[1] *Gordon M, Di Bartolo IM*. **Using Race with Caution in the ASCVD Calculator**. American family physician 2021; 104:292-294.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34523875
ABSTRACT

[2] *Rossi M, Fabris E, Barbisan D et al.* **Lipid-Lowering Drug Therapy: Critical Approach for Implementation in Clinical Practice**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34514551
ABSTRACT
Increased levels of low-density lipoprotein cholesterol (LDL-C) are recognized as a primary risk factor for atherosclerotic cardiovascular disease, which remains the leading cause of death worldwide. Lowering LDL-C levels clearly reduces the risk of cardiovascular events, with benefits related to both absolute reduction and duration of treatment; however, a threshold below which low LDL-C levels can be dangerous has never been established. Since the discovery of statins, cardiovascular research has focused on developing new lipid-lowering agents. Ezetimibe and proprotein convertase subtilisin-kexin type 9 inhibitors have been found to further reduce LDL-C values and subsequent cardiovascular risk. Novel recently approved inclisiran and bempedoic acid, currently being tested in cardiovascular outcomes studies, are further expanding our pharmacological armamentarium, enabling the clinician to diminish residual risk related to LDL-C. Moreover, new agents are paving the way to successful treatment of homozygous familial hypercholesterolemia. This review summarizes the main characteristics of current and emerging lipid-lowering therapies to assist with comprehensive evidence-based decision making.

[3] *Roy N, Rosas SE*. **IL-6 Is Associated with Progression of Coronary Artery Calcification and Mortality in Incident Dialysis Patients**. American journal of nephrology 2021; 52:745-752.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34535589
ABSTRACT
INTRODUCTION: Inflammation is important in the pathogenesis of atherosclerosis. Elevated interleukin-6 (IL-6) is associated with cardiovascular events and also predicts mortality in individuals with CKD. Our goal was to determine the association between IL-6, FGF23, and high-sensitivity C-reactive protein (hsCRP) on coronary artery calcification (CAC) progression and mortality in incident dialysis patients without prior coronary events. METHODS: A prospective cohort of incident adult dialysis participants had CAC measured by ECG-triggered multislice CT scans at baseline and at least 12 months later. Lipids, mineral metabolism markers, FGF23, and inflammatory markers, such as IL-6 and hsCRP, were measured at the baseline visit. RESULTS: Participants in the high IL-6 tertile had the highest baseline CAC score (133.25 [10.35-466.15]) compared to the low (0.25 [0-212.2]) and intermediate (29.55 [0-182.85]) tertiles. Almost half of the participants with high IL-6 (15 of 32 [46.9%]) experienced progression of CAC compared to participants with low (8 of 32 [25%]) and intermediate (9 of 32 [28.1%]) ($p = 0.05$) IL-6 levels. Each log increase in IL-6 was associated with increase in death (hazard ratio 2.2, 95% CI: 1.2-3.8; $p = 0.01$). After adjusting for smoking, age, gender, race, diabetes, phosphate, and baseline calcium score, IL-6 (log) was associated with 2.2 times (95% CI: 1.1-4.6; $p = 0.03$) increase in death. CONCLUSION: IL-6 is associated with progression of CAC and mortality in incident dialysis patients.

[4] *Donners SJA, Toorop RJ, de Kleijn DPV, de Borst GJ.* **A narrative review of plaque and brain imaging biomarkers for stroke risk stratification in patients with atherosclerotic carotid artery disease**. Annals of translational medicine 2021; 9:1260.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34532397
ABSTRACT
OBJECTIVE: In this narrative review, we aim to review imaging biomarkers that carry the potential to non-invasively guide stroke risk stratification for treatment optimization. BACKGROUND: Carotid atherosclerosis plays a fundamental part in the occurrence of ischemic stroke. International guidelines select the optimal treatment strategy still mainly based on the presence of clinical symptoms and the degree of stenosis for stroke prevention in patients with atherosclerotic carotid plaques. These guidelines, based on randomized controlled trials that were conducted three decades ago, recommend carotid revascularization in symptomatic patients with high degree of stenosis versus a conservative approach for most asymptomatic patients. Due to optimization of best medical therapy and risk factor control, it is suggested that a subgroup of symptomatic patients is at lower risk of stroke and may not benefit from revascularization, whereas a selective subgroup of high-risk asymptomatic patients would benefit from this procedure. METHODS: A literature search was performed for articles published up to December 2020 using PubMed, EMBASE and Scopus. Based on the literature found, change in stenosis degree and volume, plaque echolucency, plaque surface, intraplaque haemorrhage, lipid-rich necrotic core, thin fibrous cap, inflammation, neovascularization, microembolic signals, cerebrovascular reserve, intracranial collaterals, silent brain infarcts, diffusion weighted imaging lesions and white matters lesions have the potential to predict stroke risk. CONCLUSIONS: The applicability of imaging biomarkers needs to be further improved before the potential synergistic prognostic ability of imaging biomarkers can be verified on top of the clinical biomarkers. In the future, the routine and combined assessment of both plaque and brain imaging biomarkers might help to improve optimization of treatment strategies in individual patients with atherosclerotic carotid artery disease.

[5] *Gu HQ, Yang KX, Yang X et al.* **Guideline-directed low-density lipoprotein management in high-risk ischemic stroke or transient ischemic attack admissions in China from 2015 to 2019**. Annals of translational medicine 2021; 9:1224.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34532361
ABSTRACT
BACKGROUND: Lowering low-density lipoprotein cholesterol (LDL-C) is crucial for secondary stroke prevention in stroke patients with preexisting cardiovascular diseases (CVD) or cerebrovascular diseases (CeVD). However, data on attainment of guideline-recommended LDL-C levels are lacking. METHODS: We analyzed data from the Chinese Stroke Center Alliance (CSCA) program for patients with ischemic stroke and transient ischemic attack (TIA) hospitalized between August 2015 and July 2019. Participants were classified into different disease groups according to preexisting CeVD (stroke/TIA) or CVD [coronary heart disease (CHD) or myocardial infarction (MI)]. RESULTS: Of 858,509 patients presenting with an acute stroke/TIA, 251,176 (29.3%) had a preexisting CeVD, 44,158 (5.1%) had preexisting CVD, 33,070 (3.9%) had concomitant preexisting CeVD and CVD, and 530,105 (61.7%) had no documented history of CeVD/CVD. Overall, only 397,596 (46.3%) met the target for LDL-C <2.6 mmol/L, 128,177 (14.9%) for LDL-C <1.8 mmol/L and 55,275 (6.4%) for LDL-C

<1.4 mmol/L, and patients with concomitant CeVD and CVD had higher attainment rates than other disease groups (P<0.001). Despite improvements over time in the proportion of patients who attain LDL-C targets (P for trend <0.05), it remains suboptimal. Younger age, women, having a history of hypertension or dyslipidemia, current smoking or drinking, and being admitted to hospitals located in eastern China were associated with lower odds of meeting the LDL-C goals. CONCLUSIONS: Overall attainment of guideline LDL-C targets in a population of stroke/TIA patients is low and indicates the need for better management of dyslipidemia, particularly for high-risk stroke patients with pre-existing CeVD or CVD.

[6] *Zeng W, Tomlinson B*. **Causes and outcome of rhabdomyolysis in patients admitted to medical wards in the Prince of Wales Hospital**. Annals of translational medicine 2021; 9:1329.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34532466

ABSTRACT

BACKGROUND: Rhabdomyolysis with a marked elevation of serum creatine kinase (CK) can be caused by various conditions. Acute kidney injury (AKI) is a potential complication of severe rhabdomyolysis and leads to a rapid increase in serum creatinine. METHODS: This study was performed to identify medical cases diagnosed with rhabdomyolysis and to examine the likely causes. Patients diagnosed with rhabdomyolysis during admission to the medical wards of Prince of Wales Hospital (PWH) in Hong Kong from January 1, 2004 to May 31, 2012 were identified by searching computer records. Details of hospital admissions were retrieved, and the underlying causes of the rhabdomyolysis and clinical outcomes were analyzed. RESULTS: There were 95 Chinese patients with a median age of 72 years (range, 22-92 years) assigned a diagnosis of rhabdomyolysis. A mild degree of AKI was defined as an increase of serum creatinine more than 20% above the baseline value before onset of acute illness and with the highest creatinine greater than 120 μmol/L. Mild AKI was identified in 63 patients. Rhabdomyolysis appeared to contribute to a fatal outcome in eight patients who had multiple preexisting morbidities. The maximum CK had a median value of 9,829 U/L (range, 472-258,100 U/L). Twelve patients with peak CK levels <10× the upper limit of normal (ULN) may not have had rhabdomyolysis by this standard definition. Of the remaining 83 patients with maximum CK values >10× the ULN, the most common contributing factors were trauma (n=19) and infection (n=17). Other common underlying causes included drug abuse (heroin and alcohol) and ischemia/immobility. CONCLUSIONS: Most patients recovered with appropriate medical interventions and had a median hospital stay of 13 days. One patient was thought to have drug-related rhabdomyolysis due to taking bezafibrate during an episode of renal impairment.

[7] *Zeng X, Zhou X, Tan XR, Chen YQ*. **Admission LDL-C and long-term mortality in patients with acute aortic dissection: a survival analysis in China**. Annals of translational medicine 2021; 9:1345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34532482

ABSTRACT

BACKGROUND: The level of blood lipid is closely related to prognosis in cardiovascular diseases. This study aims to analyze the effect of serum low-density lipoprotein cholesterol (LDL-C) levels on the long-term mortality in acute aortic dissection (AAD). A lower admission LDL-C level is associated with an increased risk of long-term mortality in AAD. METHODS: We analyzed the data of 284 patients with AAD admitted to the First Affiliated Hospital of Shantou University Medical College from

February 2016 to September 2019. Patients were followed up post-discharge. All patients were divided into either an LDL-C low-level group or an LDL-C high-level group according to the optimal cut-off point obtained by the receiver operating characteristic (ROC) curve. The endpoint outcome was long-term mortality in AAD. A survival analysis and Cox proportional hazards model were used. RESULTS: According to the Youden index, the optimal cut-off point for LDL-C was 2.755 mmol/L. The Kaplan-Meier survival analysis curves showed that the long-term mortality of the LDL-C low-level group (<2.755 mmol/L) was significantly higher than that of the LDL-C high-level group (≥2.755 mmol/L) (log-rank $\chi(2)=13.912$, $P<0.001$). After multivariate Cox regression analysis, LDL-C <2.755 mmol/L was still significantly associated with long-term mortality in AAD (HR=3.287, 95% CI: 1.637-6.600, P=0.001). In addition, cystatin C was also an independent risk factor for the long-term prognosis of AAD (HR=1.253, 95% CI: 1.057-1.486, P=0.009). CONCLUSIONS: A lower admission LDL-C level may be associated with an increased risk of long-term mortality in AAD.

[8] *Momtazi-Borojeni AA, Jaafari MR, Afshar M et al.* **PCSK9 immunization using nanoliposomes: preventive efficacy against hypercholesterolemia and atherosclerosis**. Archives of medical science : AMS 2021; 17:1365-1377.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34522266

ABSTRACT

INTRODUCTION: The aim of the study was to study a nanoliposomal anti-PCSK9 vaccine as a novel approach for cholesterol lowering via PCSK9 inhibition. MATERIAL AND METHODS: An immunogenic peptide construct termed immunogenic fused PCSK9-tetanus (IFPT) was displayed on the surface of liposome nanoparticles (L-IFPT) and mixed into alum adjuvant (L-IFPTA+). The manufactured vaccine formulations IFPT, L-IFPT, L-IFPTA+, IFPTA+, and free nanoliposomes were subcutaneously injected four times with bi-weekly intervals in C57BL/6 mice on a severe atherogenic protocol. RESULTS: Among the formulations, L-IFPTA+ vaccine was found to elicit the highest IgG response against PCSK9 peptide. The induced PCSK9 antibodies inhibited PCSK9-LDLR interaction through binding to PCSK9 in vaccinated mice. Liver low-density lipoprotein receptor (LDLR) protein was increased in vaccinated mice. L-IFPTA+, L-IFPT and IFPTA+ vaccines reduced total cholesterol by up to -38.13 ±3.8% (p = 0.006), -23 ±4.1% (p = 0.027) and -19.12 ±3% (p = 0.038), and low-density lipoprotein cholesterol (LDL-C) by up to -57 ±7.7% (p = 0.0003), -41.67 ±4.2% (p = 0.03) and -36.11 ±5% (p = 0.02) in hypercholesterolemic mice, respectively, versus control mice after 8 weeks. Long-term assessment indicated that the vaccine formulations could stimulate a long-lasting humoral immune response against PCSK9 peptide, which was associated with a marked reduction of total cholesterol in L-IFPTA+, L-IFPT and IFPTA+ vaccine groups by up to -82.5 ±7.3% (p = 0.002), -70.54 ±6.2% (p = 0.013) and -72.02 ±8.7% (p = 0.004), respectively, and LDL-C by up to -88.14 ±5.6% (p = 0.002), -55.92 ±8.3% (p = 0.003) and 54.81 ±9.3% (p = 0.003), respectively, versus the pre-vaccination time point adjusted to the control group. Anti-inflammatory Th2 cells and IL-4 cytokine were considerably increased in splenocytes of vaccinated mice. CONCLUSIONS: L-IFPTA+ vaccine can induce long-lasting, functional and safe PCSK9-specific antibodies in hypercholesterolemic C57BL/6 mice, providing a long-term protective impact on dyslipidemia and atherosclerosis.

[9] *Sohrevardi SM, Nasab FS, Mirjalili MR et al.* **Effect of atorvastatin on delirium status of patients in the intensive care unit: a randomized controlled trial**. Archives of medical science : AMS 2021; 17:1423-1428.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34522273

ABSTRACT

INTRODUCTION: Delirium is one of the most prevalent complications in intensive care unit (ICU) patients, which is related to worse clinical outcomes including a longer ICU stay, longer duration of mechanical ventilation, higher mortality rates and increased risk of cognitive impairment. Observational studies have suggested that statins might have a positive effect on delirium status of hospitalized patients. To date, there has been no trial assessing the effect of atorvastatin on delirium status in critically ill patients. Thus, the aim of the current study was to determine the efficacy of atorvastatin on delirium status of patients in the ICU. METHODS: In this randomized, double-blind and controlled trial, a total of 90 patients in the general ICU who had delirium for at least 2 days were randomly divided into atorvastatin (40 mg/day) (n = 40) and control (n = 50) groups. Delirium status of the patients was determined twice a day at 10:00 a.m. and 18:00 p.m. using the Richmond Agitation-Sedation Scale (RASS). RESULTS: Administration 40 mg/day of atorvastatin significantly reduced the mean RASS score and increased delirium-free days at both morning and afternoon time points compared to the control group ($p < 0.05$). CONCLUSIONS: Administration of atorvastatin had a significant positive effect on delirium status in patients admitted to the ICU.

[10] *Peterson MN, Dykhoff HJ, Crowson CS et al.* **Risk of rheumatoid arthritis diagnosis in statin users in a large nationwide US study**. Arthritis research & therapy 2021; 23:244.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34537063

ABSTRACT

OBJECTIVE: To evaluate the association between statin use and the risk of developing rheumatoid arthritis (RA) in a large, US case-control study. METHODS: Using the OptumLabs Data Warehouse, RA cases were identified as patients aged ≥18 years with ≥2 RA diagnoses between January 1, 2010 and June 30, 2019 and ≥1 prescription fills for methotrexate within 1 year of the first RA diagnosis. The first RA diagnosis was the index date. Cases were matched 1:1 to controls on age, sex, region, year of index date, and length of baseline coverage. Statin users were defined by having ≥2 statin prescription fills at least 90 days pre-index. Patients identified as statin users were further classified by statin user status (current or former), statin use duration, and intensity of statin exposure. Odds ratios for RA risk with statin use were estimated using logistic regression. RESULTS: 16,363 RA cases and 16,363 matched controls were identified. Among RA cases, 5509 (33.7%) patients were statin users compared to 5164 (31.6%) of the controls. Statin users had a slightly increased risk of RA compared to non-users (OR 1.12, 95% CI 1.06-1.18), and former statin users had an increased RA risk compared to current users (OR 1.21, 95% CI 1.13-1.28). However, risk was eliminated following adjustment for hyperlipidemia. The risk estimates for statin use duration and intensity did not reach significance. CONCLUSION: This study demonstrates no significant increase in the risk of developing RA for statin users compared to non-users after adjustment for hyperlipidemia in addition to other relevant confounders. However, more information from prospective studies would be necessary to further understand this relationship.

[11] *Klevmoen M, Bogsrud MP, Retterstøl K et al.* **Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia**. Atherosclerosis 2021; 335:8-15.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34520888

ABSTRACT
BACKGROUND AND AIMS: Women with heterozygous familial hypercholesterolemia (FH) are recommended to initiate statin treatment at the same age as men (from 8 to 10 years of age). However, statins are contraindicated when pregnancy is planned, during pregnancy and breastfeeding. The aim of the study was to determine the duration of pregnancy-related off-statin periods and breastfeeding in FH women. METHODS: A cross-sectional study using an anonymous online self-administered questionnaire was conducted. Women with FH were recruited through Lipid Clinics in Norway and Netherlands and national FH patient organizations. RESULTS: 102 women with FH (n = 70 Norwegian and n = 32 Dutch) were included in the analysis. Total length of pregnancy-related off-statin periods was estimated for 80 women where data were available, and was median (min-max) 2.3 (0-14.2) years. Lost statin treatment time was estimated for 67 women where data were available, and was median (min-max) 18 (0-100)% at mean (SD) age of 31 (4.3) years at last pregnancy. More women breastfed in Norway (83%) and for longer time [8.5 [1-42] months] compared to the Netherlands [63%, p = 0.03; 3.6 (0-14) months, p < 0.001]. Eighty-six percent of the women reported need for more information on pregnancy and breastfeeding in relation to FH. CONCLUSIONS: Young FH women lose years of treatment when discontinuing statins in relation to pregnancy and breastfeeding periods and should be closely followed up to minimize the duration of these off-statin periods. Whether these periods of interrupted treatment increase the cardiovascular risk in FH women needs to be further elucidated.

[12] *Cui T, Wang C, Zhu Q et al.* **Association between low-density cholesterol change and outcomes in acute ischemic stroke patients who underwent reperfusion therapy**. BMC neurology 2021; 21:360.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34530762

ABSTRACT
BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) can increase cardiovascular risk. However, the association between LDL-C change and functional outcomes in acute ischemic stroke (AIS) patients who underwent reperfusion therapy remains unclear. METHODS: Patients who received reperfusion therapy were consecutively enrolled. LDL-C measurement was conducted at the emergency department immediately after admission and during hospitalization. The change of LDL-C level (ΔLDL-C) was calculated by subtracting the lowest LDL-C among all measurements during hospitalization from the admission LDL-C. Poor functional outcome was defined as modified Rankin Scale (mRS) > 2 at 90 days. RESULTS: A total of 432 patients were enrolled (mean age 69.2 ± 13.5 years, 54.6 % males). The mean LDL-C level at admission was 2.55 ± 0.93 mmol/L. The median ΔLDL-C level was 0.43 mmol/L (IQR 0.08-0.94 mmol/L). A total of 263 (60.9 %) patients had poor functional outcomes at 90 days. There was no significant association between admission LDL-C level and functional outcome (OR 0.99, 95 % CI 0.77-1.27, p = 0.904). ΔLDL-C level was positively associated with poor functional outcome (OR 1.80, 95 % CI 1,12-2.91, p = 0.016). When patients were divided into tertiles according to ΔLDL-C, those in the upper tertile (T3, 0.80-3.98 mmol/L) were positively associated with poor functional outcomes compared to patients in the lower tertile (T1, -0.91-0.13 mmol/L) (OR 2.56, 95 % CI 1.22-5.36, p = 0.013). The risk of poor functional outcome increased significantly with ΔLDL-C tertile (P-trend = 0.010). CONCLUSIONS: In AIS patients who underwent reperfusion therapy, the decrease in LDL-C level during hospitalization was significantly associated with poor functional outcomes at 90 days.

[13] *Perovic Blagojevic IM, Vekic JZ, Macut DP et al.* **Overweight and obesity in polycystic ovary syndrome: association with inflammation, oxidative stress and dyslipidaemia**. The British journal of nutrition 2021:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34511137
ABSTRACT
Polycystic ovary syndrome (PCOS) is associated with altered lipid profile and increased small, dense LDL particles (sdLDL). Considering that paraoxonase 1 (PON1) is an antioxidative enzyme located on HDL particles, the aim of this study was to investigate the connection between oxidative stress (OS) and PON1 activity with lipoprotein subclasses in PCOS depending on obesity. In 115 PCOS patients, lipoprotein subclasses distributions were determined by gradient gel electrophoresis. OS status was assessed by total oxidative status (TOS), advanced oxidation protein products, malondialdehyde (MDA), prooxidant-antioxidant balance (PAB), total antioxidative status (TAS) and superoxide dismutase (SOD) and PON1 activity. Overweight/obese PCOS patients (n 55) had increased OS compared with normal weight patients (n 60). In addition, overweight/obese group had lower HDL size and higher proportion of HDL 3a subclasses ($P < 0{\cdot}05$). PAB was in negative correlation with HDL 2a ($P < 0{\cdot}001$), whereas MDA and SOD correlated positively with HDL 3 subclasses ($P < 0{\cdot}05$). Serum PON1 activity was positively associated with proportions of PON1 activity on HDL 2b ($P < 0{\cdot}05$) and 2a ($P < 0{\cdot}01$), but negatively with the proportion on HDL 3 particles ($P < 0{\cdot}01$). LDL B phenotype patients had increased TAS, SOD and PON1 activity on HDL 2b, but decreased PON1 activity on HDL 3 subclasses. OS is associated with altered lipoprotein subclasses distribution in PCOS patients. Obesity in PCOS affects the profile of HDL subclasses, reflected through the reduced proportion of PON1 activity on HDL 3 subclasses in the presence of sdLDL particles.

[14] *Choi D, Chen Q, Goonewardena SN et al.* **Efficacy of Statin Therapy in Patients with Hospital Admission for COVID-19**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34524566
ABSTRACT
PURPOSE: COVID-19 is characterized by dysfunctional immune responses and metabolic derangements, which in some, lead to multi-organ failure and death. Statins are foundational lipid-lowering therapeutics for cardiovascular disease and also possess beneficial immune-modulating properties. Because of these immune-modulating properties, some have suggested their use in COVID-19. We sought to investigate the association between statin use and mortality in patients hospitalized with COVID-19. METHODS: Five thousand three hundred seventy-five COVID-19 patients admitted to Mount Sinai Health System hospitals in New York between February 27, 2020, and December 3, 2020, were included in this analysis. Statin use was classified as either non-user, low-to-moderate-intensity user, or high-intensity user. Multivariate Cox proportional hazards models were used to evaluate in-hospital mortality rate. Considered covariates were age, sex, race, and comorbidities. RESULTS: Compared to non-statin users, both low-to-moderate-intensity (adjusted hazard ratio; aHR 0.62, 95% confidential intervals; CI 0.51-0.76) and high-intensity statin users (aHR 0.53, 95% CI 0.43-0.65) had a reduced risk of death. Subgroup analysis of 723 coronary artery disease patients showed decreased mortality among high-intensity statin users compared to non-users (aHR 0.51, 95% CI 0.36-0.71). CONCLUSIONS: Statin use in patients hospitalized with

COVID-19 was associated with a reduced in-hospital mortality. The protective effect of statin was greater in those with coronary artery disease. These data support continued use of statin therapy in hospitalized patients with COVID-19. Clinical trials are needed to prospectively determine if statin use is effective in lowering the mortality in COVID-19 and other viral infections.

[15] *Kim J, Kang D, Park H et al.* **Moderate-Intensity Statins Plus Ezetimibe vs. High-Intensity Statins After Coronary Revascularization: A Cohort Study**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34533691

ABSTRACT

PURPOSE: Whether moderate-intensity statins plus ezetimibe could be an alternative to high-intensity statins in patients with atherosclerotic cardiovascular disease is unclear. We compared the risk of adverse cardiovascular events in patients receiving moderate-intensity statins plus ezetimibe vs. high-intensity statins after a coronary revascularization procedure using data from a large cohort study. METHOD: Population-based cohort study using nationwide medical insurance data from Korea. Study participants (n = 20,070) underwent percutaneous coronary intervention or coronary artery bypass graft surgery between January 1, 2015, and December 31, 2016, and received moderate-intensity statins (atorvastatin 10-20 mg or rosuvastatin 5-10 mg) plus ezetimibe (n = 922) or high-intensity statins (atorvastatin 40-80 mg or rosuvastatin 20 mg; n = 19,148). The primary outcome was a composite of cardiovascular mortality, hospitalization for myocardial infarction (MI), hospitalization for stroke, or revascularization. RESULTS: At 12 months, the incidence rates of the primary outcome were 138.0 vs. 154.0 per 1000 person-years in the moderate-intensity stains plus ezetimibe and the high-intensity statins group, respectively. The fully adjusted hazard ratio [HR] for the primary outcome was 1.11 (95% confidence interval [CI] 0.86-1.42; p = 0.43). The multivariable-adjusted HR for a composite of cardiovascular mortality, hospitalization for MI, or hospitalization for stroke was 1.05 (95% CI 0.74-1.47; p = 0.80). During follow-up, the proportion of patients maintaining their initial lipid-lowering therapy was significantly higher in the moderate-intensity statins plus ezetimibe group than in the high-intensity statins group. CONCLUSIONS: Patients undergoing a coronary revascularization procedure who received moderate-intensity statins plus ezetimibe showed similar rates of major adverse cardiovascular events as patients who received high-intensity statins.

[16] *Azhar A, Binari LA, Joglekar K et al.* **Association between ezetimibe usage and hepatitis C RNA levels in uninfected kidney transplant recipients who received hepatitis C infected kidneys**. Clinical transplantation 2021:e14485.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34523744

ABSTRACT

Kidney transplantation (KT) from hepatitis C virus infected (HCV+) donors to HCV negative recipients achieve excellent graft function but have relatively higher rates of post-KT co-infections presumably due to prolonged HCV viremia in transmission-and-treat approach. Ezetimibe acts as an antagonist of Niemann-Pick C1-Like 1 receptor required for HCV entry and theoretically can reduce HCV viremia. However, no data is available to examine the role of ezetimibe as a bridge therapy between KT surgery and direct acting antiviral (DAA) initiation. A retrospective cohort study including 70 HCV+ to HCV negative KT recipients from Methodist University Hospital and Vanderbilt University Medical Center was performed to determine the association between ezetimibe usage and HCV viremia.

Twenty patients received ezetimibe daily while 50 patients did not. Primary outcome of study was mean HCV RNA level at 1-2 weeks post-KT and before initiation of DAA. Median (IQR) viral load (VL) in log copies/ml was one log lower in ezetimibe group versus non-ezetimibe group (4.1 [3.7-5.3] vs. 5.1 [4.4-5.5], P = .01), and highest VL was also lower in ezetimibe group (4.2 [3.7-5.4] vs. 5.4 [4.7-5.9], P = .006). We concluded that ezetimibe bridge therapy might be associated with reduction in HCV VL while waiting for DAA initiation in HCV+ to HCV negative KT recipients.

[17] *Hernandez P, Passi N, Modarressi T et al.* **Clinical Management of Hypertriglyceridemia in the Prevention of Cardiovascular Disease and Pancreatitis**. Current atherosclerosis reports 2021; 23:72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34515873
ABSTRACT
PURPOSE OF REVIEW: Hypertriglyceridemia (HTG) is common and is a significant contributor to atherosclerosis and pancreatitis risk. Specific HTG treatments have had variable success in reducing atherosclerosis risk. Novel therapies for severe HTG treatment and pancreatitis risk reduction are likely to be available soon. These novel therapies are expected to have broader applications for more moderate HTG and atherosclerosis risk reduction as well. RECENT FINDINGS: NHANES 2012 data has confirmed a reduction in average triglyceride (TG) levels in the US population. Dietary modification and weight reduction when needed remain the core treatment elements for all individuals with HTG, while statin therapy is a foundational pharmacologic care for atherosclerotic cardiovascular disease (ASCVD) event risk reduction. In addition, the REDUCE-IT study provides evidence for additional benefit from the use of high-dose icosapent ethyl (IPE) on top of background medical therapy in adults with moderate HTG and ASCVD or type 2 diabetes mellitus (T2D) and additional ASCVD risk factors. However, treatment with eicosapentaenoic acid (EPA) combined with docosahexanoic acid (DHA) did not reduce ASCVD in a similar population studied in the STRENGTH trial. Furthermore, novel therapeutics targeting PPAR-α, as well as ApoC-III and AngPTL3, effectively lower TG levels in individuals with moderate and severe HTG, respectively. These treatments may have applicability for reducing risk from ASCVD among individuals with chylomicronemia; in addition, ApoC-III and AngPTL3 treatments may have a role in treating individuals with the rare monogenic familial chylomicronemia syndrome (FCS) at risk for acute pancreatitis (AP). Residual ASCVD risk in individuals treated with contemporary care may be due in part to non-LDL lipid abnormalities including HTG. The findings from REDUCE-IT, but not STRENGTH, confirm that consumption of high-dose EPA may reduce ASCVD risk, while combination therapy of EPA plus DHA does not reduce ASCVD in a similar population. TG lowering likely reduces ASCVD risk in individuals with HTG, but ASCVD risk is multifactorial; the added benefit of IPE to contemporary preventive therapy is the consequence of differential non-TG biologic properties between the two fatty acids. Acute pancreatitis is more difficult to study prospectively since it is less common; however, TG lowering is likely critical for the care of at-risk individuals. Additional benefit from novel therapy that has an impact on this otherwise refractory condition is anticipated.

[18] *Barrios V, Soronen J, Carter AM, Anastassopoulou A*. **Lipid management across Europe in the real-world setting: a rapid evidence review**. Current medical research and opinion 2021:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34517739
ABSTRACT

OBJECTIVE: To provide a contemporary overview of recent real-world lipid-lowering therapy (LLT) practices and outcomes in patients with hypercholesterolemia/dyslipidemia at high/very high risk of atherosclerotic cardiovascular disease in Europe. METHODS: A structured literature review of recent (July 2015-July 2020) real-world studies reporting lipid management and outcomes was conducted using a rapid evidence synthesis. Outcomes included patient characteristics, LLT treatment practices, adherence and low-density lipoprotein cholesterol (LDL-C) goal attainment. RESULTS: Fifty-three real-world observational studies in high/very high risk patients were selected after screening 5664 records (n = 50 national [sample size range 38-237,279] and n = 3 multinational studies [sample size range 6648-8456]). Mean age ranged from 33 to 77 years; hypertension, diabetes and obesity were commonly reported comorbidities. Statins were the most common LLT; patients without familial hypercholesterolemia (FH) mostly received high or moderate intensity statins/LLT, while patients with FH mostly received high intensity statins/LLT. The proportion of patients receiving ezetimibe was low overall (ezetimibe + statin use in those with and without familial hypercholesterolemia [FH] range 5%-59% and 1%-22%, respectively). Overall, the use of proprotein convertase subtilisin/kexin 9 inhibitor (PCSK9i) therapy was limited. Adherence to LLT therapies was defined variably and ranged from 46%-92%. LDL-C goal attainment was suboptimal, irrespective of LLT (overall range in goal attainment with oral LLT was 2%-73% [FH: 2%-23%] and with PCSK9i was 20%-65%). CONCLUSIONS: LDL-C control is suboptimal and the available LLT armamentarium, most importantly combination therapy, is being underutilized in high/very high risk patients leading to inadequate management of cardiovascular risk.

[19] *Santoleri F, Romagnoli A, Costantini A*. **Adherence and persistence in the use of statins and ezetimibe over 8 years in a real-life study**. Current medical research and opinion 2021:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34515600

ABSTRACT

BACKGROUND: Adherence and persistence to treatment are crucial in statin therapy as they are synonymous with efficacy and quality of care. The aim of this study was the real-life assessment of adherence and persistence over eight years in treatment-naive patients receiving atorvastatin, lovastatin, simvastatin, pravastatin, ezetimibe. METHODS: Adherence to treatment was calculated using the 'proportion of days covered' method and persistence as the difference between the start and end of the therapy under study. RESULTS: Treatment adherence was consistently above 85% for all drugs under study in each year. Treatment persistence was shown to half halved already from the first year. CONCLUSION: Adherent patients had a higher persistence than non-adherent patients.

[20] *Kadoglou NPE, Velidakis N, Khattab E et al.* **The interplay between statins and adipokines. Is this another explanation of statins' 'pleiotropic' effects?** Cytokine 2021; 148:155698.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34537488

ABSTRACT

Statin therapy comprises an integral part of secondary and to a lesser extent of primary cardiovascular disease prevention. This is attributed not only to their lipid-lowering properties, but as well to a plethora of pleiotropic actions. Recently, the cytokines secreted by adipose tissue, the so-called adipokines, have been proved to play a critical role in various pathophysiological functions, among which inflammation and atherosclerosis development and vulnerability. The aim of this literature review was to summarize the effects of statins and the underlying mechanisms on the

circulating levels of the most common adipokines regulating atherosclerosis process, as a part of their pleiotropic function. Up to now, robust evidence implicates a significant statin-induced reduction of pro-inflammatory adipokines IL-6, TNF-a and visfatin. Weak evidence from limited, small and mostly non-randomized studies suggest increased levels of anti-inflammatory adipokines apelin, vaspin and omentin-1 after statin therapy. In the rest of most known adipokines, statins have shown either controversial (adiponectin, retinol binding protein-4 and fetuin-A) or negligible effects (leptin and resistin) on their circulating levels. Therefore, statins may favourably alter the balance of inflammatory/anti-inflammatory adipokines, implicating a novel atheroprotective mechanism. However, the interplay between statins and adipokines is still not fully elucidated and its potential clinical relevance is warranted.

[21] *Barre DE, Mizier-Barre KA*. **Selected 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors. A look into their use and potential in pre-diabetes and type 2 diabetes**. Endocr Regul 2021; 55:182-192.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34523296
ABSTRACT
Objectives. This review assesses the comparative safety and efficacy of selected 3-hydroxy-3-methylglutaric acid coenzyme A inhibitors (statins, cinnamic acids. 3-hydroxy-3-methyl glutaric acid) on the pre-onset type 2 diabetes (PT2D) and post-onset type 2 diabetes (T2D)-related cluster of seven features (central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation). Methods. Google scholar and PubMed were searched for statin*, flaxseed lignan complex (FLC), cinnamic acid (CA)*, and 3-hydroxy-3-methylglutaric acid (HMGA) in conjunction with each of PT2D, T2D and the cluster of seven. An introduction was followed by findings or absence thereof on the impacts of each of statins, FLC, CAs and HMGA on each member of the cluster of seven. Results. Pravastatin manages three features in PT2D, while a number of the statins improve five in T2D. FLC is negative in PT2D but controls four in T2D; it is not clear if the CAs and HMGA in FLC play a role in this success. CAs have potential in six and HMGA has potential in three of the cluster of seven though yet CAs and HMGA are untested in PT2D and T2D in humans. There are safety concerns with some statins and HMGA but FLC and CAs appear safe in the doses and durations tested. Conclusions. Selected statins, FLC, CAs and HMGA can manage or have a potential to manage at least three features of the cluster of seven. Most of the literature-stated concerns are with select statins but there are concerns (one actual and two potential) with HMGA.

[22] *Shim SY, Lee GB, Shim JS et al.* **Association between a family history of diabetes and carotid artery atherosclerosis in Korean adults**. Epidemiology and health 2021; 43:e2021049.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34525777
ABSTRACT
OBJECTIVES: Diabetes is a well-known risk factor for atherosclerosis, but the association between a family history of diabetes and atherosclerosis remains unknown. In this study, we assessed the association between a family history of diabetes and increased carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis, in a middle-aged Korean population. METHODS: This cross-sectional study included 3,974 community-dwelling adults (1,404 male and 2,570 female) aged 30-64 years from the Cardiovascular and Metabolic Diseases Etiology Research Center cohort. The presence of a family history of diabetes was assessed through face-to-face interviews using a

standardized questionnaire. Carotid IMT was assessed using B-mode ultrasonography, and increased IMT was defined as a value in the top quartile of the IMT values of all participants. Multivariate logistic regression was used to evaluate independent associations between a family history of diabetes and increased IMT. RESULTS: A family history of diabetes was significantly associated with increased carotid IMT (odds ratio, 1.23; 95% confidence interval, 1.03 to 1.48) after adjusting for sex; age; body mass index; systolic blood pressure; total cholesterol, triglyceride, and hemoglobin A1c levels; smoking; alcohol consumption; exercise; use of antidiabetic, antihypertensive, and antilipidemic drugs; and a family history of hypertension. The positive association remained significant after excluding participants with diabetes (odds ratio, 1.21; 95% confidence interval, 1.00 to 1.47). CONCLUSIONS: A family history of diabetes was positively associated with increased carotid IMT, even in participants without diabetes. Therefore, information on a family history of diabetes may help identify individuals at high risk of atherosclerotic cardiovascular disease.

[23] *Oyama K, Giugliano RP, Tang M et al.* **Effect of evolocumab on acute arterial events across all vascular territories : results from the FOURIER trial**. European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34537830
ABSTRACT
AIMS: We assessed the impact of the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor evolocumab on acute arterial events across all vascular territories, including coronary, cerebrovascular, and peripheral vascular beds, in patients with established atherosclerotic cardiovascular disease (ASCVD). METHODS AND RESULTS: In the FOURIER trial, 27 564 patients with stable ASCVD on statin therapy were randomly assigned to evolocumab or placebo. Acute arterial events were a composite of acute coronary (coronary heart disease death, myocardial infarction, or urgent coronary revascularization), cerebrovascular (ischaemic stroke, transient ischaemic attack, or urgent cerebral revascularization), or peripheral vascular (acute limb ischaemia, major amputation, or urgent peripheral revascularization) events. Of the 2210 first acute arterial events, 74% were coronary, 22% were cerebrovascular, and 4% were peripheral vascular. Evolocumab reduced first acute arterial events by 19% (hazard ratio [HR] 0.81 [95% confidence interval 0.74-0.88]; $P < 0.001$), with significant individual reductions in acute coronary (HR 0.83 [0.75-0.91]), cerebrovascular (HR 0.77 [0.65-0.92]), and peripheral vascular (HR 0.58 [0.38-0.88]) events. There were 3437 total events (first plus recurrent), with evolocumab reducing total events by 24% (incidence rate ratio 0.76 [0.69-0.85]). The magnitude of reduction in acute arterial events with evolocumab numerically increased over time, with a 16% reduction (HR 0.84 [0.75-0.95]) in the first year followed by a 24% reduction (HR 0.76 [0.67-0.85]) thereafter. CONCLUSION: The addition of the PCSK9 inhibitor evolocumab to statin therapy reduced acute arterial events across all vascular territories with a robust effect over time, indicating a pan-vascular impact of aggressive lipid-lowering therapy on these acute and clinically meaningful events. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01764633.

[24] *Osborne-Grinter M, Kwiecinski J, Doris M et al.* **Association of coronary artery calcium score with qualitatively and quantitatively assessed adverse plaque on coronary CT angiography in the SCOT-HEART trial**. European heart journal cardiovascular Imaging 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34529050
ABSTRACT

AIMS: Coronary artery calcification is a marker of cardiovascular risk, but its association with qualitatively and quantitatively assessed plaque subtypes is unknown. METHODS AND RESULTS: In this post-hoc analysis, computed tomography (CT) images and 5-year clinical outcomes were assessed in SCOT-HEART trial participants. Agatston coronary artery calcium score (CACS) was measured on non-contrast CT and was stratified as zero (0 Agatston units, AU), minimal (1-9 AU), low (10-99 AU), moderate (100-399 AU), high (400-999 AU), and very high (≥1000 AU). Adverse plaques were investigated by qualitative (visual categorization of positive remodelling, low-attenuation plaque, spotty calcification, and napkin ring sign) and quantitative (calcified, non-calcified, low-attenuation, and total plaque burden; Autoplaque) assessments. Of 1769 patients, 36% had a zero, 9% minimal, 20% low, 17% moderate, 10% high, and 8% very high CACS. Amongst patients with a zero CACS, 14% had non-obstructive disease, 2% had obstructive disease, 2% had visually assessed adverse plaques, and 13% had low-attenuation plaque burden >4%. Non-calcified and low-attenuation plaque burden increased between patients with zero, minimal, and low CACS ($P<0.001$), but there was no statistically significant difference between those with medium, high, and very high CACS. Myocardial infarction occurred in 41 patients, 10% of whom had zero CACS. CACS >1000 AU and low-attenuation plaque burden were the only predictors of myocardial infarction, independent of obstructive disease, and 10-year cardiovascular risk score. CONCLUSION: In patients with stable chest pain, zero CACS is associated with a good but not perfect prognosis, and CACS cannot rule out obstructive coronary artery disease, non-obstructive plaque, or adverse plaque phenotypes, including low-attenuation plaque.

[25] *Cheung B, Hwang J, Stolarczyk A et al.* **Case study of hypertriglyceridemia from COVID-19 Pfizer-BioNTech vaccination in a patient with familial hypercholesteremia**. European review for medical and pharmacological sciences 2021; 25:5525-5528.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34533798
ABSTRACT
The Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine is the first novel nucleoside-modified messenger ribonucleic acid (modRNA) vaccine to receive Emergency Use Authorization from the Food and Drug Administration in the United States. It is indicated to be used in patients ≥12 years-of-age as of May 25th, 2021, including populations with high atherosclerotic cardiovascular disease (ASCVD) burden. However, little is known about the potential impact this vaccine may have on serum lipoprotein levels in patients with familial hypercholesteremia (FH), who are predisposed to high ASCVD burden due to elevated low-density lipoprotein cholesterol (LDL-C). We present an interesting case where a patient with heterozygous FH (HeFH) and elevated triglycerides (TG)-controlled for years on medication and apheresis-experienced significantly elevated TG, one day after receiving his second Pfizer-BioNTech COVID-19 vaccine dose. It is not known whether this adverse event may be seen in other FH patients and may be worth assessing in such patients to determine the possibility of a rare adverse reaction from a COVID-19 vaccine.

[26] *Yildirim AM, Koca AO, Beyan E et al.* **Association of serum proprotein convertase Subtilisin/Kexin Type 9 (PCSK9) level with thyroid function disorders**. European review for medical and pharmacological sciences 2021; 25:5511-5517.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34533801
ABSTRACT

OBJECTIVE: We aimed at demonstrating the effect of thyroid function status on proprotein convertase subtilisin kexin type 9 (PCSK9) and determining the effect of thyroid hormones on lipid metabolism by comparing the PCSK9 levels of patients with subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism. PATIENTS AND METHODS: 124 patients with thyroid disorders, aged between 18 and 65 years, were included in this study. The participants were divided into 3 groups. Group 1 comprised 52 patients with subclinical hypothyroidism, Group 2 comprised 40 patients with overt hypothyroidism, and Group 3 comprised 32 patients with hyperthyroidism. In all of these groups, the thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, total cholesterol, fasting serum glucose, antithyroid peroxidase antibody, antithyroglobulin antibody, and PCSK9 levels were measured. RESULTS: No significant difference was found between the 3 groups in terms of age, gender, and body mass indices. Median PCSK9 measurements were 14.55 ng/mL in Group 1, 14.895 ng/mL in Group 2, and 9.775 ng/mL in Group 3. There was a significant difference in the PCSK9 levels between Group 1-Group 3 and Group 2-Group 3 ($p < 0.0001$ and $p < 0.0001$, respectively). A positive correlation between PCSK9 and the TSH levels ($r = 0.211$, $p = 0.019$), and a negative correlation ($r = -0,239$, $p = 0.009$ and $r = -, 0.218$, $p = 0.015$) between the fT3 and fT4 levels were found. CONCLUSIONS: The serum PCSK9 levels were shown to be associated with thyroid dysfunction. However, no relationship was observed between the serum PCSK9 level and thyroid autoantibody positivity, and obesity in this study.

[27] *Lin B, Yang J, Song Y et al.* **Exosomes and Atherogenesis**. Frontiers in cardiovascular medicine 2021; 8:738031.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34513963
ABSTRACT
Myocardial infarction and ischemic stroke are the leading causes of mortality worldwide. Atherosclerosis is their common pathological foundation. It is known that atherosclerosis is characterized by endothelial activation/injury, accumulation of inflammatory immune cells and lipid-rich foam cells, followed by the development of atherosclerotic plaque. Either from arterial vessel wall or blood circulation, endothelial cells, smooth muscle cells, macrophages, T-lymphocytes, B-lymphocytes, foam cells, and platelets have been considered to contribute to the pathogenesis of atherosclerosis. Exosomes, as natural nano-carriers and intercellular messengers, play a significant role in modulation of cell-to-cell communication. Under physiological or pathological conditions, exosomes can deliver their cargos including donor cell-specific proteins, lipids, and nucleic acids to target cells, which in turn affect the function of the target cells. In this review, we will describe the pathophysiological significance of various exosomes derived from different cell types associated with atherosclerosis, and the potential applications of exosome in clinical diagnosis and treatment.

[28] *Zeng CY, Xu J, Liu X, Lu YQ*. **Cardioprotective Roles of Endothelial Progenitor Cell-Derived Exosomes**. Frontiers in cardiovascular medicine 2021; 8:717536.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34513956
ABSTRACT
With the globally increasing prevalence, cardiovascular diseases (CVDs) have become the leading cause of mortality. The transplantation of endothelial progenitor cells (EPCs) holds a great promise due to their potential for vasculogenesis, angiogenesis, and protective cytokine release, whose

mechanisms are essential for CVD therapies. In reality, many investigations have attributed the therapeutic effects of EPC transplantation to the secretion of paracrine factors rather than the differentiation function. Of note, previous studies have suggested that EPCs could also release exosomes (diameter range of 30-150 nm), which carry various lipids and proteins and are abundant in microRNAs. The EPC-derived exosomes (EPC-EXs) were reported to act on the heart and blood vessels and were implicated in anti-inflammation, anti-oxidation, anti-apoptosis, the inhibition of endothelial-to-mesenchymal transition (EndMT), and cardiac fibrosis, as well as anti-vascular remodeling and angiogenesis, which were considered as protective effects against CVDs. In this review, we summarize the current knowledge on using EPC-EXs as therapeutic agents and provide a detailed description of their identified mechanisms of action to promote the prognosis of CVDs.

[29] *Shinohara K, Ikeda S, Enzan N et al.* **Efficacy of intensive lipid-lowering therapy with statins stratified by blood pressure levels in patients with type 2 diabetes mellitus and retinopathy: Insight from the EMPATHY study**. Hypertension research : official journal of the Japanese Society of Hypertension 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34526672
ABSTRACT
Intensive lipid-lowering therapy is recommended in individuals exhibiting type 2 diabetes mellitus (T2DM) with microvascular complications (as high-risk patients), even without known cardiovascular disease (CVD). However, evidence is insufficient to stratify the patients who would benefit from intensive therapy among them. Hypertension is a major risk factor, and uncontrolled blood pressure (BP) is associated with increased CVD risk. We evaluated the efficacy of intensive vs. standard statin therapy for primary CVD prevention among T2DM patients with retinopathy stratified by BP levels. We used the dataset from the EMPATHY study, which compared intensive statin therapy targeting low-density lipoprotein cholesterol (LDL-C) levels of <70 mg/dL and standard therapy targeting LDL-C levels ranging from ≥100 to <120 mg/dL in T2DM patients with retinopathy without known CVD. A total of 4980 patients were divided into BP ≥ 130/80 mmHg (systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg, n = 3335) and BP < 130/80 mmHg (n = 1645) subgroups by baseline BP levels. During the median follow-up of 36.8 months, 281 CVD events were observed. Consistent with previous studies, CVD events occurred more frequently in the BP ≥ 130/80 mmHg subgroup than in the BP < 130/80 mmHg subgroup (P < 0.001). In the BP ≥ 130/80 mmHg subgroup, intensive statin therapy was associated with lower CVD risk (HR 0.70, P = 0.015) than standard therapy after adjustment. No such association was observed in the BP < 130/80 mmHg subgroup. The interaction between BP subgroup and statin therapy was significant. In conclusion, intensive statin therapy targeting LDL-C < 70 mg/dL provided benefits in primary CVD prevention when compared with standard therapy among T2DM patients with retinopathy and BP ≥ 130/80 mmHg.

[30] *Tang Y, Hu L, Liu Y et al.* **Possible mechanisms of cholesterol elevation aggravating COVID-19**. International journal of medical sciences 2021; 18:3533-3543.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34522180
ABSTRACT
Importance: Despite the availability of a vaccine against the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), humans will have to live with this virus and the after-effects of the coronavirus disease 2019 (COVID-19) infection for a long time. Cholesterol plays an important role in

the infection and prognosis of SARS-CoV-2, and the study of its mechanism is of great significance not only for the treatment of COVID-19 but also for research on generic antiviral drugs. Observations: Cholesterol promotes the development of atherosclerosis by activating NLR family pyrin domain containing 3 (NLRP3), and the resulting inflammatory environment indirectly contributes to COVID-19 infection and subsequent deterioration. In in vitro studies, membrane cholesterol increased the number of viral entry sites on the host cell membrane and the number of angiotensin-converting enzyme 2 (ACE2) receptors in the membrane fusion site. Previous studies have shown that the fusion protein of the virus interacts with cholesterol, and the spike protein of SARS-CoV-2 also requires cholesterol to enter the host cells. Cholesterol in blood interacts with the spike protein to promote the entry of spike cells, wherein the scavenger receptor class B type 1 (SR-B1) plays an important role. Because of the cardiovascular protective effects of lipid-lowering therapy and the additional anti-inflammatory effects of lipid-lowering drugs, it is currently recommended to continue lipid-lowering therapy for patients with COVID-19, but the safety of extremely low LDL-C is questionable. Conclusions and Relevance: Cholesterol can indirectly increase the susceptibility of patients to SARS-CoV-2 and increase the risk of death from COVID-19, which are mediated by NLRP3 and atherosclerotic plaques, respectively. Cholesterol present in the host cell membrane, virus, and blood may also directly participate in the virus cell entry process, but the specific mechanism still needs further study. Patients with COVID-19 are recommended to continue lipid-lowering therapy.

[31] *Bhatia HS, Yeang C, Baruch A et al.* **PCSK9 Inhibition and Oxidized Phospholipids**. Journal of the American College of Cardiology 2021; 78:1288-1289.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34531030
ABSTRACT

[32] *Howard JP, Wood FA, Finegold JA et al.* **Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment**. Journal of the American College of Cardiology 2021; 78:1210-1222.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34531021
ABSTRACT
BACKGROUND: Most people who begin statins abandon them, most commonly because of side effects. OBJECTIVES: The purpose of this study was to assess daily symptom scores on statin, placebo, and no treatment in participants who had abandoned statins. METHODS: Participants received 12 1-month medication bottles, 4 containing atorvastatin 20 mg, 4 placebo, and 4 empty. We measured daily symptom intensity for each using an app (scale 1-100). We also measured the "nocebo" ratio: the ratio of symptoms induced by taking statin that was also induced by taking placebo. RESULTS: A total of 60 participants were randomized and 49 completed the 12-month protocol. Mean symptom score was 8.0 (95% CI: 4.7-11.3) in no-tablet months. It was higher in statin months (16.3; 95% CI: 13.0-19.6; $P < 0.001$), but also in placebo months (15.4; 95% CI: 12.1-18.7; $P < 0.001$), with no difference between the 2 ($P = 0.388$). The corresponding nocebo ratio was 0.90. In the individual-patient daily data, neither symptom intensity on starting (OR: 1.02; 95% CI: 0.98-1.06; $P = 0.28$) nor extent of symptom relief on stopping (OR: 1.01; 95% CI: 0.98-1.05; $P = 0.48$) distinguished between statin and placebo. Stopping was no more frequent for statin than placebo ($P = 0.173$), and subsequent symptom relief was similar between statin and placebo. At 6 months after the trial, 30 of 60 (50%) participants were back taking statins. CONCLUSIONS: The majority of symptoms caused by statin tablets were nocebo. Clinicians should not interpret symptom intensity or

timing of symptom onset or offset (on starting or stopping statin tablets) as indicating pharmacological causation, because the pattern is identical for placebo. (Self-Assessment Method for Statin Side-effects Or Nocebo [SAMSON]; NCT02668016).

[33] *Bai L, Scott MKD, Steinberg E et al.* **Computational drug repositioning of atorvastatin for ulcerative colitis**. J Am Med Inform Assoc 2021; 28:2325-2335.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34529084
ABSTRACT
OBJECTIVE: Ulcerative colitis (UC) is a chronic inflammatory disorder with limited effective therapeutic options for long-term treatment and disease maintenance. We hypothesized that a multi-cohort analysis of independent cohorts representing real-world heterogeneity of UC would identify a robust transcriptomic signature to improve identification of FDA-approved drugs that can be repurposed to treat patients with UC. MATERIALS AND METHODS: We performed a multi-cohort analysis of 272 colon biopsy transcriptome samples across 11 publicly available datasets to identify a robust UC disease gene signature. We compared the gene signature to in vitro transcriptomic profiles induced by 781 FDA-approved drugs to identify potential drug targets. We used a retrospective cohort study design modeled after a target trial to evaluate the protective effect of predicted drugs on colectomy risk in patients with UC from the Stanford Research Repository (STARR) database and Optum Clinformatics DataMart. RESULTS: Atorvastatin treatment had the highest inverse-correlation with the UC gene signature among non-oncolytic FDA-approved therapies. In both STARR (n = 827) and Optum (n = 7821), atorvastatin intake was significantly associated with a decreased risk of colectomy, a marker of treatment-refractory disease, compared to patients prescribed a comparator drug (STARR: HR = 0.47, P = .03; Optum: HR = 0.66, P = .03), irrespective of age and length of atorvastatin treatment. DISCUSSION & CONCLUSION: These findings suggest that atorvastatin may serve as a novel therapeutic option for ameliorating disease in patients with UC. Importantly, we provide a systematic framework for integrating publicly available heterogeneous molecular data with clinical data at a large scale to repurpose existing FDA-approved drugs for a wide range of human diseases.

[34] *Harada-Shiba M, Ako J, Hirayama A et al.* **Familial Hypercholesterolemia in Patients with Acute Coronary Syndrome: Genetic Insights from EXPLORE-J**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34526433
ABSTRACT
AIM: Genetic testing can provide a definitive diagnosis of familial hypercholesterolemia (FH). However, accessibility of genetic testing may be limited in certain countries where it is not considered "standard of care," including Japan. In addition, mutations responsible for FH cannot be identified in approximately 30% of patients. METHODS: EXPLORE-J is a multicenter, prospective, observational study of patients presenting with acute coronary syndrome (ACS). The genetic data were analyzed and adjudicated as pathogenic, indeterminate, or nondetectable pathogenic variant. RESULTS: Of 1,944 patients, 431 underwent genetic screening. Overall, most patients had nonpathogenic variants of LDLR, LDLRAP1, or PCSK9 (n=396, 91.9%). Of the 25 (5.8%) patients with pathogenic variants, variants of the LDLR gene and the PCSK9 gene were seen in 10 and 15 patients, respectively. Indeterminate variants were observed in 10 (2.3%) patients. Of the 431 patients, eight (1.9%) met the

criteria for a diagnosis of FH using the Japanese Atherosclerosis Society (JAS) 2017 guidelines. When genetic data were incorporated, 33 (7.7%) patients met the JAS guidelines. No patients with FH pathogenic variants satisfied the JAS clinical criteria for a diagnosis of FH. CONCLUSIONS: The results revealed a higher prevalence of genetic mutations of FH among Japanese patients with ACS and a low sensitivity of the FH diagnostic criteria of the JAS 2017 guidelines. These findings highlight the difficulties of FH diagnosis in patients with ACS in the acute phase and suggest the importance of genetic testing and family history.

[35] *Asakura M, Hibi K, Shimizu W et al.* **Design and rationale of the EVOCATION trial: A prospective, randomized, exploratory study comparing the effect of evolocumab on coronary microvascular function after percutaneous coronary intervention in patients with stable coronary artery disease**. J Cardiol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34518072
ABSTRACT
Percutaneous coronary intervention (PCI) is a standard treatment in patients with stable coronary artery disease (CAD); however, periprocedural myocardial infarction (PMI) remains a common complication of PCI. Aggressive lipid-lowering therapy with statin has shown to reduce the incidence of PMI by preventing coronary microvascular dysfunction. It is unclear whether evolocumab, a potent lipid-lowering agent, could diminish microvascular damage after PCI. The EVOCATION trial (jRCTs051180022) is a multicenter, randomized, open-label, active-controlled, parallel-group, exploratory, investigator-initiated clinical study to evaluate whether pretreatment with evolocumab could decrease the index of microvascular resistance (IMR) after PCI in patients with stable CAD. This study population consists of 100 patients with stable CAD who will undergo PCI and have high low-density lipoprotein cholesterol levels despite administration of maximum tolerated dose of statins for at least 2 weeks. Eligible patients are randomized in a 1:1 ratio to receive either evolocumab 140 mg every 2 weeks in addition to standard of care treatment or standard of care treatment only for 2-6 weeks before PCI. The primary endpoint is IMR after PCI. The EVOCATION trial will evaluate whether pretreatment with evolocumab reduces periprocedural microvascular damage in patients with stable CAD undergoing PCI.

[36] *Lu MM, Peng P, Hatsukami TS et al.* **A comparison of carotid atherosclerosis in symptomatic patients between 2002-2005 and 2012-2015 cohorts using multi-contrast magnetic resonance vessel wall imaging**. Journal of geriatric cardiology : JGC 2021; 18:623-630.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34527028
ABSTRACT
OBJECTIVE: To compare the morphological and compositional characteristics of carotid plaques in two cohorts (2002-2005 and 2012-2015) of Chinese patients using magnetic resonance vessel wall imaging. METHODS: Symptomatic patients with carotid atherosclerotic plaques who underwent carotid vessel wall magnetic resonance imaging between 2002-2005 and 2012-2015 were retrospectively recruited. Plaque morphology [including mean wall area, wall thickness, and maximum normalized wall index (NWI)] and composition [including calcification, intraplaque hemorrhage, and lipid-rich necrotic core (LRNC)] in symptomatic carotid arteries were evaluated and compared between patients in these two time periods. RESULTS: A total of 258 patients, including 129 patients in the 2002-2005 cohort and 129 patients in the 2012-2015 cohort, were recruited. Statin use

(49.6%vs. 32.6%, P = 0.004) and hypertension (76.0% vs. 62.8%, P = 0.015) were significantly more common in the 2012-2015 cohort than in the 2002-2005 cohort. Patients in the 2012-2015 cohort also exhibited significantly low plaque burden parameters (allP < 0.05), as well as a lower prevalence (68.2% vs. 89.9%, P < 0.001) and volume percentages of LRNC (11.2% ± 14.2% vs. 25.7% ± 17.7%, P < 0.001). These differences remained significant after adjustment for clinical factors. The differences in the volume percentages of LRNC also remained significant after an additional adjustment for maximum NWI (P < 0.001). CONCLUSIONS: Patients in the 2012-2015 cohort had a lower plaque burden and volume percentages of LRNC in symptomatic carotid arteries than those in the 2002-2005 cohort. These findings indicate that carotid plaques in the recent cohort had a lower severity and vulnerability.

[37] *Thompson AG, Talbot K, Turner MR*. **Higher blood high density lipoprotein and apolipoprotein A1 levels are associated with reduced risk of developing amyotrophic lateral sclerosis**. J Neurol Neurosurg Psychiatry 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34518331
ABSTRACT
BACKGROUND: Premorbid body mass index, physical activity, diabetes and cardiovascular disease have been associated with an altered risk of developing amyotrophic lateral sclerosis (ALS). There is evidence of shared genetic risk between ALS and lipid metabolism. A very large prospective longitudinal population cohort permits the study of a range of metabolic parameters and the risk of subsequent diagnosis of ALS. METHODS: The risk of subsequent ALS diagnosis in those enrolled prospectively to the UK Biobank (n=502 409) was examined in relation to baseline levels of blood high and low density lipoprotein (HDL, LDL), total cholesterol, total cholesterol:HDL ratio, apolipoproteins A1 and B (apoA1, apoB), triglycerides, glycated haemoglobin A1c (HbA1c) and creatinine, plus self-reported exercise and body mass index. RESULTS: Controlling for age and sex, higher HDL (HR 0.84, 95% CI 0.73 to 0.96, p=0.010) and apoA1 (HR 0.83, 95% CI 0.72 to 0.94, p=0.005) were associated with a reduced risk of ALS. Higher total cholesterol:HDL was associated with an increased risk of ALS (HR 1.17, 95% CI 1.05 to 1.31, p=0.006). In models incorporating multiple metabolic markers, higher LDL or apoB was associated with an increased risk of ALS, in addition to a lower risk with higher HDL or apoA. Coronary artery disease, cerebrovascular disease and increasing age were also associated with an increased risk of ALS. CONCLUSIONS: The association of HDL, apoA1 and LDL levels with risk of ALS contributes to an increasing body of evidence that the premorbid metabolic landscape may play a role in pathogenesis. Understanding the molecular basis for these changes will inform presymptomatic biomarker development and therapeutic targeting.

[38] *Gao F, Wang ZJ, Ma XT et al.* **Effect of alirocumab on coronary plaque in patients with coronary artery disease assessed by optical coherence tomography**. Lipids in health and disease 2021; 20:106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34511134
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have been demonstrated to produce significantly greater reduction in LDL cholesterol levels and cardiovascular events than standard statin therapy. However, evidence on the impact of PCSK9 inhibitors on coronary plaque composition and morphology is limited. METHODS: In this open-label randomized

study, eligible patients with intermediate coronary lesions and elevated LDL cholesterol values were randomized to either alirocumab 75 mg Q2W plus statin (atorvastatin 20 mg/day or rosuvastatin 10 mg/day) therapy or standard care. Optical coherence tomography (OCT) assessments for target lesions were obtained at baseline and at 36 weeks of follow-up. RESULTS: LDL cholesterol levels were significantly decreased in both the alirocumab and standard care arms, whereas the absolute reduction in LDL cholesterol was significantly greater in patients treated with alirocumab (1.72 ± 0.51 vs. 0.96 ± 0.59, P < 0.0001). Compared with standard care, the addition of alirocumab to statins was associated with significantly greater increases in minimum fibrous cap thickness (18.0 [10.8-29.2] μm vs 13.2 [7.4-18.6] μm; P = 0.029), greater increases in minimum lumen area (0.20[0.10-0.33] mm(2) vs 0.13 [0.12-0.24] mm(2); P = 0.006) and a greater diminution in maximum lipid arc (15.1° [7.8-24.5] vs. 8.4° [2.0-10.5]; P = 0.008). CONCLUSIONS: The addition of alirocumab to statins can not only provide additional LDL cholesterol lowering effects but also have a potential role in promoting a more stable plaque phenotype. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT04851769 . Registered 2 Mar 2019.

[39] *Hu H, Chen R, Hu Y et al.* **The LDLR c.501C>A is a disease-causing variant in familial hypercholesterolemia**. Lipids in health and disease 2021; 20:101.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34511120
ABSTRACT
BACKGROUND: As an autosomal dominant disorder, familial hypercholesterolemia (FH) is mainly attributed to disease-causing variants in the low-density lipoprotein receptor (LDLR) gene. The aim of this study was to explore the molecular mechanism of LDLR c.501C>A variant in FH and assess the efficacy of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor treatment for FH patients. METHODS: The whole-exome sequencing was performed on two families to identify disease-causing variants, which were verified by Sanger sequencing. The function of LDLR variant was further explored in HEK293 cells by Western Blot and confocal microscopy. Besides, the therapeutic effects of PCSK9 inhibitor treatment for two probands were assessed for 3 months. RESULTS: All members of the two families with the LDLR c.501C>A variant showed high levels of LDLC. The relationship between the clinical phenotype and LDLR variants was confirmed in the current study. Both in silico and in vitro analyses showed that LDLR c.501C>A variant decreased LDLR expression and LDL uptake. PCSK9 inhibitor treatment lowered the lipid level in proband 1 by 24.91%. However, the treatment was ineffective for proband 2. A follow-up study revealed that the PCSK9 inhibitor treatment had low ability of lipid-lowering effect in the patients. CONCLUSIONS: LDLR c.501C>A variant might be pathogenic for FH. The PCSK9 inhibitor therapy is not a highly effective option for treatment of FH patients with LDLR c.501C>A variant.

[40] *Kawamoto R, Kikuchi A, Akase T et al.* **Low density lipoprotein cholesterol and all-cause mortality rate: findings from a study on Japanese community-dwelling persons**. Lipids in health and disease 2021; 20:105.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34511127
ABSTRACT
BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) independently impacts aging-related health outcomes and plays a critical role in cardiovascular diseases (CVDs). However, there are limited predictive data on all-cause mortality, especially for the Japanese community population. In

this study, it was examined whether LDL-C is related to survival prognosis based on 7 or 10 years of follow-up. METHODS: Participants included 1610 men (63 ± 14 years old) and 2074 women (65 ± 12 years old) who participated in the Nomura cohort study conducted in 2002 (first cohort) and 2014 (second cohort) and who continued throughout the follow-up periods (follow-up rates: 94.8 and 98.0%). Adjusted relative risk estimates were obtained for all-cause mortality using a basic resident register. The data were analyzed by a Cox regression with the time variable defined as the length between the age at the time of recruitment and that at the end of the study (the age of death or censoring), and risk factors including gender, age, body mass index (BMI), presence of diabetes, lipid levels, renal function, serum uric acid levels, blood pressure, and history of smoking, drinking, and CVD. RESULTS: Of the 3684 participants, 326 (8.8%) were confirmed to be deceased. Of these, 180 were men (11.2% of all men) and 146 were women (7.0% of all women). Lower LDL-C levels, gender (male), older age, BMI under 18.5 kg/m(2), and the presence of diabetes were significant predictors for all-cause mortality. Compared with individuals with LDL-C levels of 144 mg/dL or higher, the multivariable-adjusted Hazard ratio (and 95% confidence interval) for all-cause mortality was 2.54 (1.58-4.07) for those with LDL-C levels below 70 mg/dL, 1.71 (1.15-2.54) for those with LDL-C levels between 70 mg/dL and 92 mg/dL, and 1.21 (0.87-1.68) for those with LDL-C levels between 93 mg/dL and 143 mg/dL. This association was particularly significant among participants who were male (P for interaction = 0.039) and had CKD (P for interaction = 0.015). CONCLUSIONS: There is an inverse relationship between LDL-C levels and the risk of all-cause mortality, and this association is statistically significant.

[41] *Grundy SM, Stone NJ, Blumenthal RS et al.* **High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better**. Mayo Clinic proceedings 2021; 96:2660-2670.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34531060

ABSTRACT

Review of the US and European literature indicates that most patients at high risk for atherosclerotic cardiovascular disease (ASCVD are not treated with high-intensity statins, despite strong clinical-trial evidence of maximal statin benefit. High-intensity statins are recommended for 2 categories of patients: those with ASCVD (secondary prevention) and high-risk patients without clinical ASCVD. Most patients with ASCVD are candidates for high-intensity statins, with a goal for low-density lipoprotein cholesterol reduction of 50% or greater. A subgroup of patients with ASCVD are at very high risk and can benefit by the addition of nonstatin drugs (ezetimibe with or without bile acid sequestrant or bempedoic acid and/or a proprotein convertase subtilisin/kexin type 9 inhibitor). High-risk primary prevention patients are those with severe hypercholesterolemia, diabetes with associated risk factors, and patients aged 40 to 75 years with a 10-year risk for ASCVD of 20% or greater. In patients with a 10-year risk of 7.5% to less than 20%, coronary artery calcium scoring is an option; if the coronary artery calcium score is 300 or more Agatston units, the patient can be up-classified to high risk. If high-intensity statin treatment is not tolerated in high-risk patients, a reasonable approach is to combine a moderate-intensity statin with ezetimibe. In very high-risk patients, proprotein convertase subtilisin/kexin type 9 inhibitors lower low-density lipoprotein cholesterol levels substantially and hence reduce risk as well.

[42] *Trias F, Pintó X, Corbella E et al.* **Differences in the diabetogenic effect of statins in patients with prediabetes. The PRELIPID study**. Medicina clinica 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34517987

ABSTRACT

INTRODUCTION: Statins are used with the understanding that a slightly increased risk of diabetes is outweighed by their cardiovascular benefits. However, it may be necessary to reconsider whether statin therapy really increase this risk mainly in the population with prediabetes. METHODS: A multicenter, cross-sectional, observational study was conducted to assess the relationship between statin therapy and glucose metabolism in 407 patients aged 63.1 years (11SD) diagnosed with dyslipidemia and prediabetes treated in specialized lipid clinics in Spain. RESULTS: Significant differences were found in HbA1c values among treatment groups (p=0.015). Patients treated with pitavastatin (1-4mg/day) showed the lowest HbA1c levels, with significant differences compared to patients treated with atorvastatin 40-80mg/day (p=0.016) and simvastatin 10-40mg/day (p=0.036). By contrast, patients treated with atorvastatin 40-80mg/day showed the highest HbA1c levels compared to those receiving atorvastatin 10-20mg/day (p=0.003), pitavastatin 1-4mg/day (p=0.016), pravastatin 20-40mg/day (p=0.027), rosuvastatin 5-10mg/day (p=0.043), and no statin treatment (p=0.004). Patients treated with simvastatin 10-40mg/day also had higher values than those treated with atorvastatin 10-20mg/day (p=0.016) and pitavastatin 1-4mg/day (p=0.036) or with no statin treatment (p=0.018). CONCLUSIONS: This study suggests that there are differences in the diabetogenic effect of statins. Simvastatin and high doses of atorvastatin may be associated with greater impairment in glucose metabolism than pitavastatin and other statins with less lipid-lowering potency such as pravastatin.

[43] *Jamialahmadi T, Baratzadeh F, Reiner Ž et al.* **The Effects of Statin Dose, Lipophilicity, and Combination of Statins plus Ezetimibe on Circulating Oxidized Low-Density Lipoprotein Levels: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Mediators of inflammation 2021; 2021:9661752.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34526854

ABSTRACT

BACKGROUND: Elevated plasma low-density lipoprotein cholesterol (LDL-C) is the main risk factor for atherosclerotic cardiovascular disease (ASCVD). Statins are the drugs of choice for decreasing LDL-C and are used for the prevention and management of ASCVD. Guidelines recommend that subjects with high and very high ASCVD risk should be treated with high-intensity statins or a combination of high-intensity statins and ezetimibe. The lipophilicity or hydrophilicity (solubility) of statins is considered to be important for at least some of their LDL-C lowering independent pleiotropic effects. Oxidative modification of LDL (ox-LDL) is considered to be the most important atherogenic modification of LDL and is supposed to play a crucial role in atherogenesis and ASCVD outcomes. OBJECTIVE: The aim of this systematic review and meta-analysis was to find out what are the effects of statin intensity, lipophilicity, and combination of statins plus ezetimibe on ox-LDL. METHODS: PubMed, Scopus, Embase, and Web of Science were searched from inception to February 5, 2021, for randomized controlled trials (RCTs). Two independent and blinded authors evaluated eligibility by screening the titles and abstracts of the studies. Risk of bias in the studies included in this meta-analysis was evaluated according to the Cochrane instructions. Meta-analysis was performed using Comprehensive Meta-Analysis (CMA) V2 software. Evaluation of funnel plot, Begg's rank correlation, and Egger's weighted regression tests were used to assess the presence of publication bias. RESULTS: Among the 1427 published studies identified by a systematic databases search, 20 RCTs

were finally included in the systematic review and meta-analysis. A total of 1874 patients are included in this meta-analysis. This meta-analysis suggests that high-intensity statin treatment is associated with a significant decrease in circulating concentrations of ox-LDL when compared with low-to-moderate treatment (SMD: -0.675, 95% CI: -0.994, -0.357, p < 0.001; I (2): 55.93%). There was no difference concerning ox-LDL concentration between treatments with hydrophilic and lipophilic statins (SMD: -0.129, 95% CI: -0.330, -0.071, p = 0.206; I (2): 45.3%), but there was a significant reduction in circulating concentrations of ox-LDL associated with statin plus ezetimibe combination therapy when compared with statin monotherapy (SMD: -0.220, 95% CI: -0.369, -0.071, p = 0.004; I (2): 0%). CONCLUSION: High-dose statin or combination of statins with ezetmibe reduces plasma ox-LDL in comparison low-to-moderate intensity statin therapy alone. Statin lipophilicity is not associated with reduction in ox-LDL plasma concentrations.

[44] *Corrao G, Rea F, Mancia G et al.* **Cost-effectiveness of the adherence with recommendations for clinical monitoring of patients with diabetes**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021; 31:3111-3121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34531108
ABSTRACT
BACKGROUND AND AIMS: To validate a set of indicators for monitoring the quality of care of patients with diabetes in 'real-life' practice through its relationship with measurable clinical outcomes and healthcare costs. METHODS AND RESULTS: A population-based cohort study was carried out by including the 20,635 patients, residents in the Lombardy Region (Italy), who in the year 2012 were newly taken-in-care for diabetes. Adherence with clinical recommendations (i.e., controls for glycated haemoglobin, lipid profile, urine albumin excretion and serum creatinine) was recorded during the first year after the patient was taken-in-care, and categorized according whether he/she complied with none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) the recommendations, respectively denoted as poor, intermediate and high adherence. Short- and long-term complications of diabetes, and healthcare cost incurred by the National Health Service, were assessed during follow-up. Compared with patients with poor adherence, those with intermediate and high adherence respectively showed (i) a delay in outcome occurrence of 13 days (95% CI, -2 to 27) and 23 days (9-38), and (ii) a lower healthcare cost of 54 € and 77 €. In average, a gain of 18 Euros and 15 Euros for each day free from diabetic complication by increasing adherence respectively from poor to intermediate and from poor to high were observed. CONCLUSION: Close control of patients with diabetes through regular clinical examinations must be considered the cornerstone of national guidance, national audits, and quality improvement incentive schemes.

[45] *Wu AJ, Aris IM, Rifas-Shiman SL et al.* **Associations of midchildhood to early adolescence central adiposity gain with cardiometabolic health in early adolescence**. Obesity (Silver Spring, Md.) 2021; 29:1882-1891.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34529343
ABSTRACT
OBJECTIVE: This study examined the associations of central adiposity gain from midchildhood to early adolescence with cardiometabolic health markers in early adolescence. METHODS: A total of 620 participants were studied in Project Viva. In midchildhood (mean age = 7.8 years) and early adolescence (12.9 years), waist circumference and dual-energy x-ray absorptiometry-measured

visceral adipose tissue, subcutaneous abdominal adipose tissue, and trunk fat were obtained. Central adiposity gain was calculated as change per year between visits. Cardiometabolic health markers, including blood pressure, lipids, markers of insulin resistance, inflammation, and adipokines, were collected in early adolescence. RESULTS: Greater waist circumference gain was associated with higher log triglycerides (β 0.07 mg/dL; 95% CI: 0.02-0.13), log alanine aminotransferase (0.07 U/L; 95% CI: 0.03-0.12), log high-sensitivity C-reactive protein (0.43 mg/L; 95% CI: 0.28-0.58), and other cardiometabolic markers in early adolescence. Directly measured central adiposity gains were associated with higher systolic blood pressure z score in early adolescence (visceral adipose tissue [0.13 SD units; 95% CI: 0.04-0.23], subcutaneous abdominal adipose tissue [0.18 SD units; 95% CI: 0.04-0.31], and trunk fat [0.21 SD units; 95% CI: 0.06-0.36]). These associations were independent of baseline and change in total adiposity from midchildhood to early adolescence. CONCLUSIONS: Monitoring central adiposity gain may enable identification and intervention in children vulnerable to developing cardiometabolic health risks.

[46] *Squier K, Scott A, Hunt MA et al.* **The effects of cholesterol accumulation on Achilles tendon biomechanics: A cross-sectional study**. PloS one 2021; 16:e0257269.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34529718

ABSTRACT

Familial hypercholesterolemia, a common genetic metabolic disorder characterized by high cholesterol levels, is involved in the development of atherosclerosis and other preventable diseases. Familial hypercholesterolemia can also cause tendinous abnormalities, such as thickening and xanthoma (tendon lipid accumulation) in the Achilles, which may impede tendon biomechanics. The objective of this study was to investigate the effect of cholesterol accumulation on the biomechanical performance of Achilles tendons, in vivo. 16 participants (10 men, 6 women; 37±6 years) with familial hypercholesterolemia, diagnosed with tendon xanthoma, and 16 controls (10 men, 6 women; 36±7 years) underwent Achilles biomechanical assessment. Achilles biomechanical data was obtained during preferred pace, shod, walking by analysis of lower limb kinematics and kinetics utilizing 3D motion capture and an instrumented treadmill. Gastrocnemius medialis muscle-tendon junction displacement was imaged using ultrasonography. Achilles stiffness, hysteresis, strain and force were calculated from displacement-force data acquired during loading cycles, and tested for statistical differences using one-way ANOVA. Statistical parametric mapping was used to examine group differences in temporal data. Participants with familial hypercholesterolemia displayed lower Achilles stiffness compared to the control group (familial hypercholesterolemia group: 87±20 N/mm; controls: 111±18 N/mm; p = 0.001), which appeared to be linked to Achilles loading rate rather than an increased strain (FH: 5.27±1.2%; controls: 4.95±0.9%; p = 0.413). We found different Achilles loading patterns in the familial hypercholesterolemia group, which were traced to differences in the centre of pressure progression that affected ankle moment. This finding may indicate that individuals with familial hypercholesterolemia use different Achilles loading strategies. Participants with familial hypercholesterolemia also demonstrated significantly greater Achilles hysteresis than the control group (familial hypercholesterolemia: 57.5±7.3%; controls: 43.8±10%; p<0.001), suggesting that walking may require a greater metabolic cost. Our results indicate that cholesterol accumulation could contribute to reduced Achilles function, while potentially increasing the chance of injury.

[47] *Handhle A, Viljoen A, Wierzbicki AS*. **Elevated Lipoprotein(a): Background, Current Insights and Future Potential Therapies**. Vascular health and risk management 2021; 17:527-542.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34526771

ABSTRACT

Lipoprotein(a) forms a subfraction of the lipid profile and is characterized by the addition of apolipprotein(a) (apo(a)) to apoB100 derived particles. Its levels are mostly genetically determined inversely related to the number of protein domain (kringle) repeats in apo(a). In epidemiological studies, it shows consistent association with cardiovascular disease (CVD) and most recently with extent of aortic stenosis. Issues with standardizing the measurement of Lp(a) are being resolved and consensus statements favor its measurement in patients at high risk of, or with family histories of CVD events. Major lipid-lowering therapies such as statin, fibrates, and ezetimibe have little effect on Lp(a) levels. Therapies such as niacin or cholesterol ester transfer protein (CETP) inhibitors lower Lp(a) as well as reducing other lipid-related risk factors but have failed to clearly reduce CVD events. Proprotein convertase subtilisin kexin-9 (PCSK9) inhibitors reduce cholesterol and Lp(a) as well as reducing CVD events. New antisense therapies specifically targeting apo(a) and hence Lp(a) have greater and more specific effects and will help clarify the extent to which intervention in Lp(a) levels will reduce CVD events.