[1] *Seedat F, Raal F, Martinson N, Variava E.* **LIPID AND LIPOPROTEIN LEVELS IN HIV-INFECTED ADULTS WITH SEPSIS COMPARED TO HEALTHY HIV- INFECTED CONTROLS**. Afr J Infect Dis 2020; 14:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33884344

ABSTRACT

BACKGROUND: In acute sepsis, reduced lipid and lipoprotein levels occur in HIV negative patients, in particular, low high-density lipoprotein cholesterol (HDL-c) levels are inversely correlated with sepsis severity and increased mortality. However, due to the limited data describing lipid and lipoprotein levels in septic HIV-infected individuals we aimed to investigate the changes in this subgroup. MATERIALS AND METHODS: A prospective cross-sectional observational study of HIV-infected patients comparing admitted HIV - infected patients with sepsis to healthy controls from the antiretroviral therapy (ART) clinic. Non fasting - lipograms, ART use, diagnosis of tuberculosis (TB), markers of infection, renal function and mortality outcome to 3 months post discharge were reviewed. RESULTS: Total cholesterol (TC), low-density lipoprotein (LDL-c) and HDL-c were all significantly lower in the sepsis group ($p < 0.001$). HDL-c was significantly associated with a higher white cell count ($p = 0.018$), higher C- reactive protein ($p = 0.036$) and low serum albumin ($p < 0.001$). In those with active TB (55%) HDL-c was reduced even further (0.55 vs. 0.72mmol/L, $p = 0.013$). Acute kidney injury ($p = 0.560$) and mortality at discharge ($p = 0.097$) or 3 months follow up ($p = 0.953$) was not associated with reduced HDL-c. CONCLUSION: Septic HIV-infected patients had significantly reduced lipid and lipoprotein levels at admission. Of note however, a low HDL-c was associated with markers of infection and reductions in HDL-c was more marked in those with active TB.

[2] *MacEwan JP, Zhao LM, Everson K et al.* **Two steps forward, one step back: 50 years of societal value from LDL-C-lowering therapies**. The American journal of managed care 2021; 27:162-168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33877775

ABSTRACT

OBJECTIVES: To assess the evolving landscape of low-density lipoprotein cholesterol-lowering therapies (LLTs) and quantify their effect on cardiovascular disease (CVD)-related mortality and morbidity. STUDY DESIGN: Secondary data came from LLT clinical trials and 1999-2014 National Health and Nutrition Examination Survey (NHANES) data. 1996-2016 Medical Expenditure Panel Survey (MEPS) data were used to estimate LLT spending. Nonfatal CVD events prevented by LLTs were calculated from clinical trials and NHANES. The value of nonfatal events prevented was calculated as the product of event treatment costs and the number of events prevented. The value of mortality reduction was calculated as the product of a value of a life-year and the life expectancy gain from LLTs. This was compared with LLT spending estimated using MEPS. METHODS: Total LLT expenditures were calculated based on MEPS LLT utilization and expenditure data. Values of prevented hospitalizations, prevented CVD events, and other LLT utilization-related outcomes were pulled from the published literature. RESULTS: Combined, statins and ezetimibe prevented 2.8 million nonfatal heart attacks and 1.7 million nonfatal strokes from 1999 to 2014. Statin use generated $2.6 trillion in societal value through CVD deaths avoided from 1987 to 2014, and 85% accrued to patients. CONCLUSIONS: LLTs have yielded significant societal value, and the majority of this value has accrued to patients.

[3] *Bastani M, Khosravi MB, Shafa M et al.* **Evaluation of high-dose atorvastatin pretreatment influence in patients preconditioning of post coronary artery bypass graft surgery: A prospective triple blind randomized clinical trial**. Annals of cardiac anaesthesia 2021; 24:209-216.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33884978

ABSTRACT

CONTEXT: Atorvastatin is considered as lipid reductive drugs with anti-inflammatory and pleotherapic effects in coronary artery bypass graph (CABG). AIM: This study is conducted to evaluate the effects of atorvastatin in CABG. SETTING AND DESIGN: Patients with a coronary bypass graph procedure in Nemazee hospital in Shiraz were divided into two 50-groups receiving high-dose (80 mg) and low-dose (20 mg) atorvastatin. MATERIALS AND METHODS: Troponin I, creatinine kinase-MB (CK-MB), atrial fibrillation (AF) after CABG, duration of mechanical ventilation, inotrope duration of consumption, blood sugar profile, liver and renal function, death during 30 days of CABG, MACE (major advance cardiac events) during admission in ICU, and 1 month follow up were surveyed. STATISTICAL ANALYSIS: Collected data were analyzed by independent and paired t-test and Chi square. RESULTS: AST was increased, ALT, ALK-P after CABG were decreased, and urine volume in the second day of admission in ICU was increased in the high-dose group. There was an increase and following decrease in blood sugar of patients in the high-dose after CABG. An inflammatory marker after CABG was raised in both groups, ck-mb had an increase, and then followed by a reduction. Troporin had no significant differences between groups. Patients with high-dose atorvastatin had better glomerular filtration rate and renal performance. Along with decreasing AF in the case group, hemodynamics' disorder reduced and there was less bleeding. CONCLUSION: According to the above, it seems that a short-time prescription of high dose of atorvastatin in CABG can lead to better renal function, decreasing of arrhythmia and AF.

[4] *Schmidt A, Moreira HT, Volpe GJ et al.* **Statins Prescriptions and Lipid Levels in a Tertiary Public Hospital**. Arquivos brasileiros de cardiologia 2021; 116:736-741.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33886720

ABSTRACT

BACKGROUND: The development of a new class of medications that are highly capable of reducing LDL-cholesterol renewed the interest in the characterization of familial hypercholesterolemia patients. Nevertheless, little is known about the lipid profile of patients in tertiary healthcare centers in Brazil in order to better estimate the real occurrence of familial hypercholesterolemia, with initial suspect of LDL-cholesterol levels above 190 mg/d/L. OBJECTIVES: This study evaluated the lipid profile (total cholesterol and LDL-cholesterol) in ambulatory patients from a general tertiary public hospital. METHODS: Retrospective study comparing prescriptions of statins and lipid profile results. The significance level was established in 5%. RESULTS: In one year, 9,594 individuals received statin prescriptions, of whom 51.5% were females and the mean age was 63.7±12.9 years-old (18 to 100 years-old). Thirty-two medical specialties prescribed statins. Cardiology was responsible for 43% of the total. Nearly 15% of those patients with a prescription did not have a recent total cholesterol result and 1,746 (18%) did not have a recent LDL-cholesterol measurement. The occurrence of the latter between 130 and 190 mg/dL was present in 1,643 (17.1%) individuals, and 228 (2.4%) patients had an LDL-cholesterol ≥190mg/dL among those using statins at distinct doses. Only two statins were used: simvastatin and atorvastatin. The first was prescribed in 77.6% of the prescriptions. CONCLUSION: In this cross-sectional cohort at a tertiary general hospital, statins have been widely

prescribed but with little success in achieving recognized levels of control. There is probably a significant number of FH individuals in this cohort that need to be properly diagnosed in order to receive adequate treatment due to its prognostic implications.

[5] *Averna M, Banach M, Bruckert E et al.* **Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force**. Atherosclerosis 2021; 325:99-109.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892925

ABSTRACT

BACKGROUND AND AIMS: This European Atherosclerosis Society (EAS) Task Force provides practical guidance for combination therapy for elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) in high-risk and very-high-risk patients. METHODS: Evidence-based review. RESULTS: Statin-ezetimibe combination treatment is the first choice for managing elevated LDL-C and should be given upfront in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be added if LDL-C levels remain high. In high and very-high-risk patients with mild to moderately elevated TG levels (>2.3 and < 5.6 mmol/L [>200 and < 500 mg/dL) on a statin, treatment with either a fibrate or high-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks. Combination with fenofibrate may be considered for both macro- and microvascular benefits in patients with type 2 diabetes mellitus. CONCLUSIONS: This guidance aims to improve real-world use of guideline-recommended combination lipid modifying treatment.

[6] *Heidemann BE, Wolters FJ, Kavousi M et al.* **Adiposity and the development of dyslipidemia in APOE ε2 homozygous subjects: A longitudinal analysis in two population-based cohorts**. Atherosclerosis 2021; 325:57-62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892328

ABSTRACT

BACKGROUND AND AIMS: Familial dysbetalipoproteinemia (FD), characterized by remnant lipoprotein accumulation and premature cardiovascular disease, occurs in homozygous carriers of the APOE ε2 allele, but genetic predisposition alone does not suffice for the clinical phenotype. Cross-sectional studies suggest that a second metabolic hit - notably adiposity or insulin resistance - is required, but the association between these risk factors and development of FD has not been studied prospectively. METHODS: For this study, we evaluated 18,987 subjects from two large prospective Dutch population-based cohorts (PREVEND and Rotterdam Study) of whom 118 were homozygous APOE ε2 carriers. Of these, 69 subjects were available for prospective analyses. Dyslipidemia - likely to be FD - was defined as fasting triglyceride (TG) levels >3 mmol/L in untreated subjects or use of lipid lowering medication. The effect of weight, body mass index (BMI), waist circumference, type 2 diabetes mellitus and non-TG metabolic syndrome on development of dyslipidemia was investigated. RESULTS: Eleven of the 69 ε2ε2 subjects (16%) developed dyslipidemia - likely FD - during follow-up. Age-, sex- and cohort-adjusted risk factors for the development of FD were BMI (OR 1.19; 95%CI 1.04-1.39), waist circumference (OR 1.26 95%CI 1.01-1.61) and presence of non-TG metabolic syndrome (OR 4.39; 95%CI 1.04-18.4) at baseline. Change in adiposity during follow-up was not associated with development of dyslipidemia. CONCLUSIONS: Adiposity increases the risk of

developing an FD-like lipid phenotype in homozygous APOE ε2 subjects. These results stress the importance of healthy body weight in subjects at risk of developing FD.

[7] *Meier S, Frick M, Liu M et al.* **Reduced adrenal stress response in patients on PCSK9 inhibitor therapy**. Atherosclerosis 2021; 325:63-68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892329

ABSTRACT

BACKGROUND AND AIMS: Treatment with proprotein convertase subtilisin-kexin type 9 inhibitors (PCSK9i), in addition to statin therapy, reduces LDL-cholesterol (LDL-c) in some patients to extremely low levels (i.e.< 20 mg/dl or < 0.52 mmol/l). There is concern that at such low levels, the physiologic role of cholesterol may be impaired, e.g. the adrenal cortisol stress response might be compromised. We therefore evaluated the effect of PCSK9i therapy on the cortisol response to ACTH in patients with LDL-c down to extremely low levels. METHODS: Nineteen patients on PCSK9i therapy and 18 controls matched for age, gender and comorbidities were included. The cortisol response to adrenocorticotropic hormone (ACTH) was tested after application of 250 µg ACTH. RESULTS: LDL-c levels ranged from 0.42 to 3.32 mmol/l (mean 1.38 ± 0.84 mmol/l) in the PCSK9i group and 0.81-4.82 mmol/l (mean 2.10 ± 0.97) in the control group. By analysis of covariance (ANCOVA), the PCSK9i group had significantly lower cortisol response compared to the control group (- 97.26 nmol/l, -178.60 to -15.93, p = 0.02) after 60 min. There was a significant positive correlation between the duration of PCSK9i treatment and cortisol levels (r = 0.59, p = 0.009). Extremely low LDL-c levels down to 0.42 mmol/l were not associated with lower stimulated cortisol levels. CONCLUSIONS: Patients on PCSK9i therapy showed a significantly lower cortisol response to ACTH. Stimulated cortisol levels were lower in the first months of PCSK9i treatment, suggesting an adaptive phenomenon. We conclude that the adrenal stress response in patients on PCSK9 inhibitor therapy is reduced.

[8] *Giglio RV, Stoian AP, Haluzik M et al.* **Novel molecular markers of cardiovascular disease risk in type 2 diabetes mellitus**. Biochimica et biophysica acta. Molecular basis of disease 2021:166148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892081

ABSTRACT

Diabetes represents the leading risk factor for the development of cardiovascular disease (CVD). Chronic hyperglycemia and/or acute post-prandial changes in blood glucose determine an increase in reactive oxygen species (ROS), which play a fundamental role in endothelial dysfunction and in the nuclear transport of pro-atherogenic transcription factors that activate the "inflammasome". In addition, the glycemic alteration favors the formation and stabilization of atherosclerotic plaque through the mechanism of non-enzymatic glycation of different molecules, with the establishment of the so-called "advanced glycosylation end products" (AGE). Laboratory information provided by the level of biomarkers could make a quantitative and qualitative contribution to the clinical process of screening, prediction, prevention, diagnosis, prognosis and monitoring of cardiovascular (CV) risk linked to diabetes. This review describes the importance of specific biomarkers, with particular focus on novel ones, for stratifying and management of diabetes CV risk.

[9] *Kong MT, Nunes MP, Leong KF*. **Diabetic ketoacidosis with acute severe hypertriglyceridaemia-induced pancreatitis as first presentation of type 2 diabetes**. BMJ case reports 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33875498
ABSTRACT
Acute pancreatitis (AP) is an acute destructive inflammatory condition of the pancreas. Hypertriglyceridaemia is the third most common worldwide cause of AP. Although the presentation of hypertriglyceridaemic pancreatitis (HTGP) is usually similar to other forms of AP, it may cause more severe AP and worse symptoms. Therefore, apart from the supportive care and treatment for AP, it is necessary to treat the underlying aetiology. There are no established guidelines for managing HTGP. Many treatment modalities have been reported, including intravenous insulin infusion, heparin and plasmapheresis. Randomised trials comparing their efficacy are lacking. Diabetic ketoacidosis (DKA) may be a risk factor for AP, but it is uncertain if AP triggers DKA or vice versa. Here, we describe a case of a 44-year-old man who presented with DKA concurrent with acute severe HTGP as first manifestation of type 2 diabetes mellitus. He was successfully managed with supportive care and intravenous insulin infusion.

[10] *Bhardwaj A, Embury MD, Rojo RD et al.* **Efficacy of fluvastatin and aspirin for prevention of hormonally insensitive breast cancer**. Breast cancer research and treatment 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33893908
ABSTRACT
PURPOSE: Primary prevention of hormonally insensitive breast cancers remains an important clinical need and repurposing existing low-toxicity drugs represents a low-cost, efficient strategy for meeting this goal. This study targeted the cholesterol pathway using fluvastatin, a cholesterol-lowering drug, and aspirin, an AMPK activator that acts as a brake in the cholesterol pathway, in a transgenic mouse model of triple-negative breast cancer (TNBC). METHODS: Using SV40C3 TAg mice, the efficacy and mechanism of fluvastatin, aspirin, or both in combination were compared with vehicle alone. RESULTS: Sixteen-weeks of fluvastatin treatment resulted in significant delay in onset of tumors (20 weeks vs. 16.8 weeks in vehicle treatment, $p = 0.01$) and inhibited tumor incidence and tumor multiplicity by 50% relative to the vehicle control. In animals that developed tumors, fluvastatin treatment inhibited tumor weight by 75% relative to vehicle control. Aspirin alone did not significantly affect tumor latency, tumor incidence or tumor burden compared to vehicle control. Fluvastatin and aspirin in combination delayed the onset of tumors but failed to inhibit tumor incidence and tumor multiplicity. The growth-inhibitory effects of fluvastatin were mediated through increased FAS/FASL mediated apoptotic cell death that was characterized by increased cleaved PARP and driven in part by depletion of an isoprenoid, geranyl geranyl pyrophosphate (GGPP). CONCLUSIONS: In line with NCI's emphasis to repurpose low-toxicity drugs for prevention of cancer, fluvastatin was effective for prevention of TNBC and warrants further clinical testing. Aspirin did not provide chemopreventive benefit.

[11] *He M, Hu J, Fang T et al.* **Protein convertase subtilisin/Kexin type 9 inhibits hepatocellular carcinoma growth by interacting with GSTP1 and suppressing the JNK signaling pathway**. Cancer Biol Med 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33893729

ABSTRACT
OBJECTIVE: Protein convertase subtilisin/Kexin type 9 (PCSK9) has been found to be closely associated with the occurrence and development of numerous tumors. However, the precise role of PCSK9 and its relationship to the development of hepatocellular carcinoma (HCC) remain largely unknown. This study aimed to clarify these issues. METHODS: The expression levels of PCSK9 in HCC tissues and HCC cell lines were determined by the quantitative reverse transcription polymerase chain reaction, Western blot, and immunohistochemical analyses, and the effects of PCSK9 expression on HCC cell biological traits were investigated by overexpressing and downregulating PCSK9 expression in vivo and in vitro. Additionally, the mechanism by which PCSK9 mediated dissociation of glutathione S-transferase Pi 1 (GSTP1) dimers and phosphorylation of the Jun N-terminal kinase (JNK) pathway components were investigated. RESULTS: PCSK9 expression levels were significantly lower in HCC tissues than in adjacent non-tumor samples. In vivo and in vitro experiments suggested that PCSK9 inhibited HCC cell proliferation and metastasis. Further analysis showed that PCSK9 interacted with GSTP1 and promoted GSTP1 dimer dissociation and JNK signaling pathway inactivation in HCC cells. Moreover, the relationships between PCSK9 protein expressions and clinical outcomes were investigated. The PCSK9-lo group displayed a significantly shorter overall survival (OS; median OS: 64.2 months vs. 83.2 months; log-rank statistic: 4.237; P = 0.04) and recurrence-free survival (RFS; median RFS: 26.5 months vs. 46.6 months; log-rank statistic: 10.498; P = 0.001) time than the PCSK9-hi group. CONCLUSIONS: PCSK9 inhibited HCC cell proliferation, cell cycle progression, and apoptosis by interacting with GSTP1 and suppressing JNK signaling, suggesting that PCSK9 might act as a tumor suppressor and be a therapeutic target in HCC patients.

[12] *Hemenway G, Frishman WH*. **Therapeutic Implications of NLRP3-Mediated Inflammation in Coronary Artery Disease**. Cardiology in review 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33883451

ABSTRACT
Atherosclerosis is considered a chronic, inflammatory disease responsible for more than 15% of all global deaths, secondary to its complications of myocardial infarction, vascular disease, and stroke. Current treatment regimens consist of lipid-lowering pharmaceuticals, control of risk factors, and prevention of plaque rupture and thrombosis with anti-platelet agents. However, a significant burden on society remains due to the morbidity and mortality of coronary artery disease (CAD) despite our best practices. In addition to dyslipidemia and hemostasis, inflammation has now moved to the proverbial forefront as the remaining obstacle to appropriate management of atherosclerosis. A complex dance of endothelial dysfunction, complement activation, and immune cell-mediated cytokine release underlie the pathogenesis of atherosclerotic plaque development, destabilization, and rupture. Cholesterol-induced sterile inflammation is thought to be central to this process via activation of a protein complex called the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome. The focus of this review article will be to examine the NLRP3 inflammasome, which directs the release of interleukin-1, leading to downstream pro-inflammatory effects, and its potential for therapeutic targeting using currently available and future tools in our pharmacologic arsenal. In particular, we focus on the results of several large, recently concluded clinical trials including the Canakinumab Antiinflammatory Thrombosis Outcome Study, Colchicine Cardiovascular Outcomes Trial, and the Low-Dose Colchicine Study, examining the efficacy of direct inhibition of interleukin-1

with canakinumab or a multimodal approach to inhibiting the NLRP3 inflammasome using colchicine, as well as an overview of novel small molecule inhibitors that are still in development.

[13] *Fischer LT, Hochfellner DA, Knoll L et al.* **Real-world data on metabolic effects of PCSK9 inhibitors in a tertiary care center in patients with and without diabetes mellitus**. Cardiovascular diabetology 2021; 20:89.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33894772
ABSTRACT
BACKGROUND: The lipid-lowering and positive cardiovascular effect of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors was shown in several studies, hence, they are more widely used in the lipid-lowering management of individuals with high cardiovascular risk. As real-world data are still scarce, specifically in patients with type 2 diabetes (T2D), the aim of this retrospective analysis was to investigate the efficacy of PCSK9 inhibitors in lowering low-density lipoprotein cholesterol (LDL-C) in an outpatient clinic of a tertiary care center in routine care. METHODS: A retrospective analysis of data extracted from the electronic patient record was performed. Patients who were routinely prescribed with PCSK9 inhibitor therapy (alirocumab or evolocumab) during the years 2016 and 2019 were included in the analysis. Characteristics of the patient population, the effects on LDL-C and HbA1c levels as well as subsequent cardiovascular events were assessed over an observation period of 18 months. RESULTS: We identified 237 patients treated with PCSK9 inhibitors between January 2016 and September 2019. Almost all patients (97.5%) received PCSK9 inhibitors for secondary prevention. 26.2% of the population had a concomitant diabetes diagnosis. Intolerance to statins (83.1%), ezetimibe (44.7%) or both agents (42.6%) was reported frequently. Three months after initiation of PCSK9 inhibitor therapy, 61.2% of the patients achieved LDL-C levels<70 mg/dl, and 44.1% LDL-C levels<55 mg/dl. The median LDL-C was lowered from 141 mg/dl at baseline, to 60 mg/dl after 3 months and 66 mg/dl after 12 months indicating a reduction of LDL-C as follows: 57.5% after 3 months and 53.6% after 12 months. After 3 months of observation, target achievement of LDL-C was higher in patients with T2D compared to non-diabetes patients; <55 mg/dl: 51% vs. 41.5%; <70 mg/dl 69.4 vs. 58.5%. After 12 months even more pronounced target LDL achievement in T2D was demonstrated <55 mg/dl: 58.8% vs. 30.1%; <70 mg/dl 70.6 vs. 49.6%. Patients with insufficiently controlled T2D (HbA1c>54 mmol/mol) had a higher reduction in LDL-C but still were more likely to subsequent cardiovascular events. CONCLUSIONS: Significant reductions in LDL-C and a high percentage of patients achieving recommended treatment targets were observed. The percentage of patients with T2D meeting recommended LDL-C targets was higher than in those without T2D. Still some patients did not achieve LDL-C levels as recommended in current guidelines. Special attention to the characteristics of these patients is required in the future to enable achievement of treatment goals and avoid adverse cardiovascular outcomes.

[14] *Mazzolai L, Alatri A, Rivière AB et al.* **Progress in aorta and peripheral cardiovascular disease research**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892507
ABSTRACT
Although COVID-19 seems to be the leading topic in researcha number of outstanding studies have been published in the field of aorta and peripheral vascular diseases likely affecting our clinical practice in the near future. This review article highlights key research on vascular diseases published

in 2020. Some studies have shed light in the pathophysiology of aortic aneurysm and dissection suggesting a potential role for kinase inhibitors as new therapeutic options. A first proteogenomic study on fibromuscular (FMD) dysplasia revealed a promising novel disease gene and provided proof-of-concept for a protein/lipid-based FMD blood test. The role of NADPH oxidases in vascular physiology, and particularly endothelial cell differentiation, is highlighted with potential for cell therapy development. Imaging of vulnerable plaque has been an intense field of research. Features of plaque vulnerability on MRI as an under-recognized cause of stroke is discussed. Major clinical trials on lower extremity peripheral artery disease have shown added benefit of dual antithrombotic (aspirine plus rivaroxaban) treatment.

[15] *Aranzulla TC, Piazza S, Ricotti A et al.* **CARotid plaqUe StabilizatiOn and regression with evolocumab: Rationale and design of the CARUSO study**. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33893754

ABSTRACT

BACKGROUND: While the experience with PCSK9i in patients with coronary artery disease has been wide, and coronary plaque regression has been documented, little is known regarding the role of these drugs on carotid plaque regression. The CARotid plaqUe StabilizatiOn and regression with evolocumab (CARUSO) study is a randomized, single-center, investigator-initiated trial aiming at evaluating carotid plaque morphological stabilization and regression following, respectively, 6 and 12 months of therapy with evolocumab. METHODS: Asymptomatic patients with uni- or bilateral de novo carotid artery stenosis ≥50% and LDL-C values ≥100 mg/dl despite maximum tolerated lipid lowering therapy (LLT) will be randomized to evolocumab 140 mg s.c. every 2 weeks on top of ongoing LLT, or no additional treatment. 100 patients (50 in each arm) will be enrolled. Serial carotid duplex ultra-sonography will be performed to monitor the carotid plaque morphology and stenosis over time. RESULTS: The primary end point of the study is, (a) carotid plaque morphological stabilization at 6 months, defined as defined as the disappearance of ulcerations and fluffy components and the achievement of a regular plaque morphology with prevalence of fibrous atheroma and/or (b) carotid plaque regression at 12 months, defined as reduction of the entity of the stenosis and/or peak systolic velocity by at least 5%, as compared with baseline. CONCLUSION: The CARUSO trial will test the superiority of evolocumab on top of ongoing LLT versus ongoing LLT alone regarding carotid plaque morphological stabilization and regression. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

[16] *Zheng P, Ding Y, Lu F et al.* **Atorvastatin reverses high cholesterol-induced cardiac remodeling and regulates mitochondrial quality-control in a cholesterol-independent manner: an experimental study**. Clinical and experimental pharmacology & physiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33891707

ABSTRACT

Mitochondria are key regulators of cell fate, maintaining self-stability by a fine-tuned quality-control network including mitophagy, biogenesis, fission and fusion processes. Myocardial mitochondria can be impaired by hypercholesterolemia. Statins, such as atorvastatin, are considered the cornerstone in the management of hypercholesterolemia primarily due to their marked cholesterol-lowering ability.

The direct effect of atorvastatin on myocardial mitochondria remains unclear. We aimed to explore whether atorvastatin could attenuate myocardial mitochondrial defects induced by high cholesterol, and whether cycloastragenol, a potent telomerase activator, could be used as a potential complementary bioactive compound for obesity and hypercholesterolemia treatment. We found that atorvastatin at a low dose (3 mg/kg) did not reduce elevated serum cholesterol, but reversed cardiac remodeling and dysfunction in C57BL/6J mice fed with high-fat diet (HFD). Atorvastatin reversed the upregulated mitophagy, mitochondrial fission and fusion, accompanied by mitochondrial biogenesis activation in HFD-fed mice hearts. Mitochondrial structural impairments were attenuated by atorvastatin in HFD-fed mice and oxidized low-density lipoprotein (ox-LDL) exposed HL-1 cardiomyocytes. The depolarized mitochondrial membrane potential and increased mitochondrial oxygen consumption rates in ox-LDL exposed HL-1 cells were recovered by atorvastatin. Furthermore, atorvastatin co-treated with cycloastragenol had better effects on reducing body weight, improving cardiac remodeling and dysfunction, and protecting mitochondria in high cholesterol. Conclusively, low-dose atorvastatin exhibited a cholesterol-independent cardioprotective effect through improving the mitochondrial quality-control network and repairing mitochondrial ultrastructure in high cholesterol. Atorvastatin plus cycloastragenol supplement therapy has a better effect on treating obesity and hypercholesterolemia.

[17] *Cheng MP, Cau A, Lee TC et al.* **Acute Cardiac Injury in Coronavirus Disease 2019 and Other Viral Infections-A Systematic Review and Meta-Analysis**. Critical care medicine 2021. **PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=33870918

ABSTRACT

OBJECTIVES: Severe acute respiratory syndrome-related coronavirus-2 binds and inhibits angiotensin-converting enzyme-2. The frequency of acute cardiac injury in patients with coronavirus disease 2019 is unknown. The objective was to compare the rates of cardiac injury by angiotensin-converting enzyme-2-binding viruses from viruses that do not bind to angiotensin-converting enzyme-2. DATA SOURCES: We performed a systematic review of coronavirus disease 2019 literature on PubMed and EMBASE. STUDY SELECTION: We included studies with ten or more hospitalized adults with confirmed coronavirus disease 2019 or other viral pathogens that described the occurrence of acute cardiac injury. This was defined by the original publication authors or by: 1) myocardial ischemia, 2) new cardiac arrhythmia on echocardiogram, or 3) new or worsening heart failure on echocardiogram. DATA EXTRACTION: We compared the rates of cardiac injury among patients with respiratory infections with viruses that down-regulate angiotensin-converting enzyme-2, including H1N1, H5N1, H7N9, and severe acute respiratory syndrome-related coronavirus-1, to those with respiratory infections from other influenza viruses that do not bind angiotensin-converting enzyme-2, including Influenza H3N2 and influenza B. DATA SYNTHESIS: Of 57 studies including 34,072 patients, acute cardiac injury occurred in 50% (95% CI, 44-57%) of critically ill patients with coronavirus disease 2019. The overall risk of acute cardiac injury was 21% (95% CI, 18-26%) among hospitalized patients with coronavirus disease 2019. In comparison, 37% (95% CI, 26-49%) of critically ill patients with other respiratory viruses that bind angiotensin-converting enzyme-2 ($p = 0.061$) and 12% (95% CI, 7-22%) of critically ill patients with other respiratory viruses that do not bind angiotensin-converting enzyme-2 ($p < 0.001$) experienced a cardiac injury. CONCLUSIONS: Acute cardiac injury may be associated with whether the virus binds angiotensin-converting enzyme-2.

Acute cardiac injury occurs in half of critically ill coronavirus disease 2019 patients, but only 12% of patients infected by viruses that do not bind to angiotensin-converting enzyme-2.

[18] *Mohamed F, Botha TC, Raal FJ*. **Inhibition of angiopoietin-like 3 for the management of severe hypercholesterolemia**. Current opinion in lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33883446
ABSTRACT
PURPOSE FOR REVIEW: Despite the therapeutic advances for patients with severe hypercholesterolemia, particularly those with homozygous familial hypercholesterolemia (HoFH), most patients are unable to achieve target low-density lipoprotein cholesterol (LDL-C) levels with the current available standard lipid-lowering therapy (LLT). We review the role of angiopoietin-like 3 (ANGPTL3) inhibition as an additional therapeutic option for severe hypercholesterolemia, particularly HoFH. RECENT FINDINGS: Evinacumab is a monoclonal antibody against ANGPTL3, and reduces LDL-C independent of LDL-receptor activity. ANGPTL3 inhibitors are effective in lowering LDL-C in patients with FH, with a 50% reduction in LDL-C in those with HoFH. Longer-term efficacy and safety have been demonstrated with reductions in LDL-C maintained following 48weeks of therapy. Gene silencing strategies directed against ANGPTL3 include antisense oligonucleotide and small-interfering ribonucleic acid (siRNA). ARO-ANG3 is a siRNA directed against ANGPTL3 messenger ribonucleic acid and is associated with up to a 42% reduction in LDL-C. SUMMARY: With the promise of these emerging novel therapeutics directed against ANGPTL3 on the horizon, achieving acceptable target LDL-C levels in HoFH without the need for lipoprotein apheresis may finally be a realistic goal and we can anticipate a decrease in cardiovascular morbidity and mortality in these difficult to treat patients.

[19] *Sniderman A, Langlois M, Cobbaert C*. **Update on apolipoprotein B**. Current opinion in lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33870931
ABSTRACT
PURPOSE OF REVIEW: The 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines concluded that apolipoprotein B (apoB) was a more accurate measure of cardiovascular risk and a better guide to the adequacy of lipid lowering than low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (HDL-C). Also, they stated that apoB can be measured more accurately than LDL-C or non-HDL-C. This strong endorsement of the central role of apoB contrasts with the limited endorsement of apoB by the 2018 American College of Cardiology/American Heart Association Multisociety Guidelines. Nevertheless, both retained LDL-C as the primary metric to guide statin/ezetimibe/Proprotein convertase subtilisin/kexin type 9 (PCSK9) therapy. RECENT FINDINGS: This essay will review the most important recent advances in knowledge about apoB with particular emphasis on the results of Mendelian randomization studies and a new discordance analysis in subjects on statin therapy. We will also lay out why using LDL-C to guide the adequacy of lipid lowering therapy represents an interpretive error of the results of the statin/ezetimibe/PCSK9 inhibitor randomized clinical trials and therefore why apoB should be the primary metric to guide statin/ezetimibe/PCSK9 therapy. SUMMARY: There is now a robust body of evidence demonstrating the superiority of apoB over LDL-C and non-HDL-C as a clinical marker of cardiovascular risk. LDL-C is not the appropriate marker to assess the benefits of statin/ezetimibe/PCSK9 therapy.

[20] *Liberis A, Petousis S, Tsikouras P*. **Lipid disorders in pregnancy**. Current pharmaceutical design 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33882801
ABSTRACT
Dyslipidemia represents a major risk factor for cardiovascular disease. In addition, severe hypertriglyceridemia is an important cause of acute pancreatitis. Accordingly, the increase in serum lipid levels that are observed during pregnancy have potentially important implications. The management of dyslipidemia in pregnancy is further complicated by the lack of safety data during this period for most of the lipid-lowering agents. In the present review, we discuss the most important lipid disorders in pregnant women and their management. Pregnancy is characterized by increases in both low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, which might result in severe complications both for the mother and the fetus. Accordingly, LDL-C and triglyceride levels should be monitored during pregnancy, particularly in women with a history of dyslipidemia. Diet is the mainstay of management of dyslipidemia in pregnant women and apheresis can also be considered in patients with homozygous familial hypercholesterolemia or severe hypertriglyceridemia. However, there is a pressing need for studies that with evaluate the safety of lipid-lowering agents during pregnancy.

[21] *Henry BM, Szergyuk I, de Oliveira MHS et al.* **Alterations in the lipid profile associate with a dysregulated inflammatory, prothrombotic, anti-fibrinolytic state and development of severe acute kidney injury in coronavirus disease 2019 (COVID-19): A study from Cincinnati, USA**. Diabetes & metabolic syndrome 2021; 15:863-868.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33878674
ABSTRACT
BACKGROUND AND AIMS: Reduction of atherogenic lipoproteins is often the ultimate goal of nutritional interventions, however this is complicated given that hypolipidemia is frequently observed in coronavirus disease 2019 (COVID-19) patients. We aimed to explore the association of hypolipidemia with patient outcomes in terms of immunothrombosis and multiorgan injury, focusing on specialized apolipoproteins apo A1 and apo B. METHODS: Lipid profiles of 50 COVID-19 patients and 30 sick controls presenting to the Emergency Department (ED) were measured in this prospective observational study. The primary outcome was development of severe acute kidney injury (AKI). Need for hospitalization and ICU admission were secondary outcomes. Lipoproteins were analyzed for independent association with serum creatinine (SCr) increase ratio and correlated with a wide panel of biomarkers. RESULTS: COVID-19 cohort had significantly lower apo A1 ($p = 0.006$), and higher apo B/apo A1 ratio ($p = 0.041$). Patients developing severe AKI had significantly lower LDL-C ($p = 0.021$). Apo B/apo A1 was associated with 2.25-fold decrease in serum SCr increase ratio, while LDL-C with a 1.5% decrease. Hypolipidemia correlated with low plasminogen, ADAMTS13 activity/VWF:Ag, and high inflammatory biomarkers (CRP, IL-6, IL-8, IL-10), plasminogen activator inhibitor-1 (PAI-1), ED creatinine, and SCr increase ratio. CONCLUSION: Although favored in dietetics, findings of a low LDL-C in COVID-19 patients should be alarming in light of our observations. Low apo B/apo A1 ratio and LDL-C are predictive of renal deterioration in COVID-19 patients, and low LDL-C in particular may potentially serve to indicate COVID-19 related AKI driven by disrupted fibrinolysis and a secondary thrombotic microangiopathy-like process.

[22] *Abrilla AA, Nico Nahar IPA, Jimeno CA*. **Metformin extended-release versus metformin immediate-release for adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials**. Diabetes Res Clin Pract 2021:108824.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33887354

ABSTRACT
AIM: To compare the efficacy and tolerability metformin extended-release (MXR) and the conventional metformin immediate-release (MIR) in adults with type 2 diabetes mellitus (T2DM) METHODS: PubMed, the Cochrane Library, ClinicalTrials.gov and other sources were searched for randomized controlled trials (RCTs) that compared equal daily doses of MXR and MIR in adults with T2DM from platform inception to 19 March 2021. Random-effects model meta-analysis was performed to obtain, with 95% confidence intervals (CIs), pooled mean difference (MD) of change from baseline for continuous outcomes and risk ratio (RR) for dichotomous outcomes. Primary outcomes were HbA1c and key gastrointestinal (GI) symptoms (abdominal discomfort or pain, diarrhea, dyspepsia, and nausea & vomiting); fasting and post-prandial plasma glucose, other GI and serious adverse events (AEs), serum lipid control, and anthropometrics served as secondary outcomes. RESULTS: Nine RCTs that randomized a total of 2609 adults revealed that MIR was statistically associated with better HbA1c lowering (MD 0.09% [0.01%, 0.17%]) and serum lipid control, and MXR only with reduced dyspepsia (RR 0.58 [0.34, 0.98]). MXR and MIR were similar in other considered outcomes. CONCLUSIONS: MXR was associated with statistically worse but likely clinically insignificant HbA1c lowering, similar plasma glucose control, and minimal improvement of metformin intolerance versus MIR. Protocol Registration: PROSPERO (CRD42019148008).

[23] *Tomlinson B, Patil NG, Fok M, Lam CWK*. **Role of PCSK9 Inhibitors in Patients with Familial Hypercholesterolemia**. Endocrinol Metab (Seoul) 2021; 36:279-295.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33866776

ABSTRACT
Patients with familial hypercholesterolemia (FH) are at high or very high risk for cardiovascular disease. Those with heterozygous FH (HeFH) often do not reach low-density lipoprotein cholesterol (LDL-C) targets with statin and ezetimibe therapy, and those with homozygous FH (HoFH) usually require additional lipid-modifying therapies. Drugs that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) offer a novel approach to reduce LDL-C. The monoclonal antibodies, alirocumab and evolocumab, given by subcutaneous injection every 2 or 4 weeks produce reductions in LDL-C of 50% to 60% in patients with HeFH, allowing many of them to achieve their LDL-C goals. Patients with HoFH show a reduced and more variable LDL-C response, which appears to depend on residual LDL receptor activity, and those with receptor-negative mutations may show no response. Inclisiran is a long-acting small interfering RNA therapeutic agent that inhibits the synthesis of PCSK9. Subcutaneous doses of 300 mg can reduce LDL-C by more than 50% for at least 6 months and the responses in HeFH and HoFH patients are similar to those achieved with monoclonal antibodies. These PCSK9 inhibitors are generally well tolerated and they provide a new opportunity for effective treatment for the majority of patients with FH.

[24] *Engell AE, Svendsen ALO, Lind BS et al.* **Drug-drug interactions between vitamin K antagonists and statins: a systematic review**. Eur J Clin Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33895864

ABSTRACT
PURPOSE: Concomitant use of vitamin K antagonists (VKA) and statins is frequent in cardiovascular patients. However, clinical guidelines on this drug combination are divergent. Therefore, we performed a systematic review to evaluate the effect of statin initiation on coagulation among VKA users. METHODS: Following the PRISMA guidelines, we applied two broad search strategies for the drug interaction between VKA and statins in both Embase and Pubmed; 8623 unique hits were obtained. In the final sample, eight studies were included. RESULTS: The most frequently used VKA in the studies was warfarin, while simvastatin was the most commonly initiated statin. All included studies showed a minor increase in the anticoagulant effect of VKA following statin initiation during VKA treatment. The reported increases in mean international normalized ratio (INR) ranged from 0.15-0.65. CONCLUSION: The anticoagulant effect of statin initiation in patients treated with VKA is likely to be of limited clinical relevance but should be evaluated individually.

[25] *Cao YX, Liu HH, Jin JL et al.* **Plasma proprotein convertase subtilisin/kexin type 9 concentration and recurrent cardiovascular events in patients with familial hypercholesterolemia**. European journal of preventive cardiology 2021; 28:272-279.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33891693

ABSTRACT
AIMS: Familial hypercholesterolemia patients are characterized by early onset of coronary artery calcification and atherosclerosis, and high incidence of cardiovascular events. Plasma proprotein convertase subtilisin/kexin type 9 was reported to be a predictor for cardiovascular risk in the general population. However, its prognostic value for predicting recurrent cardiovascular events in familial hypercholesterolemia patients remains undetermined. METHODS: A total of 249 patients with molecularly and/or clinically (Dutch Lipid Clinic Network score >6) defined familial hypercholesterolemia who had experienced a first cardiovascular event were consecutively included and plasma proprotein convertase subtilisin/kexin type 9 concentrations were measured by enzyme-linked immunosorbent assay. Coronary artery calcification was measured using Agatston method and coronary severity was assessed by Gensini score, respectively. All patients received standard lipid-lowering therapy and were followed-up for recurrent cardiovascular events. Univariate and multivariate regression and Cox analyses was used to calculate hazard ratios with 95% confidence interval. RESULTS: Circulating proprotein convertase subtilisin/kexin type 9 concentrations were positively associated with coronary artery calcification scores and Gensini score by both univariate and multivariate analyses. During a mean follow-up of 43 ± 19 months, 29 (11.51%) recurrent cardiovascular events occurred. Kaplan-Meier analysis showed that patients with the highest proprotein convertase subtilisin/kexin type 9 levels had the lowest event-free survival time. Multivariable Cox regression analysis revealed that proprotein convertase subtilisin/kexin type 9 was independently associated with recurrent cardiovascular events (hazard ratio: 1.45, 95% confidence interval: 1.11-1.88). The combination of proprotein convertase subtilisin/kexin type 9 to Cox prediction model led to an enhanced predictive value for recurrent cardiovascular events. CONCLUSIONS: Increased level of proprotein convertase subtilisin/kexin type 9 was a significant risk factor of atherosclerosis and independently predicted future recurrent cardiovascular events in familial hypercholesterolemia patients receiving standard lipid-lowering treatment.

[26] *Danese MD, Pemberton-Ross P, Catterick D, Villa G*. **Estimation of the increased risk associated with recurrent events or polyvascular atherosclerotic cardiovascular disease in the United Kingdom**. European journal of preventive cardiology 2021; 28:335-343.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33891694

ABSTRACT

AIMS: The aims of this study were to re-estimate the international REduction of Atherothrombosis for Continued Health (REACH) risk equation using United Kingdom data and to distinguish different relative hazards for specific atherosclerotic cardiovascular disease event histories. METHODS AND RESULTS: Patients in the UK Clinical Research Practice Datalink (CPRD) were included as of 1 January 2005 if they were 40 years or older, had 2 or more years of prior data, received one or more moderate or high-intensity statin in the previous year, and had a history of myocardial infarction, ischemic stroke, or other atherosclerotic cardiovascular disease. Patients were followed until a composite endpoint of myocardial infarction, ischemic stroke or cardiovascular death, loss to follow-up, or end of observation. We re-estimated the REACH risk equation hazard ratios (HRs) using CPRD data (re-estimated REACH model). Our event history model replaced the REACH vascular bed variables with more specific event histories. There were 60,838 patients with 5.25 years of mean follow-up. In the validation model, HRs were in the same direction, and generally greater than REACH. In the event history model, HRs compared to other atherosclerotic cardiovascular disease alone included: recurrent myocardial infarction (HR 1.19, 95% confidence interval (CI) 1.05-1.34), recurrent ischemic stroke (HR 1.36, 95% CI 1.03-1.80), myocardial infarction and other atherosclerotic cardiovascular disease (HR 1.31, 95% CI 1.23-1.38), ischemic stroke and other atherosclerotic cardiovascular disease (HR 1.40, 95% CI 1.23-1.60), myocardial infarction and ischemic stroke (HR 1.94, 95% CI 1.23-3.04), and myocardial infarction, ischemic stroke and other atherosclerotic cardiovascular disease (HR 1.93, 95% CI 1.47-2.54). CONCLUSION: A detailed cardiovascular event history may be useful for estimating the relative risk of future cardiovascular events.

[27] *Drosos GC, Konstantonis G, Sfikakis PP, Tektonidou MG*. **Underperformance of clinical risk scores in identifying vascular ultrasound-based high cardiovascular risk in systemic lupus erythematosus**. European journal of preventive cardiology 2021; 28:346-352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33891687

ABSTRACT

AIMS: The aim of this study was to assess the performance of eight clinical risk prediction scores to identify individuals with systemic lupus erythematosus (SLE) at high cardiovascular disease (CVD) risk, as defined by the presence of atherosclerotic plaques. METHODS: CVD risk was estimated in 210 eligible SLE patients without prior CVD or diabetes mellitus (female: 93.3%, mean age: 44.8 ± 12 years) using five generic (Systematic Coronary Risk Evaluation (SCORE), Framingham Risk Score (FRS), Pooled Cohort Risk Equations (ASCVD), Globorisk, Prospective Cardiovascular Münster Study risk calculator (PROCAM)) and three 'SLE-adapted' (modified-SCORE, modified-FRS, QRESEARCH risk estimator, version 3 (QRISK3)) CVD risk scores, as well as ultrasound examination of the carotid and femoral arteries. Calibration, discrimination and classification measures to identify high CVD risk based on the presence of atherosclerotic plaques were assessed for all risk models. CVD risk reclassification was applied for all scores by incorporating ultrasound results. RESULTS: Moderate calibration (p-value range from 0.38 to 0.63) and discrimination (area

under the curve 0.73-0.84), and low-to-moderate sensitivity (8.3-71.4%) and classification ability (Matthews correlation coefficient (MCC) 0.25-0.47) were observed for all risk models to identify patients with plaques at any arterial site as high-risk. MCC was improved for modified-FRS versus FRS (0.43 vs 0.36), but not for modified-SCORE versus SCORE (0.25 vs 0.25). Based on plaque presence, CVD risk was upgraded to high-risk in 10%, 16.1%, 20.5%, 21.5%, 24%, 28.2% and 28.6% of cases classified as non-high-risk by QRISK3, modified-FRS, Globorisk, FRS/PROCAM, ASCVD, modified-SCORE and SCORE, respectively. CONCLUSIONS: Most of the five generic and three 'SLE-adapted' clinical risk scores underestimated high CVD risk defined by atherosclerotic plaque presence in patients with SLE.

[28] *Koskinas KC, Mach F, Räber L*. **Lipid-lowering therapy and percutaneous coronary interventions**. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2021; 16:1389-1403.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33875408

ABSTRACT

Although technological and procedural advances have resulted in substantial improvements in clinical outcomes following percutaneous coronary interventions (PCI), recurrent coronary events may occur despite achieving optimal procedural results. Beyond myocardial revascularisation failure related to anatomical or stent-related factors, adverse cardiovascular events post PCI often arise from non-culprit lesions not treated during index interventions. While stenting treats a focal manifestation of a systemic, progressive disease, the residual risk following an acute coronary syndrome (ACS) or elective PCI is largely related to the systemic pro-atherogenic effects of suboptimally controlled cardiovascular risk factors. Lowering atherogenic lipid levels, in particular low-density lipoprotein cholesterol (LDL-C), can halt the progression of coronary atherosclerosis and improve cardiovascular outcomes to an extent that is proportional to the magnitude of LDL-C reduction. Early (in-hospital) initiation of intensive statin therapy leads to a very early clinical benefit following ACS, and prolonged adherence to optimised lipid-lowering treatment effectively reduces longer-term cardiovascular events following PCI. Therefore, achieving guideline-recommended treatment goals for LDL-C with statins and, if indicated, with the addition of non-statin lipid-lowering drugs should become a priority for all physicians involved in the treatment of patients with coronary heart disease, including comprehensive strategies initiated during the in-hospital care of patients undergoing coronary interventions. This review article summarises current evidence on the role of LDL-C in the development and progression of coronary atherosclerosis, discusses the clinical benefits of intensive lipid-lowering treatments, and presents current guideline recommendations, with emphasis on patients undergoing PCI.

[29] *Guo LL, Chen YQ, Lin QZ et al.* **Non-HDL-C Is More Stable Than LDL-C in Assessing the Percent Attainment of Non-fasting Lipid for Coronary Heart Disease Patients**. Frontiers in cardiovascular medicine 2021; 8:649181.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33869310

ABSTRACT

This study aimed to compare the percentage attainment of fasting and non-fasting LDL-C and non-HDL-C target levels in coronary heart disease (CHD) patients receiving short-term statin therapy. This study enrolled 397 inpatients with CHD. Of these, 197 patients took statins for <1 month (m) or did not take any statin before admission (CHD1 group), while 204 patients took statins for ≥1 m before

admission (CHD2 group). Blood lipid levels were measured at 0, 2, and 4 h after a daily breakfast. Non-fasting LDL-C and non-HDL-C levels significantly decreased after a daily meal ($P < 0.05$). Both fasting and non-fasting LDL-C or non-HDL-C levels were significantly lower in the CHD2 group. The percentage attainment of LDL-C <1.4 mmol/L at 2 and 4 h after a daily breakfast was significantly higher than that during fasting ($P < 0.05$), but the percent attainment of non-fasting non-HDL-C <2.2 mmol/L was close to its fasting value ($P > 0.05$). Analysis of c-statistic showed that non-fasting cut-off points for LDL-C and non-HDL-C were 1.19 and 2.11 mmol/L, corresponding to their fasting goal levels of 1.4 and 2.2 mmol/L, respectively. When post-prandial LDL-C and non-HDL-C goal attainments were re-evaluated using non-fasting cut-off points, there were no significant differences in percentage attainment between fasting and non-fasting states. Non-HDL-C is more stable than LDL-C in assessing the percent attainment of non-fasting lipid for coronary heart disease patients. If we want to use LDL-C to assess the percent attainment of post-prandial blood lipids, we may need to determine a lower non-fasting cut-off point.

[30] *Ma L, Wang S, Zhao H et al.* **Susceptibility of ApoB and PCSK9 Genetic Polymorphisms to Diabetic Kidney Disease Among Chinese Diabetic Patients**. Frontiers in medicine 2021; 8:659188.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33889589
ABSTRACT
This study aimed to investigate the susceptibility of 8 polymorphisms in ApoB and PCSK9 genes to diabetic kidney disease (DKD) in Chinese patients with type 2 diabetes mellitus. This is a case-control association study, including 575 DKD cases and 653 controls. Genotypes were determined using ligase detection reaction method, and data are analyzed using STATA software. The genotype distributions of rs1042034 and rs12720838 differed significantly between the two groups ($P < 0.001$ and $P = 0.008$, respectively). After adjusting for confounding factors, the mutations of rs1042034 and rs12720838 were associated with the significantly increased risk of DKD. For instance, carriers of rs1042034 T allele (CT and TT genotypes) were 1.07 times more likely to have DKD than carriers of rs1042034 CC genotype [odds ratio (OR) = 1.07, 95% confidence interval (CI): 1.03-1.10, $P < 0.001$]. Further, haplotype T-A-G-T in ApoB gene was overrepresented in cases (18.10%) compared with controls (12.76%) (P(Simulated) = 0.045), and haplotype T-A-G-T was associated with a 33% increased risk of DKD (OR = 1.33, 95% CI: 1.04, 1.70). In further haplotype-phenotype analysis, significant association was only noted for hypertension and omnibus haplotypes in ApoB gene (P(Simulated) = 0.001). Our findings indicate that ApoB gene is a candidate gene for DKD in Chinese patients with type 2 diabetes mellitus.

[31] *Dubrovsky AMK, Bowlus CL.* **Statins, Fibrates, and Other Peroxisome Proliferator-Activated Receptor Agonists for the Treatment of Cholestatic Liver Diseases**. Gastroenterol Hepatol (N Y) 2020; 16:31-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33867886
ABSTRACT
Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are autoimmune cholestatic liver diseases that commonly result in the need for liver transplantation. The lack of an effective therapy for PSC remains a largely unmet need in hepatology, and although the majority of patients with PBC will have an adequate response to ursodeoxycholic acid and/or obeticholic acid,

there is a need for treatment among patients who do not respond completely to these therapies. Investigations of statins, fibrates, and other peroxisome proliferator-activated receptor (PPAR) agonists suggest clinical benefit with some of these agents. Statins have recently been suggested to improve outcomes in patients with PSC but have not demonstrated benefit in patients with PBC, whereas fibrates and newer PPAR agonists appear to improve biochemical markers linked to better clinical outcomes in patients with PBC. Further research is needed to fully understand the clinical efficacy of these agents in the treatment of PBC and PSC.

[32] *Abudureyimu S, Abulaiti P, Li H et al.* **Roles of endothelial lipase gene related single nucleotide polymorphisms in patients with coronary artery disease**. Gene 2021; 788:145669.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33882321

ABSTRACT

The current work focused on evaluating the roles of endothelial lipase gene (LIPG) related single nucleotide polymorphisms (SNPs) in patients with coronary artery disease (CAD). This study involved 1,883 subjects with 959 CAD patients and 924 healthy controls. Data were harvested to assess the association of LIPG related SNPs including rs3744841, rs3744843, rs3813082 and rs2000813 with the risk of CAD. The CC + AC genotype in rs3813082 played a protective role for CAD [odds ratio (OR) = 0.709, P = 0.039]. Differences existed in apolipoprotein-A1 (Apo-A1) and high-density lipoprotein-cholesterol (HDL-C) levels in rs3744843 variant between control and CAD groups. The rs3744841 variant increased the levels of total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), Apo-A1 and Lipoprotein a (LPa) in the CAD group and TC, LDL-C, HDL-C, Apo-B, Apo-A1 in the control group. The triglyceride (TG) level was lower in rs2000813 variant in the CAD group and elevated in the control group. The rs2000813 variant decreased the number of vascular stenosis while rs3744843 and rs3744841 variants increased the number of vascular stenosis in CAD patients. This study explored the roles of LIPG related SNPs in CAD, showing that CC + AC genotype in rs3813082 was a protective factor for CAD. The rs3744843, rs3744841 and rs2000813 variants were associated with the levels of lipid parameters in CAD patients. The rs3744843, rs3744841 and rs2000813 variants influenced the number of vascular stenosis in CAD patients. The results of our study might be a promising reference for preventing CAD.

[33] *Goyal R, Bhakhri BK, Goyal JP et al.* **Appropriateness of Lower Waist Circumference Cutoffs for Predicting Derangement in Metabolic Parameters Among Asian Children and Adolescents: A Pilot Study**. Indian Pediatr 2021; 58:392-394.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33883316

ABSTRACT

Waist circumference (WC) >90th percentile cut-off effectively screens children for metabolic syndrome, as some specific metabolic derangements (high fasting serum levels of insulin and triglycerides) may be better associated with lower (70th percentile) waist circumference cut off. We evaluated a subset of children and adolescents found obese or overweight following the anthropometric screening in a school-based survey. Metabolic parameters (fasting insulin levels, fasting blood sugar and fasting lipid profile and blood pressure) were compared among 3 groups of obese or overweight children divided on the basis of WC percentiles (>90th, 70th-90th and <70th). 78 children (aged 11-18 years, 45 boys) were evaluated. The proportion of participants with high triglycerides and fasting insulin among those with WC<70th (28.6%, 19%) was significantly lower than

that in the group with WC >90th (76.9%, 53.8%) as well as in group with WC 70th-90th percentile (38.7%, 41.9%).

[34] *Hirsh Raccah B, Yanovsky A, Treves N et al.* **Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors and the risk for neurocognitive adverse events: A systematic review, meta-analysis and meta-regression**. International journal of cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892045

ABSTRACT

BACKGROUND: It has been suggested that lipid lowering therapy causes impaired cognitive changes. The association between the use of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors and the risk of neurocognitive adverse events remains unclear. This meta-analysis aims to assess neurocognitive safety of PCSK9 inhibitors in randomized controlled trials (RCTs). METHODS AND RESULTS: The research was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed (MEDLINE), Embase and Cochrane library were searched through September 2019. Selection criteria included RCTs that addressed to neurocognitive adverse events of participants using Alirocumab, Evolocumab or Bococizumab, with a follow up duration of at least 6 months. The search results were screened by two independent reviewers. Safety data from included papers were extracted. Random effects meta-analysis was used to pool results, and meta-regression was utilized when applicable. Twenty-one studies were included. Among 59,733 patients, 31,611 were treated with PCSK9 inhibitors. The follow-up period ranged from 24 weeks to 48 months. No significant difference in the incidence of neurocognitive adverse effects between the groups was identified (RR = 1.01, 95% CI: 0.86-1.19, I(2) = 3%). Similar results were seen in subgroup analysis for each of the medications (alirocumab- RR = 0.88, 95% CI: 0.72-1.08, I(2) = 0%, evolocumab- RR = 1.42, 95% CI: 0.74-2.73, I(2) = 55%). A meta-regression analysis for evolocumab revealed that prolonged study duration was associated with decreased risk for neurocognitive adverse events (β(week) = -0.0037, p-value = 0.03). CONCLUSIONS: Pooled results of our meta-analysis and meta-regression show that exposure to PCSK9 inhibitors is not associated with an increased risk of neurocognitive adverse effects.

[35] *D'Erasmo L, Minicocci I, Di Costanzo A et al.* **Clinical Implications of Monogenic Versus Polygenic Hypercholesterolemia: Long-Term Response to Treatment, Coronary Atherosclerosis Burden, and Cardiovascular Events**. Journal of the American Heart Association 2021; 10:e018932.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33890476

ABSTRACT

Background Familial hypercholesterolemia (FH) may arise from deleterious monogenic variants in FH-causing genes as well as from a polygenic cause. We evaluated the relationships between monogenic FH and polygenic hypercholesterolemia in influencing the long-term response to therapy and the risk of atherosclerosis. Methods and Results A cohort of 370 patients with clinically diagnosed FH were screened for monogenic mutations and a low-density lipoprotein-rising genetic risk score >0.69 to identify polygenic cause. Medical records were reviewed to estimate the response to lipid-lowering therapies and the occurrence of major atherosclerotic cardiovascular events during a median follow-up of 31.0 months. A subgroup of patients (n=119) also underwent coronary computed tomographic angiography for the evaluation of coronary artery calcium score and severity of coronary

stenosis as compared with 135 controls. Two hundred nine (56.5%) patients with hypercholesterolemia were classified as monogenic (FH/M+), 89 (24.1%) as polygenic, and 72 (19.5%) genetically undefined (FH/M-). The response to lipid-lowering therapy was poorest in monogenic, whereas it was comparable in patients with polygenic hypercholesterolemia and genetically undetermined. Mean coronary artery calcium score and the prevalence of coronary artery calcium >100 units were significantly higher in FH/M+ as compared with both FH/M- and controls. Finally, after adjustments for confounders, we observed a 5-fold higher risk of incident major atherosclerotic cardiovascular events in FH/M+ (hazard ratio, 4.8; 95% CI, 1.06-21.36; P(adj)=0.041). Conclusions Monogenic cause of FH is associated with lower response to conventional cholesterol-lowering therapies as well as with increased burden of coronary atherosclerosis and risk of atherosclerotic-related events. Genetic testing for hypercholesterolemia is helpful in providing important prognostic information.

[36] *Arai H, Bujo H, Masuda D et al.* **Integrated Analysis of Two Probucol Trials for the Secondary Prevention of Atherosclerotic Cardiovascular Events: PROSPECTIVE and IMPACT**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33867420

ABSTRACT

AIMS: In this study, we integrated two randomized control trials, PROSPECTIVE and IMPACT, to address the effect of probucol on cerebrocardiovascular events and carotid intima-media thickness (IMT) in Japanese, Korean, and Chinese patients with coronary artery disease (CAD). METHODS: A total of 1,025 patients from the PROSPECTIVE and IMPACT studies were enrolled. The time to the first major adverse cerebrocardiovascular event, in addition to carotid IMT and lipid levels, was compared between the control and probucol groups. RESULTS: In the integrated analysis, the adjusted hazard ratio (HR) and 95% confidence interval (CI) were 0.67 and 0.44-1.03, respectively, indicating a tendency to show the effect of probucol on cerebrocardiovascular events in secondary prevention. We also found no significant differences between the control and probucol groups in the mean IMT of the carotid arteries and its changes. However, we found a significant decrease in cerebrocardiovascular events in patients with reduced levels of HDL cholesterol (HDL-C) (≥ 6.25 mg/dL) compared with those with levels ＜6.25 mg/dL (p=0.024), without any increase in adverse events such as severe ventricular arrhythmias. CONCLUSION: We demonstrated a marginal effect of probucol on cerebrocardiovascular events in Asian patients with CAD, with reasonable safety profiles. A larger study may be needed to support the effect of probucol for cardiovascular prevention.

[37] *Nohara A, Tada H, Ogura M et al.* **Homozygous Familial Hypercholesterolemia**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33867421

ABSTRACT

Familial hypercholesterolemia (FH) is an inherited disorder with retarded clearance of plasma LDL caused by mutations of the genes involved in the LDL receptor-mediated pathway and most of them exhibit autosomal dominant inheritance. Homozygotes of FH (HoFH) may have plasma LDL-C levels, which are at least twice as high as those of heterozygous FH (HeFH) and therefore four times higher than normal levels. Prevalence of HoFH had been estimated as 1 in 1,000,000 before but more recent genetic analysis surveys predict 1 in 170,000 to 300,000. Since LDL receptor activity is

severely impaired, HoFH patients do not or very poorly respond to medications to enhance activity, such as statins, and have a poorer prognosis compared to HeFH. HoFH should therefore be clinically distinguished from HeFH. Thorough family studies and genetic analysis are recommended for their accurate diagnosis. Fatal cardiovascular complications could develop even in the first decade of life for HoFH, so aggressive lipid-lowering therapy should be initiated as early as possible. Direct removal of plasma LDL by lipoprotein apheresis has been the principal measure for these patients. However, this treatment alone may not achieve stable LDL-C target levels and combination with drugs should be considered. The lipid-lowering effects of statins and PCSK9 inhibitors substantially vary depending on the remaining LDL receptor activity of individual patients. On the other hand, the action an MTP inhibitor is independent of LDL receptor activity, and it is effective in most HoFH cases. This review summarizes the key clinical issues of HoFH as well as insurance coverage available under the Japanese public healthcare system.

[38] *Onfiani G, Nascimbeni F, Carubbi F*. **A case of statin-induced liver injury with positive rechallenge with a second statin. Is there a class effect?** Journal of basic and clinical physiology and pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33882199
ABSTRACT
OBJECTIVES: Statins have proved to reduce cardiovascular morbidity and mortality in high-risk population and are generally well tolerated, although adverse events can occur. Up to 3% of patients develop aminotransferases elevation, which usually normalizes with continued treatment and hardly is associated with clinical symptoms. Serious statin-related liver injury is exceedingly rare. Furthermore, literature regarding rechallenge with a second statin is extremely poor. Some authors caution that re-exposure to these drugs is associated with a more serious liver injury but safe switching to a second statin after drug-induced liver injury (DILI) is also reported. CASE PRESENTATION: We describe a case of a middle-aged woman who developed hepatocellular liver injury after simvastatin dose escalation; a rechallenge with low dose rosuvastatin caused rapid recurrence of DILI. CONCLUSIONS: In our opinion, clinicians should be very cautious upon rechallenge and closely follow-up patients who experienced statin-induced liver injury when trying re-exposure to another statin.

[39] *Liu A, Kollipara R, Hoss E, Goldman MP*. **Lower eyelid xanthelasma following hyaluronic acid filler injections to the tear troughs**. J Cosmet Dermatol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33877741
ABSTRACT
INTRODUCTION: Adverse effects from dermal fillers are uncommon. We report a case of filler-induced xanthelasma at the bilateral infraorbital region in a 43-year-old woman after multiple injections of hyaluronic acid to correct tear trough depression. MATERIAL AND METHODS: We report a case of a 43-year-old woman with a chief complaint of skin discoloration of the bilateral lower eyelids. Her history was significant for ten sessions of hyaluronic acid filler for tear trough deformity between December 2008 and May 2016. On clinical examination, she exhibited thin, soft, and yellow papules to her lower medial infraorbital hollows. A punch biopsy showed foamy histiocytes with a background of hypervascularization and focal extracellular lipid in the superficial dermis, consistent with xanthelasma. RESULTS: Xanthelasma was treated with multiple passes of Er:YAG laser (Sciton

Contour TRL) with a 4 mm spot size, fluence 7.5 J/cm2, and ablate/coagulate 50/50 at 6 Hz until clearance occurred. The perilesional skin was treated with 1-2 passes, fluence 7.5 J/cm2, ablate/coagulate 50/0 to blend in the cosmetic unit. Six-month follow-up showed notable improvement of all lesions. DISCUSSION: There is a paucity of treatments described for filler-induced xanthelasma reaction. While broad conclusions cannot be drawn from one case, our experience indicates that complete resolution can be achieved with Er:YAG ablation. We hypothesize that this laser is an optimal treatment, as it can vaporize the lipid contents while minimizing adverse effects, such as scars and hyperpigmentation.

[40] *Xu HR, Yang Q, Xiang SY et al.* **Rosuvastatin Enhances Alveolar Fluid Clearance in Lipopolysaccharide-Induced Acute Lung Injury by Activating the Expression of Sodium Channel and Na,K-ATPase via the PI3K/AKT/Nedd4-2 Pathway**. Journal of inflammation research 2021; 14:1537-1549.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33889010

ABSTRACT

BACKGROUND: Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are devastating clinical conditions characterized by pulmonary epithelial damage and protein-rich fluid accumulation in the alveolar spaces. Statins are a class of HMG-CoA reductase inhibitors, which exert cholesterol-lowering and anti-inflammatory effects. METHODS: Rosuvastatin (1 mg/kg) was injected intravenously in rats 12 h before lipopolysaccharide (LPS, 10 mg/kg) administration. Eight hours later after LPS challenge, alveolar fluid clearance (AFC) was detected in rats (n = 6-8). Rosuvastatin (0.3 μmol/mL) and LPS were cultured with primary rat alveolar type II epithelial cells for 8 h. RESULTS: Rosuvastatin obviously improved AFC and attenuated lung-tissue damage in ALI model. Moreover, it enhanced AFC by increasing sodium channel and Na,K-ATPase protein expression. It also up-regulated P-Akt via reducing Nedd4-2 in vivo and in vitro. Furthermore, LY294002 blocked the increase in AFC in response to rosuvastatin. Rosuvastatin-induced AFC was found to be partly rely on sodium channel and Na,K-ATPase expression via the PI3K/AKT/Nedd4-2 pathway. CONCLUSION: In summary, the findings of our study revealed the potential role of rosuvastatin in the management of ALI/ARDS.

[41] *Feng Y, Li Q, Ou G et al.* **Bile acid sequestrants: a review of mechanism and design**. The Journal of pharmacy and pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33885783

ABSTRACT

OBJECTIVE: Bile acid sequestrants (BAS) are used extensively in the treatment of hypercholesterolaemia. This brief review aimed to describe the design and evaluation of three types of BAS: amphiphilic copolymers, cyclodextrin/poly-cyclodextrin and molecular imprinted polymers. The mechanisms underlying the action of BAS are also discussed. KEY FINDINGS: BAS could lower plasma cholesterol, improve glycemic control in patients with type 2 diabetes and regulate balance energy metabolism via receptors or receptor-independent mediated mechanisms. Different types of BAS have different levels of ability to bind to bile acids, different stability and different in-vivo activity. CONCLUSIONS: A growing amount of evidence suggests that bile acids play important roles not only in lipid metabolism but also in glucose metabolism. The higher selectivity, specificity, stability and in-vivo activity of BAS show considerable potential for lipid-lowering therapy.

[42] *Thomas CM, Vicent M, Moore S et al.* **Treatment of Severe Hypertriglyceridemia With Insulin Infusions in Severe COVID-19: A Case Series**. Journal of pharmacy practice 2021:8971900211010473.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33882724

ABSTRACT

PURPOSE: Rapid onset of severe hypertriglyceridemia was quickly recognized in critical COVID-19 patients. Associated causes have been due to secondary hemophagocytic lymphohystiocytosis (HLH) syndrome, medication-induced, or acute liver failure. Statins, omega-3 polyunsaturated acids, niacin, and fibrates are common oral lipid lowering therapy options in patients at risk for hypertriglyceridemia. The severity of hypertriglyceridemia in COVID-19 patients with triglyceride values reaching greater than 1,000 mg/dL put them at a heightened risk of pancreatitis and therefore an essential need to acutely lower their levels. We present a case series of 5 patients who achieved rapid triglyceride lowering through continuous insulin infusion therapy. METHODS: A retrospective chart review of 48 critical COVID-19 patients who were admitted from March 22 to April 15, 2020 was conducted. Inclusion criteria consisted of mechanical ventilation and continuous insulin infusion to treat severe hypertriglyceridemia resulting with 5 eligible patients in this case report. RESULTS AND CONCLUSION: In addition to standard oral lipid lowering therapies, continuous insulin infusion successfully treated severe hypertriglyceridemia in critically ill COVID-19 patients. None of the patients experienced pancreatitis or hypoglycemia necessitating cessation of insulin. Further studies are needed to show the optimum dose and duration of insulin infusion as monotherapy and in combination with oral therapies.

[43] *Heeren J, Scheja L*. **Metabolic-associated fatty liver disease and lipoprotein metabolism**. Molecular metabolism 2021:101238.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33892169

ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease, or as recently proposed 'metabolic-associated fatty liver disease' (MAFLD), is characterized by pathological accumulation of triglycerides and other lipids in hepatocytes. This common disease can progress from simple steatosis to steatohepatitis, and eventually end-stage liver diseases. MAFLD is closely related to disturbances in systemic energy metabolism, including insulin resistance and atherogenic dyslipidemia. SCOPE OF REVIEW: The liver is the central organ in lipid metabolism by secreting very low density lipoproteins (VLDL) and, on the other hand, by internalizing fatty acids and lipoproteins. This review article discusses recent research addressing hepatic lipid synthesis, VLDL production, and lipoprotein internalization as well as the lipid exchange between adipose tissue and the liver in the context of MAFLD. MAJOR CONCLUSIONS: Liver steatosis in MAFLD is triggered by excessive hepatic triglyceride synthesis utilizing fatty acids derived from white adipose tissue (WAT), de novo lipogenesis (DNL) and endocytosed remnants of triglyceride-rich lipoproteins. Consequently, high hepatic lipid content VLDL secretion is enhanced, which is the primary cause of complex dyslipidemia typical for subjects with MAFLD. Interventions reducing VLDL secretory capacity attenuate dyslipidemia while they exacerbate MAFLD, indicating that the balance of lipid storage versus secretion in hepatocytes is a critical parameter determining disease outcome. Proof of concept studies have shown that promoting lipid storage and energy combustion in adipose tissues reduces hepatic lipid load and thus

ameliorates MAFLD. Moreover, hepatocellular triglyceride synthesis from DNL and WAT-derived fatty acids can be targeted to treat MAFLD. However, more research is needed to understand how individual transporters, enzymes, and their isoforms affect steatosis and dyslipidemia in vivo, and whether these two aspects of MAFLD can be selectively treated. Processing of cholesterol-enriched lipoproteins appears less important for steatosis. It may, however, modulate inflammation and consequently MAFLD progression.

[44] *Pan C, Lin J, Zheng J et al.* **An intelligent T(1)-T(2) switchable MRI contrast agent for the non-invasive identification of vulnerable atherosclerotic plaques**. Nanoscale 2021; 13:6461-6474.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33885526
ABSTRACT
Unlike stable atherosclerotic plaques, vulnerable plaques are very likely to cause serious cardio-cerebrovascular diseases. Meanwhile, how to non-invasively identify vulnerable plaques at early stages has been an urgent but challenging problem in clinical practices. Here, we propose a macrophage-targeted and in situ stimuli-triggered T(1)-T(2) switchable magnetic resonance imaging (MRI) nanoprobe for the non-invasive diagnosis of vulnerable plaques. Precisely, single-dispersed iron oxide nanoparticles (IONPs) modified with hyaluronic acid (HA), denoted as IONP-HP, show macrophage targetability and T(1) MRI enhancement (r(2)/r(1) = 3.415). Triggered by the low pH environment of macrophage lysosomes, the single-dispersed IONP-HP transforms into a cluster analogue, which exhibits T(2) MRI enhancement (r(2)/r(1) = 13.326). Furthermore, an in vivo switch of T(1)-T(2) enhancement modes shows that the vulnerable plaques exhibit strong T(1) enhancement after intravenous administration of the nanoprobe, followed by a switch to T(2) enhancement after 9 h. In contrast, stable plaques show only slight T(1) enhancement but without T(2) enhancement. It is therefore imperative that the intelligent and novel nanoplatform proposed in this study achieves a substantial non-invasive diagnosis of vulnerable plaques by means of a facile but effective T(1)-T(2) switchable process, which will significantly contribute to the application of materials science in solving clinical problems.

[45] *Ciccacci F, Majid N, Petrolati S et al.* **Hypercholesterolemia and related risk factors in a cohort of patients with diabetes and hypertension in Maputo, Mozambique**. The Pan African medical journal 2021; 38:102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33889268
ABSTRACT
INTRODUCTION: some studies reported that 25.5% of African population presents hypercholesterolemia; however, epidemiology of hypercholesterolemia in Africa is poorly described. Mozambique is experiencing a constant growth of non-communicable diseases, but scarce data are available about hypercholesterolemia. Our study aims at describing the prevalence of hypercholesterolemia in patients with diabetes and hypertension in Mozambique and investigate possible risk factors. METHODS: we conducted a cross-sectional study involving all the patients diagnosed with hypertension and/or diabetes from June 2018 to November 2020 in the Zimpeto DREAM Centre (Maputo, Mozambique). For each patient, anthropometric, clinical and laboratory data were collected. Hypercholesterolemia was defined as total blood cholesterol >200 mg/dL. Univariable and multivariable analysis were perfumed. RESULTS: a total of 885 patients were included, 76.2%

(n=674) female. Hypertension alone was diagnosed in 670 (75.7%) patients, diabetes in 109 (12.3%) patients and 106 (11.9%) both diseases. Hypercholesterolemia was present in 410 (46.3%) patients and it was more prevalent in patients diagnosed with both diabetes and hypertension (52.8%), as compared to the patients diagnosed with hypertension (46.9%) or diabetes alone (36.7%). In the multivariable analysis, the only factors independently associated with hypercholesterolemia were female sex (aOR 1.77, 95% CI 1.26-2.48, p=0.001) and a body mass index >25kg/m(2) (aOR 1.50, 95% CI 1.11-2.04, p=0.008). CONCLUSION: our results highlight the need for a specific focus on female and obese/overweight patients, especially if diagnosed with both hypertension and diabetes, to promptly detect metabolic disorders and establish temporary preventive measures for cardiovascular events.

[46] *Danielsson H, Tebani A, Zhong W et al.* **Blood protein profiles related to preterm birth and retinopathy of prematurity**. Pediatric research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33895781
ABSTRACT
BACKGROUND: Nearly one in ten children is born preterm. The degree of immaturity is a determinant of the infant's health. Extremely preterm infants have higher morbidity and mortality than term infants. One disease affecting extremely preterm infants is retinopathy of prematurity (ROP), a multifactorial neurovascular disease that can lead to retinal detachment and blindness. The advances in omics technology have opened up possibilities to study protein expressions thoroughly with clinical accuracy, here used to increase the understanding of protein expression in relation to immaturity and ROP. METHODS: Longitudinal serum protein profiles the first months after birth in 14 extremely preterm infants were integrated with perinatal and ROP data. In total, 448 unique protein targets were analyzed using Proximity Extension Assays. RESULTS: We found 20 serum proteins associated with gestational age and/or ROP functioning within mainly angiogenesis, hematopoiesis, bone regulation, immune function, and lipid metabolism. Infants with severe ROP had persistent lower levels of several identified proteins during the first postnatal months. CONCLUSIONS: The study contributes to the understanding of the relationship between longitudinal serum protein levels and immaturity and abnormal retinal neurovascular development. This is essential for understanding pathophysiological mechanisms and to optimize diagnosis, treatment and prevention for ROP. IMPACT: Longitudinal protein profiles of 14 extremely preterm infants were analyzed using a novel multiplex protein analysis platform combined with perinatal data. Proteins associated with gestational age at birth and the neurovascular disease ROP were identified. Among infants with ROP, longitudinal levels of the identified proteins remained largely unchanged during the first postnatal months. The main functions of the proteins identified were angiogenesis, hematopoiesis, immune function, bone regulation, lipid metabolism, and central nervous system development. The study contributes to the understanding of longitudinal serum protein patterns related to gestational age and their association with abnormal retinal neuro-vascular development.

[47] *Gormley M, Yarmolinsky J, Dudding T et al.* **Using genetic variants to evaluate the causal effect of cholesterol lowering on head and neck cancer risk: A Mendelian randomization study**. PLoS genetics 2021; 17:e1009525.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33886544
ABSTRACT

Head and neck squamous cell carcinoma (HNSCC), which includes cancers of the oral cavity and oropharynx, is a cause of substantial global morbidity and mortality. Strategies to reduce disease burden include discovery of novel therapies and repurposing of existing drugs. Statins are commonly prescribed for lowering circulating cholesterol by inhibiting HMG-CoA reductase (HMGCR). Results from some observational studies suggest that statin use may reduce HNSCC risk. We appraised the relationship of genetically-proxied cholesterol-lowering drug targets and other circulating lipid traits with oral (OC) and oropharyngeal (OPC) cancer risk using two-sample Mendelian randomization (MR). For the primary analysis, germline genetic variants in HMGCR, NPC1L1, CETP, PCSK9 and LDLR were used to proxy the effect of low-density lipoprotein cholesterol (LDL-C) lowering therapies. In secondary analyses, variants were used to proxy circulating levels of other lipid traits in a genome-wide association study (GWAS) meta-analysis of 188,578 individuals. Both primary and secondary analyses aimed to estimate the downstream causal effect of cholesterol lowering therapies on OC and OPC risk. The second sample for MR was taken from a GWAS of 6,034 OC and OPC cases and 6,585 controls (GAME-ON). Analyses were replicated in UK Biobank, using 839 OC and OPC cases and 372,016 controls and the results of the GAME-ON and UK Biobank analyses combined in a fixed-effects meta-analysis. We found limited evidence of a causal effect of genetically-proxied LDL-C lowering using HMGCR, NPC1L1, CETP or other circulating lipid traits on either OC or OPC risk. Genetically-proxied PCSK9 inhibition equivalent to a 1 mmol/L (38.7 mg/dL) reduction in LDL-C was associated with an increased risk of OC and OPC combined (OR 1.8 95%CI 1.2, 2.8, p = 9.31 x10-05), with good concordance between GAME-ON and UK Biobank (I2 = 22%). Effects for PCSK9 appeared stronger in relation to OPC (OR 2.6 95%CI 1.4, 4.9) than OC (OR 1.4 95%CI 0.8, 2.4). LDLR variants, resulting in genetically-proxied reduction in LDL-C equivalent to a 1 mmol/L (38.7 mg/dL), reduced the risk of OC and OPC combined (OR 0.7, 95%CI 0.5, 1.0, p = 0.006). A series of pleiotropy-robust and outlier detection methods showed that pleiotropy did not bias our findings. We found limited evidence for a role of cholesterol-lowering in OC and OPC risk, suggesting previous observational results may have been confounded. There was some evidence that genetically-proxied inhibition of PCSK9 increased risk, while lipid-lowering variants in LDLR, reduced risk of combined OC and OPC. This result suggests that the mechanisms of action of PCSK9 on OC and OPC risk may be independent of its cholesterol lowering effects; however, this was not supported uniformly across all sensitivity analyses and further replication of this finding is required.

[48] *Boldeanu I, Sadouni M, Mansour S et al.* **Prevalence and Characterization of Subclinical Coronary Atherosclerotic Plaque with CT among Individuals with HIV: Results from the Canadian HIV and Aging Cohort Study**. Radiology 2021:203297.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33876969

ABSTRACT

Background People living with HIV (PLWH) have a higher risk of myocardial infarction. Coronary atherosclerotic plaque CT characterization helps to predict cardiovascular risk. Purpose To measure CT characteristics of coronary plaque in PLWH without known cardiovascular disease and healthy volunteers without HIV. Materials and Methods In this prospective study, noncontrast CT (all participants, n = 265) was used for coronary artery calcium (CAC) scoring in asymptomatic PLWH and healthy volunteers without HIV, without known cardiovascular disease, from 2012 to 2019. At coronary CT angiography (n = 233), prevalence, frequency, and volume of calcified, mixed, and noncalcified plaque were measured. Poisson regressions were used with adjustment for

cardiovascular risk factors. Results There were 181 PLWH (mean age, 56 years ± 7; 167 men) and 84 healthy volunteers (mean age, 57 years ± 8; 65 men) evaluated by using noncontrast CT. CT angiography was performed in 155 PLWH and 78 healthy volunteers. Median 10-year Framingham risk score was not different between PLWH and healthy volunteers (10% vs 9%, respectively; P = .45), as were CAC score (odds ratio [OR], 1.06; 95% CI: 0.58, 1.94; P = .85) and overall plaque prevalence (prevalence ratio, 1.07; 95% CI: 0.86, 1.32; P = .55) after adjustment for cardiovascular risk. Noncalcified plaque prevalence (prevalence ratio, 2.5; 95% CI: 1.07, 5.67; P = .03) and volume (OR, 2.8; 95% CI: 1.05, 7.40; P = .04) were higher in PLWH. Calcified plaque frequency was reduced in PLWH (OR, 0.6; 95% CI: 0.40, 0.91; P = .02). Treatment with protease inhibitors was associated with higher volume of overall (OR, 1.8; 95% CI: 1.09, 2.85; P = .02) and mixed plaque (OR, 1.6; 95% CI: 1.04, 2.45; P = .03). Conclusion Noncalcified coronary plaque burden at coronary CT angiography was two- to threefold higher in asymptomatic people living with HIV without known cardiovascular disease compared with healthy volunteers without HIV. © RSNA, 2021 Online supplemental material is available for this article. See also the editorial by Lai in this issue.

[49] *Le Lay JE, Du Q, Mehta MB et al.* **Blocking endothelial lipase with monoclonal antibody MEDI5884 durably increases high density lipoprotein in nonhuman primates and in a phase 1 trial**. Science translational medicine 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33883272
ABSTRACT
Cardiovascular disease (CVD) is the leading global cause of death, and treatments that further reduce CV risk remain an unmet medical need. Epidemiological studies have consistently identified low high-density lipoprotein cholesterol (HDL-C) as an independent risk factor for CVD, making HDL elevation a potential clinical target for improved CVD resolution. Endothelial lipase (EL) is a circulating enzyme that regulates HDL turnover by hydrolyzing HDL phospholipids and driving HDL particle clearance. Using MEDI5884, a first-in-class, EL-neutralizing, monoclonal antibody, we tested the hypothesis that pharmacological inhibition of EL would increase HDL-C by enhancing HDL stability. In nonhuman primates, MEDI5884 treatment resulted in lasting, dose-dependent elevations in HDL-C and circulating phospholipids, confirming the mechanism of EL action. We then showed that a favorable lipoprotein profile of elevated HDL-C and reduced low-density lipoprotein cholesterol (LDL-C) could be achieved by combining MEDI5884 with a PCSK9 inhibitor. Last, when tested in healthy human volunteers, MEDI5884 not only raised HDL-C but also increased HDL particle numbers and average HDL size while enhancing HDL functionality, reinforcing EL neutralization as a viable clinical approach aimed at reducing CV risk.

[50] *Zhu Y, Gou H, Ma L et al.* **Effects of double-dose statin therapy for the prevention of post-stroke epilepsy: A prospective clinical study**. Seizure 2021; 88:138-142.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33895389
ABSTRACT
BACKGROUND: To determine treatment effects on the incidence of post-stroke epilepsy (PSE) using different doses of statin, a prospective hospital-based cohort study was designed to explore whether a double-dose statin treatment can better prevent the occurrence of PSE. METHODS: A total of 1152 patients with newly diagnosed ischemic stroke admitted to our hospital from March to August 2017 were selected, 1033 of whom were followed-up. Patients were divided into two treatment groups:(1)

standard-dose (20 mg atorvastatin or 10 mg rosuvastatin,daily oral; 788 patients); and (2) double-dose (40 mg atorvastatin or 20 mg rosuvastatin, daily oral; 245 patients).At 18 months follow-up was conducted to compare the incidence of PSE between groups. RESULTS: In general, in the standard-dose group we observed two cases of early seizure (ES) (0.25%), 22 cases oflate seizure (LS) (2.79%) and 20 cases of PSE (2.54%). In the double-dose group, onepatient had ES (0.41%), two patients had LS (0.82%), and onepatient had PSE (0.41%). The incidence of PSE was significantly lower in the double-dose group as compared to the standard-dose group. There was a higher proportion of PSE in patients younger than 65 years and in males. Three patients had ES; one presented with focal aware seizure (FAS), and two had focal to bilateral tonic-clonic seizure (FBTCS). Among the 21 patients with PSE, there were two cases of FAS, five cases of focal impaired awareness seizure (FIAS), five cases of FBTCS, and nine cases of GTCS, suggesting that partial seizure is the most common type of PSE. Cerebral cortex was involved in 85.75% of cases with PSE, and multiple lobes were involved in 61.9% of cases with PSE. CONCLUSION: Increasing the dose of statin treatment during the acute phase of ischemic stroke reduces the incidence of PSE. Further research is needed to understand the mechanisms underlying the potential preventative effects of statins against PSE.

[51] *Shaya GE, Leucker TM, Jones SR et al.* **Coronary heart disease risk: Low-density lipoprotein and beyond**. Trends in cardiovascular medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33872757

ABSTRACT

Coronary heart disease (CHD) is the leading cause of morbidity and mortality world-wide and has been characterized as a chronic immunoinflammatory, fibroproliferative disease fueled by lipids. Great advances have been made in elucidating the complex mechanistic interactions among risk factors associated with CHD, yielding abundant success towards preventive measures and the development of pharmaceuticals to prevent and treat CHD via attenuation of lipoprotein-mediated risk. However, significant residual risk remains. Several potentially modifiable CHD risk factors ostensibly contributing to this residual risk have since come to the fore, including systemic inflammation, diabetes mellitus, high-density lipoprotein, plasma triglycerides (TG) and remnant lipoproteins (RLP), lipoprotein(a) (Lp[a]), and vascular endothelial dysfunction (ED). Herein, we summarize the body of evidence implicating each of these risk factors in residual CHD risk.