.

[22] *Andersen P, Kragholm K, Torp-Pedersen C et al.* **The impact of peripheral artery disease on major adverse cardiovascular events following myocardial infarction**. International journal of cardiology 2021; 343:131-137.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34499974
ABSTRACT
AIMS: Peripheral artery disease (PAD) constitute a high-risk with adverse clinical outcomes. We aimed to investigate the cardiovascular outcomes following myocardial infarction (MI). METHODS AND RESULTS: This nationwide, Danish register-based follow-up study includes all patients experiencing an MI between 2000 and 2017. Patients with and without PAD were compared. Multivariable logistic regression was used to derive relative risks of 1-year major adverse cardiovascular events (MACE; all-cause mortality, reinfarction, stroke or heart failure). Individual components, cardiovascular mortality, and bleeding, standardized to age, sex and comorbidity distributions of all patients were assessed. MI patients with PAD (n = 5083, 2.9%) were older and more comorbid compared to patients without PAD (n = 174,673). After standardization, PAD was associated with higher 1-year relative risks of MACE (RR 1.21 [95% CI 1.17;1.25]), all-cause (RR 1.29 [95% CI 1.24;1.35]) and cardiovascular mortality (RR 1.3 [95% CI 1.24;1.36]), reinfarction (RR 1.17 [95% CI 1.11;1.22]), stroke (RR 1.12 [95% CI 0.92;1.32]), heart failure (RR 1.22 [95% CI 1.12;1.32]), and bleeding episodes (RR 1.25 [95% CI 1.04,1.46]). Similar results were seen in 30-day survivors after adjustment for antithrombotic post-discharge medication for MACE (RR 1.25 [95% CI 1.20,1.31]), all-cause mortality (RR 1.47 [95% CI 1.37,1.57], cardiovascular mortality (RR 1.49 [95% CI 1.37,1.61]), reinfarction (RR 1.17 [95% CI 1.08,1.12]) and heart failure (RR 1.22 [95% CI 1.12,1.32]). CONCLUSION: Comparing to patients without PAD, patients with PAD had increased 1-year relative risk of MACE, all-cause mortality, reinfarction, stroke, heart failure, cardiovascular mortality and bleeding following MI. The low prevalence of PAD is suggestive of considerable under-diagnosing.

[23] *Nakajima A, Subban V, Russo M et al.* **Coronary plaque and clinical characteristics of South Asian (Indian) patients with acute coronary syndromes: An optical coherence tomography study**. International journal of cardiology 2021; 343:171-179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34487786
ABSTRACT
BACKGROUND: South Asians, and Indians in particular, are known to have a higher incidence of premature atherosclerosis and acute coronary syndromes (ACS) with worse clinical outcomes, compared to populations with different ethnic backgrounds. However, the underlying pathobiology

accounting for these differences has not been fully elucidated. METHODS: ACS patients who had culprit lesion optical coherence tomography (OCT) imaging were enrolled. Culprit plaque characteristics were evaluated using OCT. RESULTS: Among 1315 patients, 100 were South Asian, 1009 were East Asian, and 206 were White. South Asian patients were younger (South Asians vs. East Asians vs. Whites: 51.6 ± 13.4 vs. 65.4 ± 11.9 vs. 62.7 ± 11.7; $p < 0.001$) and more frequently presented with ST-segment elevation myocardial infarction (STEMI) (77.0% vs. 56.4% vs. 35.4%; $p < 0.001$). On OCT analysis after propensity group matching, plaque erosion was more frequent (57.0% vs. 38.0% vs. 50.0%; $p = 0.003$), the lipid index was significantly greater (2281.6 [1570.8-3160.6] vs. 1624.3 [940.9-2352.4] vs. 1303.8 [1090.0-1757.7]; $p < 0.001$), and the prevalence of layered plaque was significantly higher in the South Asian group than in the other two groups (52.0% vs. 30.0% vs. 34.0%; $p = 0.003$). CONCLUSIONS: Compared to East Asians and Whites, South Asians with ACS were younger and more frequently presented with STEMI. Plaque erosion was the predominant pathology for ACS in South Asians and their culprit lesions had more features of plaque vulnerability. CLINICAL TRIAL REGISTRATION: http://www.clinicaltrials.gov, NCT03479723.

[24] *Sánchez Muñoz-Torrero JF, Escudero-Sánchez G, Calderón-García JF et al.* **Systolic Blood Pressure and Outcomes in Stable Outpatients with Recent Symptomatic Artery Disease: A Population-Based Longitudinal Study**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34501937

ABSTRACT

OBJECTIVES: The most appropriate targets for systolic blood pressure (SBP) levels to reduce cardiovascular morbidity and mortality in patients with symptomatic artery disease remain controversial. We compared the rate of subsequent ischemic events or death according to mean SBP levels during follow-up. DESIGN: Prospective cohort study. FRENA is an ongoing registry of stable outpatients with symptomatic coronary (CAD), cerebrovascular (CVD) or peripheral artery disease (PAD). SETTING: 24 Spanish hospitals. PARTICIPANTS: 4789 stable outpatients with vascular disease. RESULTS: As of June 2017, 4789 patients had been enrolled in different Spanish centres. Of these, 1722 (36%) had CAD, 1383 (29%) CVD and 1684 (35%) PAD. Over a mean follow-up of 18 months, 136 patients suffered subsequent myocardial infarction, 125 had ischemic stroke, 74 underwent limb amputation, and 260 died. On multivariable analysis, CVD patients with mean SBP levels 130-140 mm Hg had a lower risk of mortality than those with levels <130 mm Hg (hazard ratio (HR): 0.39; 95% CI: 0.20-0.77), as did those with levels >140 mm Hg (HR: 0.46; 95% CI: 0.26-0.84). PAD patients with mean SBP levels >140 mm Hg had a lower risk for subsequent ischemic events (HR: 0.57; 95% CI: 0.39-0.83) and those with levels 130-140 mm Hg (HR: 0.47; 95% CI: 0.29-0.78) or >140 mm Hg (HR: 0.32; 95% CI: 0.21-0.50) had a lower risk of mortality. We found no differences in patients with CAD. CONCLUSIONS: In this real-world cohort of symptomatic arterial disease patients, most of whom are not eligible for clinical trials, the risk of subsequent events and death varies according to the levels of SBP and the location of previous events. Especially among patients with large artery atherosclerosis, PAD or CVD, SBP <130 mm Hg may result in increased mortality. Due to potential factors in this issue, Prospective, well designed studies are warranted to confirm these observational data.

[25] *Nissen SE, Hutchinson HG, Wang TY et al.* **Technology-Assisted Self-Selection of Candidates for Nonprescription Statin Therapy**. Journal of the American College of Cardiology 2021; 78:1114-1123.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34503680

ABSTRACT

BACKGROUND: Although statins reduce cardiovascular morbidity and mortality, only about one-half of eligible patients receive treatment. Safe and appropriate consumer access to statins could have a significant positive public health impact. OBJECTIVES: This study compares the concordance between a participant and clinician assessment of eligibility for statin therapy using a technology-assisted approach. METHODS: A total of 500 participants, 83 with limited literacy, completed an at-home Web-based application to assess appropriateness for treatment with rosuvastatin 5 mg. The Web application is designed to assess eligibility for a moderate-intensity statin based on current guidelines and deny access to individuals with contraindications to rosuvastatin. Subsequently, participants visited a research site where clinicians, blinded to the information the participant entered, performed an independent Web application assessment. The Web application is programmed for 1 of 3 rosuvastatin treatment outcomes: "OK to use," "not right for you," or "ask a doctor." The primary endpoint was the percent of participants whose self-selected eligibility for nonprescription rosuvastatin was concordant with clinician assessment. RESULTS: For the primary endpoint, participant selection for statin therapy was concordant with clinician selection in 481 (96.2%) of 500 participants (95% confidence interval: 94.1%-97.7%), of whom 23 (4.6%) were deemed appropriate and 458 (91.6%) were deemed inappropriate for treatment. Discordance was due to incorrect self-selection ("OK to use") in 3 cases, incorrect rejection ("not right for you") in 14 cases and an incorrect "ask a doctor" outcome in 2 cases. CONCLUSIONS: The use of a technology-assisted approach to consumer self-selection for statin therapy resulted in participant self-selection that showed substantial agreement with clinician selection.

[26] *Lin JL, Chen PS, Lin HW et al.* **Real-World Analyses of the Safety Outcome among a General Population Treated with Statins: An Asian Population-Based Study**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34497171

ABSTRACT

AIM: The safety concern of statins is still a major issue for Asians. The aim of this study is to compare the risk of statin-associated adverse events among potent statins. METHODS: We included patients from the Taiwan National Health Insurance Research Database who had been treated with atorvastatin, rosuvastatin, or pitavastatin and were without diabetes at baseline. They were classified into three groups: usual-dose statin (atorvastatin 10 mg/d or rosuvastatin 5-10 mg/d), high-dose statin (atorvastatin 20-40 mg/d and rosuvastatin 20 mg/d), and pitavastatin (2-4 mg/d). The primary endpoint is a composite of safety events, including hepatitis, myopathy, and new-onset diabetes mellitus (NODM). We matched age, sex, and year of recruitment among the three groups (n=50,935 in each group) and then used the multivariate Cox proportional hazards model to evaluate the relation between the safety endpoint and different statin groups. RESULTS: After a mean follow-up of 3.08±0.83 years, the safety events occurred in 9.84% in the pitavastatin group, 10.88% in the usual-dose statin group, and 10.49% in high-dose statin group. The multivariate Cox proportional hazards model indicated that usual-dose statin and high-dose statin were associated with a higher risk of the

composite safety events compared with pitavastatin (adjusted hazard ratio [aHR]: 1.12, 95% confidence interval [CI]: 1.08-1.17 for usual-dose statin and aHR: 1.06, 95% CI: 1.02-1.10 for high-dose statin). The risks of hepatitis requiring hospitalization and NODM were especially lower in pitavastatin group. CONCLUSIONS: Compared with atorvastatin and rosuvastatin, pitavastatin might be associated with a lower risk of safety events in Asians.

[27] *Susan-Resiga D, Girard E, Essalmani R et al.* **Asialoglycoprotein receptor 1 is a novel PCSK9-independent ligand of liver LDLR cleaved by furin**. The Journal of biological chemistry 2021; 297:101177.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34508778
ABSTRACT
The hepatic carbohydrate-recognizing asialoglycoprotein receptor (ASGR1) mediates the endocytosis/lysosomal degradation of desialylated glycoproteins following binding to terminal galactose/N-acetylgalactosamine. Human heterozygote carriers of ASGR1 deletions exhibit ~34% lower risk of coronary artery disease and ~10% to 14% reduction of non-HDL cholesterol. Since the proprotein convertase PCSK9 is a major degrader of the low-density lipoprotein receptor (LDLR), we investigated the degradation and functionality of LDLR and/or PCSK9 by endogenous/overexpressed ASGR1 using Western blot and immunofluorescence in HepG2-naïve and HepG2-PCSK9-knockout cells. ASGR1, like PCSK9, targets LDLR, and both independently interact with/enhance the degradation of the receptor. This lack of cooperativity between PCSK9 and ASGR1 was confirmed in livers of wildtype (WT) and Pcsk9(-/-) mice. ASGR1 knockdown in HepG2-naïve cells significantly increased total (~1.2-fold) and cell-surface (~4-fold) LDLR protein. In HepG2-PCSK9-knockout cells, ASGR1 silencing led to ~2-fold higher levels of LDLR protein and DiI (1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate)-LDL uptake associated with ~9-fold increased cell-surface LDLR. Overexpression of WT-ASGR1/2 primarily reduced levels of immature non-O-glycosylated LDLR (~110 kDa), whereas the triple Ala-mutant of Gln240/Trp244/Glu253 (characterized by loss of carbohydrate binding) reduced expression of the mature form of LDLR (~150 kDa), suggesting that ASGR1 binds the LDLR in both a sugar-dependent and -independent fashion. The protease furin cleaves ASGR1 at the RKMK(103)↓ motif into a secreted form, likely resulting in a loss of function on LDLR. Altogether, we demonstrate that LDLR is the first example of a liver-receptor ligand of ASGR1. We conclude that silencing of ASGR1 and PCSK9 may lead to higher LDL uptake by hepatocytes, thereby providing a novel approach to further reduce LDL cholesterol levels.

[28] *Holt R, Pedersen JH, Dinsdale E et al.* **Vitamin D supplementation improves fasting insulin levels and HDL cholesterol in infertile men**. The Journal of clinical endocrinology and metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34508607
ABSTRACT
CONTEXT: Vitamin D has been linked with glucose and lipid metabolism. Men with impaired gonadal function have a higher risk of metabolic syndrome and mortality, and vitamin D status may be a reversible modulator. OBJECTIVE: Determine the effect of daily vitamin D and calcium supplementation for 150 days on glucose and lipid homeostasis in infertile men. DESIGN: A single-center, double-blinded, randomized clinical trial (NCT01304927), 307 infertile men were randomized (1:1) to a single dose of 300,000 IU cholecalciferol followed by 1,400 IU cholecalciferol + 500 mg of

calcium daily (n=151) or placebo (n=156) for 150 days. Reported metabolic parameters including fasting plasma glucose, HbA1c, fasting serum insulin, homeostatic model assessment of insulin resistance (HOMA-IR), fasting plasma cholesterols and triglyceride were secondary endpoints. The primary endpoint semen quality has previously been reported. RESULTS: Men receiving vitamin D supplementation improved their vitamin D status, while vitamin D status was aggravated in the placebo group characterized by higher serum parathyroid hormone (PTH). At end of trial, men receiving vitamin D supplementation had 13% lower fasting serum insulin concentrations compared with the placebo-treated group (65 vs. 74 pmol/L, P = 0.018) and 19% lower HOMA-IR (2.2 vs. 2.7, P = 0.025). Moreover, men in the vitamin D group had higher high-density lipoprotein (HDL) cholesterol levels (1.38 vs. 1.32 mmol/L, P = 0.008) compared with the placebo group. CONCLUSION: High-dose vitamin D supplementation had beneficial effects on glucose homeostasis and HDL cholesterol levels in infertile men.

[29] *Smith A, Johnson D, Banks J et al.* **Trends in PCSK9 Inhibitor Prescriptions before and after the Price Reduction in Patients with Atherosclerotic Cardiovascular Disease**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34501275
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors reduce low-density lipoprotein (LDL) cholesterol and cardiovascular event rates, yet due to their high price remain underutilized and difficult to prescribe in clinical practice. In March 2018, their price was significantly reduced. We evaluated whether the price reduction would improve prescribing patterns of PCSK9 inhibitors in eligible patients with atherosclerotic cardiovascular disease (ASCVD). METHODS: We identified the number of eligible ASCVD patients and those prescribed a PCSK9 inhibitor for each year between July 2015 and December 2019. Patient demographics and clinical characteristics for those prescribed a PCSK9 inhibitor were extracted from their electronic health record. RESULTS: In total 1059 patients of eligible patients received a new prescription for a PCSK9 inhibitor. From 2015 to 2019, the rate of new prescriptions among eligible patients increased from 0.5 to 3.3% ($p < 0.001$) and continuation rates increased from 18 to 60% ($p < 0.001$). Following the price reduction, patients who were prescribed a PCSK9 inhibitor were younger and more likely to be female, but less likely to have Medicare insurance. CONCLUSIONS: Despite the reduction in the cost of PCSK9 inhibitors, most eligible patients are not prescribed one. The reduction in cost has improved adherence, primarily in patients with commercial insurance. Older patients and those on Medicare still face significant barriers in accessing a PCSK9 inhibitor. Further reductions in the price of the PCSK9 inhibitors are needed as is further study of the barriers that exist in prescribing one.

[30] *Momtazi-Borojeni AA, Jaafari MR, Abdollahi E et al.* **Impact of PCSK9 Immunization on Glycemic Indices in Diabetic Rats**. Journal of diabetes research 2021; 2021:4757170.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34504898
ABSTRACT
METHODS: To prepare the anti-PCSK9 vaccine, a peptide construct called Immunogenic Fused PCSK9-Tetanus (IFPT) was linked to the surface of nanoliposome carriers. Healthy rats received four subcutaneous injections of the vaccine at biweekly intervals. Two weeks after the last vaccination, anti-PCSK9 antibody titers, PCSK9 targeting, and inhibition of PCSK9-low-density lipoprotein

receptor (LDLR) interaction were evaluated. After verification of antibody generation, the immunized rats were intraperitoneally treated with a single dose (45 mg/kg) of streptozotocin (STZ) to induce diabetes mellitus. The levels of fasting blood glucose (FBG) were measured, and the oral glucose tolerance test (OGTT) as well as the insulin tolerance test (ITT) were carried out to assess glycemic status. At the end of the study, the total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride, and high-density lipoprotein cholesterol concentrations were assayed. Histopathology examination of the liver and pancreas was also performed using the hematoxylin-eosin staining method. RESULTS: The prepared nanoliposomal vaccine could strongly induce anti-PCSK9 antibodies in the vaccinated rats. Within one week following the STZ injection, the FBG level was lower in the vaccinated group vs. diabetic control group (49% (-171.7 ± 35 mg/dL, $p < 0.001$)). In the OGTT, the injected rats showed improved glucose tolerance as reflected by the reduction of blood glucose levels over 180 min, compared with the diabetic controls. Moreover, the ITT demonstrated that, after the insulin injection, blood glucose concentration declined by 49.3% in the vaccinated group vs. diabetic control group. Expectedly, the vaccinated rats exhibited lower (-26.65%, $p = 0.03$) plasma LDL-C levels compared with the diabetic controls. Histopathology examination of pancreas tissue demonstrated that the pancreatic islets of the vaccinated rats had a slight decline in the population of β-cells and few α-cells. Normal liver histology was also observed in the vaccinated rats. CONCLUSION: PCSK9 inhibition through the liposomal IFPT vaccine can improve the glucose and insulin tolerance impairments as well as the lipid profile in diabetes.

[31] *Tang ML, Zhou YQ, Song AQ et al.* **The Relationship between Body Mass Index and Incident Diabetes Mellitus in Chinese Aged Population: A Cohort Study**. Journal of diabetes research 2021; 2021:5581349.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34485532

ABSTRACT

OBJECTIVES: Previous studies reported that overweight older adults had a lower mortality after cardiovascular diseases attack, indicating being thinner might not always be better. However, there is an ongoing debate about what is the optimal range of body mass index (BMI) for the aged population. We aimed to evaluate the value of BMI for the prediction of incident diabetes mellitus (DM) in the Chinese elderly population. METHODS: A total number of 6,911 Chinese elderly people (4,110 men and 2,801 women, aged 71 ± 6.0 years) were included in this cohort study. BMI was measured at baseline (Jan 1, 2014, to Dec 31, 2014). All the participants were further classified into six groups: <18.5 kg/m(2), 18.5 to <22.5 kg/m(2), 22.5 to <25.0 kg/m(2), 25.0 to <27.5 kg/m(2), 27.5 to <30.0 kg/m(2), and ≥30.0 kg/m(2). Fasting blood glucose (FBG) and glycated hemoglobin A1c (HbA1c) were annually measured during follow-up (Jan 1, 2015-May 31, 2019). DM was confirmed if either FBG ≥ 7.0 mmol/L or HbA1c ≥ 6.5%. We used the Cox proportional hazard regression model to evaluate the association between BMI and the prediction of incident DM. RESULTS: Comparing individuals with a BMI range of 18.5 to <22.5 kg/m(2) (reference), the hazard ratio for incident DM was 2.13 (95% CI: 1.54~2.95), 2.14 (95% CI: 1.53~3.00), 3.17 (95% CI: 2.19~4.59), 3.15 (95% CI: 1.94~5.09), and 3.14 (95% CI: 1.94~5.09) for the group with a BMI range of 22.5 to <25.0 kg/m(2), 25.0 to <27.5 kg/m(2), 27.5 to <30.0 kg/m(2), and ≥30.0 kg/m(2) after adjusting for baseline age, sex, blood pressure, lipid profiles, and eGFR (P trend < 0.001), after adjusting for the abovementioned confounders. The association tended to be closer in men and young participants, compared with their counterparts. CONCLUSIONS: High BMI was associated with a high risk of developing DM in the

Chinese aged population. Thus, it is optimal for the aged population to maintain their body weight within a reasonable range to prevent chronic diseases.

[32] *Christensen JJ, Narverud I, Ruuth M et al.* **Children with familial hypercholesterolemia display changes in LDL and HDL function: A cross-sectional study**. Journal of internal medicine 2021; 290:1083-1097.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34506681
ABSTRACT
BACKGROUND: The functional status of lipoprotein particles contributes to atherogenesis. The tendency of plasma low-density lipoprotein (LDL) particles to aggregate and the ability of igh-density lipoprotein (HDL) particles to induce and mediate reverse cholesterol transport associate with high and low risk for cardiovascular disease in adult patients, respectively. However, it is unknown whether children with familial hypercholesterolemia (FH) display lipoprotein function alterations. HYPOTHESIS: We hypothesized that FH children had disrupted lipoprotein functions. METHODS: We analyzed LDL aggregation susceptibility and HDL-apoA-I exchange (HAE), and activity of four proteins that regulate lipoprotein metabolism (cholesteryl ester transfer protein, lecithin-cholesterol acyltransferase, phospholipid transfer protein, and paraoxonase-1) in plasma samples derived from children with FH (n = 47) and from normocholesterolemic children (n = 56). Variation in lipoprotein functions was further explored using an nuclear magnetic resonance-based metabolomics profiling approach. RESULTS: LDL aggregation was higher, and HAE was lower in FH children than in normocholesterolemic children. LDL aggregation associated positively with LDL cholesterol (LDL-C) and negatively with triglycerides, and HAE/apoA-I associated negatively with LDL-C. Generally, the metabolomic profile for LDL aggregation was opposite of that of HAE/apoA-I. CONCLUSIONS: FH children displayed increased atherogenicity of LDL and disrupted HDL function. These newly observed functional alterations in LDL and HDL add further understanding of the risk for atherosclerotic cardiovascular disease in FH children.

[33] *Ready JM*. **Toward a Best-in-Class Inhibitor of Cholesteryl Ester Transfer Protein (CETP)**. Journal of medicinal chemistry 2021; 64:13212-13214.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34498872
ABSTRACT
Inhibitors of cholesteryl ester transfer protein (CETP) elevate HDL levels human clinical trials. However, the first CETP inhibitors proved toxic in pivotal trials or showed minimal therapeutic benefit. Anacetrapib showed some clinical benefit but is high lipophilic. This Viewpoint highlights efforts to optimize anacetrapib to a best-in-class CETP inhibitor.

[34] *Bhattarai AK, Acharya A, Karki PK*. **Use of Statins as Lipid Lowering Agent in Hypercholesterolemia in a Tertiary Care Hospital: A Descriptive Cross-sectional Study**. JNMA; journal of the Nepal Medical Association 2020; 58:1031-1035.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34506382
ABSTRACT
INTRODUCTION: Lipids contribute to atherosclerosis and obesity that can lead to different cardiovascular diseases. Statins are hydroxymethylglutaryl reductase inhibitors that effectively lower the cholesterol level. It is widely prescribed in the treatment of hypercholesterolemia. Thus it

optimizes the lipoprotein profile. The selection of a particular drug by the practitioner should be primarily based on clinical outcome. This study was conducted to find the type of statins that are most preferred by the doctors for treating dyslipidemia and preferred the fixed-dose in a tertiary care hospital. METHODS: This was a descriptive cross-sectional study conducted among the practicing doctors of Kathmandu Medical College from July to August 2020. Ethical approval was taken from the Institutional Review Committee of the college (Ref: 207202006). Convenient sampling was done. A semi-structured questionnaire was used with consent. The data were analyzed with Social Statistical Package for the Social Sciences version 20. RESULTS: Statins, with the score 4.25 was accounted for most preferred for the treatment of dyslipidemia. Among different statins, atorvastatin with a score of 4.48 was most popular followed by rosuvastatin 2.9 score and simvastatin 2.1 scores. CONCLUSIONS: Statins were the most preferred agents for the treatment of dyslipidemia. Although different types of statins ought to have similar efficacy in treating dyslipidemia, atorvastatin was found to be popular and the most commonly prescribed one. The most common side effect reported with statins was myopathy.

[35] *Mehta RK, Koirala P, Mallick RL et al.* **Dyslipidemia in Patients with Type 2 Diabetes Mellitus in a Tertiary Care Centre: A Descriptive Cross-sectional Study**. JNMA; journal of the Nepal Medical Association 2021; 59:305-309.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34508529
ABSTRACT
INTRODUCTION: Dyslipidemia is highly prevalent among type 2 diabetic patients. It increases the risk of atherosclerosis and consequent mortality in diabetic patients. The aim of this study was to find out the prevalence of dyslipidemia among type 2 diabetic patients. METHODS: This was a descriptive cross-sectional study in 355 type 2 diabetic patients at tertiary care hospital from 15th May, 2020 to 15th November, 2020 after taking ethical clearence from Institutional Review Committee (Reference no. IRC-PA-052/2077-78). Convenience sampling was done. Demographic and lipid profile variables were recorded based on the structured questionnaires. Data were analyzed by Statistical Package for the Social Sciences version 20. Point estimate at 95% Confidence Interval was calculated along with frequency and percentage for binary data. RESULTS: Out of total 355 cases of type 2 Diabetes mellitus, prevalence of dyslipidemia was 224 (63.1%). It was more prevalent in male 145 (69.4%) than female 79 (54.1%). Increased Low density Lipoprotein (94.2%) was the most prevalent type followed by mixed dyslipidemia (91.1%). CONCLUSIONS: Dyslipidemia was common among type 2 diabetic patients and was higher in male gender, older age, obesity and longer duration of diabetes. Hence type 2 diabetic patient should undergo the routine monitoring of blood sugar and lipid profile so that any abnormalities can be identified and preventive measures along with interventions can be initiated at the earliest.

[36] *Lee SH*. **Role of Genetics in Preventive Cardiology: Focused on Dyslipidemia**. Korean circulation journal 2021; 51:899-907.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34494410
ABSTRACT
Dyslipidemia is a strong risk factor for cardiovascular disease as well as a major target for its prevention. Along with the progress in genetic research techniques and bioinformatics analysis, genetic knowledge helps manage individuals with dyslipidemia. Familial hypercholesterolemia, the

most common monogenic lipid disorder, can be diagnosed clinically without confirming pathogenic mutations. However, it can be difficult to do so due to uncertain family history, and genetic testing is of vital importance in such cases. Conversely, recent studies have revealed that combination effect of rare and common variants is frequent in people with other extreme lipid phenotypes. Genetic characteristics are helpful for prediction and selection of patients with high risk for cardiovascular disease or poor response to lipid-lowering therapy. In the past decade, studies using new genetic techniques have identified novel associations among lipid metabolism-associated genes, intermediate lipid phenotypes, and cardiovascular health. Such findings shed light on new drug targets. With improvements in the platforms and processes for drug development, several recent clinical trials showed promising results regarding lipid control and potential cardiovascular disease prevention.

[37] **Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)**. Lancet 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34506743

ABSTRACT

BACKGROUND: The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (FHSC) global registry provides a platform for the global surveillance of familial hypercholesterolaemia through harmonisation and pooling of multinational data. In this study, we aimed to characterise the adult population with heterozygous familial hypercholesterolaemia and described how it is detected and managed globally. METHODS: Using FHSC global registry data, we did a cross-sectional assessment of adults (aged 18 years or older) with a clinical or genetic diagnosis of probable or definite heterozygous familial hypercholesterolaemia at the time they were entered into the registries. Data were assessed overall and by WHO regions, sex, and index versus non-index cases. FINDINGS: Of the 61 612 individuals in the registry, 42 167 adults (21 999 [53·6%] women) from 56 countries were included in the study. Of these, 31 798 (75·4%) were diagnosed with the Dutch Lipid Clinic Network criteria, and 35 490 (84·2%) were from the WHO region of Europe. Median age of participants at entry in the registry was 46·2 years (IQR 34·3-58·0); median age at diagnosis of familial hypercholesterolaemia was 44·4 years (32·5-56·5), with 40·2% of participants younger than 40 years when diagnosed. Prevalence of cardiovascular risk factors increased progressively with age and varied by WHO region. Prevalence of coronary disease was 17·4% (2·1% for stroke and 5·2% for peripheral artery disease), increasing with concentrations of untreated LDL cholesterol, and was about two times lower in women than in men. Among patients receiving lipid-lowering medications, 16 803 (81·1%) were receiving statins and 3691 (21·2%) were on combination therapy, with greater use of more potent lipid-lowering medication in men than in women. Median LDL cholesterol was 5·43 mmol/L (IQR 4·32-6·72) among patients not taking lipid-lowering medications and 4·23 mmol/L (3·20-5·66) among those taking them. Among patients taking lipid-lowering medications, 2·7% had LDL cholesterol lower than 1·8 mmol/L; the use of combination therapy, particularly with three drugs and with proprotein convertase subtilisin-kexin type 9 inhibitors, was associated with a higher proportion and greater odds of having LDL cholesterol lower than 1·8 mmol/L. Compared with index cases, patients who were non-index cases were younger, with lower LDL cholesterol and lower prevalence of cardiovascular risk factors and cardiovascular diseases (all p<0·001). INTERPRETATION: Familial hypercholesterolaemia is diagnosed late. Guideline-recommended LDL cholesterol concentrations are infrequently achieved with single-drug therapy. Cardiovascular risk factors and presence of coronary disease were lower among non-index cases,

who were diagnosed earlier. Earlier detection and greater use of combination therapies are required to reduce the global burden of familial hypercholesterolaemia. FUNDING: Pfizer, Amgen, Merck Sharp & Dohme, Sanofi-Aventis, Daiichi Sankyo, and Regeneron.

[38] *Alikiaii B, Heidari Z, Bagherniya M et al.* **The Effect of Statins on C-Reactive Protein in Stroke Patients: A Systematic Review of Clinical Trials**. Mediators of inflammation 2021; 2021:7104934.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34489618

ABSTRACT

BACKGROUND: Statins reportedly have anti-inflammatory effects aside from their lipid-lowering impact. We investigated the effects of statin therapy on the level of C-reactive protein (CRP) or highly sensitive CRP (hs-CRP), a liver-derived marker of systemic inflammation, among stroke patients. METHODS: An online search was performed in Scopus, PubMed/MEDLINE, ISI Web of Science, and Google Scholar up to November 2020 to recognize clinical trials investigating the effects of statins on the CRP level in stroke patients. RESULTS: Overall, nine studies (11 treatment arms) with 1659 participants met the inclusion criteria. Six out of 9 studies (8 out of 11 arms) were categorized as studies with a high-quality methodological approach using the Cochrane Collaboration's tool. Data from 5 treatment arms indicated a significant decrease in CRP concentration, and in one treatment arm, CRP concentration did not suggest any considerable alteration following statin therapy. Moreover, two treatment arms showed a significant reduction in hs-CRP concentration and three treatment arms revealed no significant alteration in hs-CRP concentration following statin therapy. Generally, results were heterogeneous and independent of the type of statin, statin dose, treatment duration, and changes in plasma low-density lipoprotein cholesterol concentration. CONCLUSION: The results suggest that statin therapy could reduce and, therefore, could be considered in these patients as potential anti-inflammatory agents.

[39] *Ying Q, Chan DC, Barrett PHR, Watts GF*. **Unravelling lipoprotein metabolism with stable isotopes: tracing the flow**. Metabolism 2021; 124:154887.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34508741

ABSTRACT

Dysregulated lipoprotein metabolism is a major cause of atherosclerotic cardiovascular disease (ASCVD). Use of stable isotope tracers and compartmental modelling have provided deeper understanding of the mechanisms underlying lipid disorders in patients at high risk of ASCVD, including familial hypercholesterolemia (FH), elevated lipoprotein(a) [Lp(a)] and metabolic syndrome (MetS). In patients with FH, deficiency in low-density lipoprotein (LDL) receptor activity not only impairs the catabolism of LDL, but also induces hepatic overproduction and decreases catabolism of triglyceride-rich lipoproteins (TRLs). Patients with elevated Lp(a) are characterized by increased hepatic secretion of Lp(a) particles. Atherogenic dyslipidemia in MetS patients relates to a combination of overproduction of very-low density lipoprotein-apolipoprotein (apo) B-100, decreased catabolism of apoB-100-containing particles, and increased catabolism of high-density lipoprotein-apoA-I particles, as well as to impaired clearance of TRLs in the postprandial state. Kinetic studies show that weight loss, fish oils, statins and fibrates have complementary modes of action that correct atherogenic dyslipidemia. Defining the kinetic mechanisms of action of proprotein convertase subtilisin/kexin type 9 and angiopoietin-like 3 inhibitors on lipid and lipoprotein mechanism in dyslipidemic subjects will further our understanding of these therapies in decreasing the development

of ASCVD. "Everything changes but change itself. Everything flows and nothing remains the same... You cannot step twice into the same river, for other waters and yet others go flowing ever on." Heraclitus (c.535- c. 475 BCE).

[40] *Durrer C, McKelvey S, Singer J et al.* **A randomized controlled trial of pharmacist-led therapeutic carbohydrate and energy restriction in type 2 diabetes**. Nature communications 2021; 12:5367.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34508090
ABSTRACT
Type 2 diabetes can be treated, and sometimes reversed, with dietary interventions; however, strategies to implement these interventions while addressing medication changes are lacking. We conducted a 12-week pragmatic, community-based parallel-group randomized controlled trial (ClinicalTrials.gov: NCT03181165) evaluating the effect of a low-carbohydrate (<50 g), energy-restricted diet (~850-1100 kcal/day; Pharm-TCR; n = 98) compared to treatment-as-usual (TAU; n = 90), delivered by community pharmacists, on glucose-lowering medication use, cardiometabolic health, and health-related quality of life. The Pharm-TCR intervention was effective in reducing the need for glucose-lowering medications through complete discontinuation of medications (35.7%; n = 35 vs. 0%; n = 0 in TAU; $p < 0.0001$) and reduced medication effect score compared to TAU. These reductions occurred concurrently with clinically meaningful improvements in hemoglobin A1C, anthropometrics, blood pressure, and triglycerides (all $p < 0.0001$). These data indicate community pharmacists are a viable and innovative option for implementing short-term nutritional interventions for people with type 2 diabetes, particularly when medication management is a safety concern.

[41] *Cintra M, Pedraza Cezón LA, Martín Navarro JA et al.* **Acute renal failure due to rhabdomyolysis in relation to abiraterone and rosuvastatin**. Nefrologia (Engl Ed) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34503863
ABSTRACT

[42] *Li Z, Luo Y, Zhang J*. **Atorvastatin pretreatment alleviate the ischemic brain injury linked to peroxisome proliferator-activated receptor coactivator-1α and angiogenic factors in diabetic mice**. Neuro endocrinology letters 2021; 42:331-338.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34506097
ABSTRACT
OBJECTIVE: The purpose of this study was to investigated whether pretreated with Atorvastatin be helpful in diabetic or wild-type mice, and clarify the possible mechanisms. METHODS: C57/B6 and ob/ob mice treated with atorvastatin or not were subjected to middle cerebral artery occlusion (MCAO), which were killed after 2h of occlusion following by 22h of reperfusion. We used Neurological Severity Scores (NSS) to assess the severity of brain injury, and TTC staining was used to measure the infraction volume. Protein levels of PGC-1α, vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), Bcl2, Bax and signaling pathway protein of mitogen-activated protein kinase (MAPK) were estimated by western blot. RESULTS: Atorvastatin could slake the cerebral ischemic/ reperfusion injury in ob/ob diabetic mice, but do nothing on wild-type mice. The expression of PGC-1α and related angiogenic factors such as VEGF and Ang-1 were lower in the diabetic mice after MCAO than wild-type, which could be effective reversed by atorvastatin pretreatment before

MCAO. This may be one of the possible mechanisms for atorvastatin to alleviate ischemic injury. MAPK pathway and apoptosis-related proteins were also involved in this course. CONCLUSION: Impaired angiogenesis mediated by PGC-1α plays an important role in exacerbating ischemic cerebral insults in diabetic mice, and pretreatment with atorvastatin before MCAO has a protective effect through the regulation of PGC-1α and angiogenic factors.

[43] *D'Erasmo L, Gallo A, Cefalù AB et al.* **Long-term efficacy of lipoprotein apheresis and lomitapide in the treatment of homozygous familial hypercholesterolemia (HoFH): a cross-national retrospective survey**. Orphanet journal of rare diseases 2021; 16:381.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34496902

ABSTRACT

BACKGROUND: Homozygous familial hypercholesterolemia (HoFH) is a rare life-threatening condition that represents a therapeutic challenge. The vast majority of HoFH patients fail to achieve LDL-C targets when treated with the standard protocol, which associates maximally tolerated dose of lipid-lowering medications with lipoprotein apheresis (LA). Lomitapide is an emerging therapy in HoFH, but its place in the treatment algorithm is disputed because a comparison of its long-term efficacy versus LA in reducing LDL-C burden is not available. We assessed changes in long-term LDL-C burden and goals achievement in two independent HoFH patients' cohorts, one treated with lomitapide in Italy (n = 30) and the other with LA in France (n = 29). RESULTS: The two cohorts differed significantly for genotype (p = 0.004), baseline lipid profile (p < 0.001), age of treatment initiation (p < 0.001), occurrence of cardiovascular disease (p = 0.003) as well as follow-up duration (p < 0.001). The adjunct of lomitapide to conventional lipid-lowering therapies determined an additional 58.0% reduction of last visit LDL-C levels, compared to 37.1% when LA was added (p(adj) = 0.004). Yearly on-treatment LDL-C < 70 mg/dl and < 55 mg/dl goals were only achieved in 45.5% and 13.5% of HoFH patients treated with lomitapide. The long-term exposure to LDL-C burden was found to be higher in LA than in Lomitapide cohort (13,236.1 ± 5492.1 vs. 11,656.6 ± 4730.9 mg/dL-year respectively, p(adj) = 0.002). A trend towards fewer total cardiovascular events was observed in the Lomitapide than in the LA cohort. CONCLUSIONS: In comparison with LA, lomitapide appears to provide a better control of LDL-C in HoFH. Further studies are needed to confirm this data and establish whether this translates into a reduction of cardiovascular risk.

[44] *Esposito L, Cancro FP, Silverio A et al.* **COVID-19 and Acute Coronary Syndromes: From Pathophysiology to Clinical Perspectives**. Oxidative medicine and cellular longevity 2021; 2021:4936571.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34484561

ABSTRACT

Acute coronary syndromes (ACS) are frequently reported in patients with coronavirus disease 2019 (COVID-19) and may impact patient clinical course and mortality. Although the underlying pathogenesis remains unclear, several potential mechanisms have been hypothesized, including oxygen supply/demand imbalance, direct viral cellular damage, systemic inflammatory response with cytokine-mediated injury, microvascular thrombosis, and endothelial dysfunction. The severe hypoxic state, combined with other conditions frequently reported in COVID-19, namely sepsis, tachyarrhythmias, anemia, hypotension, and shock, can induce a myocardial damage due to the mismatch between oxygen supply and demand and results in type 2 myocardial infarction (MI). In

addition, COVID-19 promotes atherosclerotic plaque instability and thrombus formation and may precipitate type 1 MI. Patients with severe disease often show decrease in platelets count, higher levels of d-dimer, ultralarge von Willebrand factor multimers, tissue factor, and prolongation of prothrombin time, which reflects a prothrombotic state. An endothelial dysfunction has been described as a consequence of the direct viral effects and of the hyperinflammatory environment. The expression of tissue factor, von Willebrand factor, thromboxane, and plasminogen activator inhibitor-1 promotes the prothrombotic status. In addition, endothelial cells generate superoxide anions, with enhanced local oxidative stress, and endothelin-1, which affects the vasodilator/vasoconstrictor balance and platelet aggregation. The optimal management of COVID-19 patients is a challenge both for logistic and clinical reasons. A deeper understanding of ACS pathophysiology may yield novel research insights and therapeutic perspectives in higher cardiovascular risk subjects with COVID-19.

[45] *Niedzielski M, Broncel M, Gorzelak-Pabiś P, Woźniak E*. **A comparison of the effects of monotherapy with rosuvastatin, atorvastatin or ezetimibe versus combination treatment with rosuvastatin-ezetimibe and atorvastatin-ezetimibe on the integrity of vascular endothelial cells damaged by oxidized cholesterol**. PloS one 2021; 16:e0256996.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34492054

ABSTRACT

Dyslipidemia, atherosclerosis, and cardiovascular events can be prevented, or treated, using statins, alone or in combination with ezetimibe. The aim of the study was to compare the direct pleiotropic effects of two commonly-used statins (atorvastatin, rosuvastatin), ezetimibe and their combinations on endothelial cells damaged by oxidized cholesterol. HUVEC cultures were stimulated for 20 hours with atorvastatin (5 μM; 2793 ng/mL), rosuvastatin (10 μM; 4815 ng/mL), ezetimibe (1.22 μM; 500 ng/mL), atorvastatin plus ezetimibe (5 μM + 1.22 μM; 2793 ng/mL + 500 ng/mL) and rosuvastatin plus ezetimibe (10 μM + 1.22 μM; 4815 ng/mL + 500ng/mL) in separate groups, with or without 25-hydroxycholesterol pre-incubation (24.83 μM; 10 μg/mL; four hours then washout). HUVEC integrity was measured in the RTCA-DP xCELLigence system. The mRNA expression and protein levels of ZO-1, OCLN, ICAM-1 were analyzed by real-time PCR and ELISA. Pre-incubation with 25-OHC resulted in decreased endothelial cell integrity ($p<0.001$), decreased expression of ZO-1 mRNA ($p<0.05$) and protein levels ($p<0.05$), OCLN mRNA ($p<0.05$) and protein levels ($p<0.05$) and increased ICAM-1 mRNA ($p<0.001$) and protein levels ($p<0.001$) compared to the control group. Incubation with rosuvastatin (12h $p<0.01$; 24h $p<0.001$) and atorvastatin (only 12h $p<0.05$) restored HUVEC integrity. Subsequent incubation with rosuvastatin increased ZO-1 mRNA ($p<0.001$) and protein ($p<0.001$) levels. Subsequent addition of ezetimibe increased ZO-1 mRNA level ($p<0.001$) but not protein level. Furthermore, only incubation with rosuvastatin increased OCLN mRNA ($p<0.05$) and protein ($p<0.05$) levels. In each drug-stimulated group, both ICAM-1 mRNA and protein levels were reduced after initial incubation with oxysterol ($p<0.05$). 25-hydroxycholesterol disrupts endothelial integrity, decreases the mRNA and protein levels of tight junction, and increases those of intercellular adhesion molecules. Both rosuvastatin and atorvastatin can improve endothelial integrity, but only rosuvastatin can completely abolish the effect of oxysterol. The combination of statins with ezetimibe has less direct effect on the endothelial barrier than the statins alone.

[46] *Sahebkar A, Kiaie N, Gorabi AM et al.* **A comprehensive review on the lipid and pleiotropic effects of pitavastatin**. Progress in lipid research 2021; 84:101127.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34509516

ABSTRACT

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are administered as first line therapy for hypercholesterolemia, both in primary and secondary prevention. There is a growing body of evidence showing that beyond their lipid-lowering effect, statins have a number of additional beneficial properties. Pitavastatin is a unique lipophilic statin with a strong effect on lowering plasma total cholesterol and triacylglycerol. It has been reported to have pleiotropic effects such as decreasing inflammation and oxidative stress, regulating angiogenesis and osteogenesis, improving endothelial function and arterial stiffness, and reducing tumor progression. Based on the available studies considering the risk of statin-associated muscle symptoms it seems to be also the safest statin. The unique lipid and non-lipid effects of pitavastatin make this molecule a particularly interesting option for the management of different human diseases. In this review, we first summarized the lipid effects of pitavastatin and then strive to unravel the diverse pleiotropic effects of this molecule.

[47] *Kosekli MA, Kurtkulagii O, Kahveci G et al.* **The association between serum uric acid to high density lipoprotein-cholesterol ratio and non-alcoholic fatty liver disease: the abund study**. Rev Assoc Med Bras (1992) 2021; 67:549-554.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34495059

ABSTRACT

OBJECTIVE: Non-alcoholic fatty liver disease, which is characterized by lipid being deposited into hepatocytes, affects nearly one in three adults globally. Inflammatory markers were suggested to be related with hepatic steatosis. Uric acid to HDL cholesterol ratio is proposed as a novel inflammatory and metabolic marker. We aimed to compare Uric acid to HDL cholesterol ratio levels of patients with Non-alcoholic fatty liver disease to those of healthy controls and find out potential correlations between Uric acid to HDL cholesterol ratio and other inflammatory and metabolic markers of Non-alcoholic fatty liver disease. METHODS: Patients with a diagnosis of Non-alcoholic fatty liver disease who were on clinical follow-up in our institution were enrolled in the study as the Non-alcoholic fatty liver disease group, while healthy volunteers were enrolled as the control group. The Uric acid to HDL cholesterol ratio of the groups was compared and potential correlations were studied between Uric acid to HDL cholesterol ratio and fasting blood glucose, transaminases, serum lipids (triglyceride, LDL-cholesterol), weight, and body mass index. RESULTS: The Uric acid to HDL cholesterol ratio of the Non-alcoholic fatty liver disease (13±5%) group was significantly higher compared to the Uric acid to HDL cholesterol ratio of the control (10±4%) group ($p<0.001$). Uric acid to HDL cholesterol ratio was significantly and positively correlated with fasting blood glucose, transaminases, triglyceride, body weight, waist circumference, hip circumference, and body mass index. A ROC analysis revealed that a Uric acid to HDL cholesterol ratio level greater than 9.6% has 73% sensitivity and 51% specificity in determining Non-alcoholic fatty liver disease. CONCLUSION: Due to the inexpensive and easy-to-assess nature of Uric acid to HDL cholesterol ratio, we suggest that elevated Uric acid to HDL cholesterol ratio levels be considered a useful tool in diagnosing hepatic steatosis.

[48] *Gallone G, Elia E, Bruno F et al.* **Impact of lipid-lowering therapies on cardiovascular outcomes according to coronary artery calcium score. A systematic review and meta-analysis**. Revista espanola de cardiologia (English ed.) 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34483065

ABSTRACT

INTRODUCTION AND OBJECTIVES: Coronary artery calcium (CAC) score improves the accuracy of risk stratification for atherosclerotic cardiovascular disease (ASCVD) events compared with traditional cardiovascular risk factors. We evaluated the interaction of coronary atherosclerotic burden as determined by the CAC score with the prognostic benefit of lipid-lowering therapies in the primary prevention setting. METHODS: We reviewed the MEDLINE, EMBASE, and Cochrane databases for studies including individuals without a previous ASCVD event who underwent CAC score assessment and for whom lipid-lowering therapy status stratified by CAC values was available. The primary outcome was ASCVD. The pooled effect of lipid-lowering therapy on outcomes stratified by CAC groups (0, 1-100,> 100) was evaluated using a random effects model. RESULTS: Five studies (1 randomized, 2 prospective cohort, 2 retrospective) were included encompassing 35 640 individuals (female 38.1%) with a median age of 62.2 [range, 49.6-68.9] years, low-density lipoprotein cholesterol level of 128 (114-146) mg/dL, and follow-up of 4.3 (2.3-11.1) years. ASCVD occurrence increased steadily across growing CAC strata, both in patients with and without lipid-lowering therapy. Comparing patients with (34.9%) and without (65.1%) treatment exposure, lipid-lowering therapy was associated with reduced occurrence of ASCVD in patients with CAC> 100 (OR, 0.70; 95%CI, 0.53-0.92), but not in patients with CAC 1-100 or CAC 0. Results were consistent when only adjusted data were pooled. CONCLUSIONS: Among individuals without a previous ASCVD, a CAC score> 100 identifies individuals most likely to benefit from lipid-lowering therapy, while undetectable CAC suggests no treatment benefit.

[49] *Reinau D, Schur N, Twerenbold S et al.* **Utilisation patterns and costs of lipid-lowering drugs in Switzerland 2013-2019**. Swiss Med Wkly 2021; 151:w30018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34495601

ABSTRACT

OBJECTIVE: To analyse utilisation patterns of lipid-lowering drugs and the related costs in Switzerland between the years 2013 and 2019. METHODS: We conducted a retrospective descriptive study using administrative claims data of persons aged ≥18 years enrolled with the health insurance company Helsana. To enable statements at the Swiss population level, results were extrapolated according to age, sex and canton of residence. RESULTS: The overall prevalence of patients taking lipid-lowering drugs rose from 8.9% (n = 736,174) in 2013 to 11.6% (n = 841,682) in 2019, but varied markedly across regions, with highest values in Ticino and lowest values in Zurich. More than every third individual aged ≥65 years was treated with a lipid-lowering drug in 2019. Statins were by far the most commonly used drugs (>90% of prescriptions), followed by ezetimibe, fibrates and PCSK9 inhibitors. We observed a trend towards the prescription of more potent statins (atorvastatin, rosuvastatin) in recent years. Total costs of lipid-lowering drugs increased from CHF 222 million in 2013 to CHF 230 million in 2019 (+3.5%), whereas annual per capita costs decreased from CHF 302 in 2013 to CHF 273 in 2019 (-9.4%). CONCLUSION: The increasing use of lipid-lowering drugs reflects current therapeutic guidelines, but results in high costs for the healthcare system.