[1] *Ortega-Rivera OA, Pokorski JK, Steinmetz NF*. **A single-dose, implant-based, trivalent virus-like particle vaccine against "cholesterol checkpoint" proteins**. Adv Ther (Weinh) 2021; 4.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34541299
ABSTRACT
Cardiovascular disease is the number one cause of death globally. Lowering cholesterol levels in plasma is the mainstay therapy; however lifelong treatment and adverse effects call for improved therapeutic interventions. We developed a trivalent vaccine candidate targeting proprotein convertase subtilisin/kexin-9 (PCSK9), apolipoprotein B (ApoB), and cholesteryl ester transfer protein (CETP). Vaccine candidates were developed using bacteriophage Qβ-based virus-like particles (VLPs) displaying antigens of PCKS9, ApoB, and CETP, respectively. Vaccine candidate mixtures were formulated as slow-release PLGA:VLP implants using hot-melt extrusion. The delivery of the trivalent vaccine candidate via the implant produced antibodies against the cholesterol checkpoint proteins at levels comparable to a three-dose injection schedule with soluble mixtures. The reduction in PCSK9 and ApoB levels in plasma, inhibition of CETP (in vitro), and total plasma cholesterol decrease was achieved. All-together, we present a platform technology for a single-dose multi-target vaccination platform targeting cholesterol checkpoint proteins.

[2] *Li Z, Cao J, Bai X et al.* **Utility of Dual-Layer Spectral-Detector CTA to Characterize Carotid Atherosclerotic Plaque Components: An Imaging-Histopathology Comparison in Patients Undergoing Endarterectomy**. AJR Am J Roentgenol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34549604
ABSTRACT
Background: The composition of non-calcified portions of carotid atherosclerotic plaque represents an important marker of plaque vulnerability and ischemia risk. Objective: To assess the utility of dual-layer spectral-detector CTA (DLCTA) parameters for carotid plaque component characterization, using histologic results from carotid endarterectomy (CEA) as reference. Methods: Seven patients (5 male, 2 female; 61.6±8.5 years old) with carotid plaque awaiting CEA were prospectively enrolled and underwent preoperative supra-aortic DLCTA. A neuroradiologist and pathologist performed joint slice-by-slice review of histologic slices of resected plaques and CTA images. ROIs were placed on non-calcified components [lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH), fibrous tissue, loose matrix (LM)] on CTA images in comparison with corresponding histologic slices using anatomic landmarks. For each ROI, attenuation was recorded for polyenergetic images (CTPI) and virtual monoenergetic images with keV ranging from 40-140 (CT40-140keV); attenuation spectrum curve slope was calculated; and Z-effective value (representing effective atomic number) was recorded. DLCTA parameters were compared among plaque components. Results: Seven plaques with a total of 65 slices and 364 ROIs (159 fibrous tissue, 96 LRNC, 86 loose matrix, 23 IPH) were analyzed. All parameters (CTPI, CT40-140keV, slope from 40 to 140 keV, Z-effective value) showed significant differences between LRNC and the other components (all p<.001). For example, mean CTPI was 37.1±15.1 HU for LRNC, 58.4±21.6 HU for IPH, 69.7±20.5 HU for fibrous tissue, and 69.6±19.6 HU for loose matrix; mean CT40keV was 28.1±36.7 HU for LRNC, 87.5±48.9 HU for IPH, 106.3±47.5 HU for fibrous tissue, and 102.6±48.0 HU for loose matrix. AUC for differentiating LRNC from other components was highest (0.945) for CT40kev and decreased with higher keV; AUC for CTPI was 0.908. CT40kev also had highest accuracy (90.4%); at cutoff of 55.7 HU, CT40kev had 88.5% sensitivity and 90.9% specificity. For differentiating IPH from fibrous tissue and loose matrix, AUC

was highest at 0.652 for CTPI and 0.645 for CT40kev. Conclusion: DLCTA showed strong performance in differentiating LRNC from other non-calcified plaque components; CT40kev had highest accuracy, outperforming conventional polyenergetic images. Clinical Impact: DLCTA parameters may help characterize carotid plaque composition as a marker of vulnerable plaque and ischemia risk.

[3] *Volis I, Hislop E, Saliba W, Zafrir B*. **A safety and clinical efficacy analysis of PCSK9 monoclonal antibodies in patients with markedly elevated creatine phosphokinase levels**. Am J Blood Res 2021; 11:399-404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34540348

ABSTRACT

INTRODUCTION: PCSK9 inhibitors (PCSK9i) are often used in statin-intolerant patients, aiming to reduce low-density lipoprotein cholesterol (LDL-C). Along with the growing experience with their use, there is a lack of evidence regarding the safety, tolerability, and clinical utility of PCSK9i in patients with markedly elevated creatine phosphokinase (CPK) levels. METHODS: We screened a comprehensive HMO database for patients treated with PCSK9i (Jan 2016-Dec 2019), in whom elevated CPK levels (>1,000 U/L) were documented prior to the initiation of therapy. Treatment plans, adherence, and the levels of CPK and LDL-C were analyzed. RESULTS: Of the 1,600 patients initiating treatment with PCSK9i, 26 had prior CPK values >1,000 U/L [median (IQR): 3,687 (1,876-8,344) U/L]. All 26 patients were previously treated with statins, which presumably resulted in adverse effects (myalgia in 24, and rhabdomyolysis in 5 patients) therefore mandating their discontinuation. Concomitant secondary factors for CPK elevation were present in 11 patients, and included renal failure, rheumatoid disorders, hypothyroidism, intensive exercise, proteinuria and genetic muscular disease. Of the 26 patients treated with PCSK9i, alirocumab was administered to 12 patients, and evolocumab to 14. Following the initiation of treatment with either drug, 24 patients (92%) demonstrated a reduction in CPK of >50%, and in 12 (46%) CPK levels have returned to normal values. With regard to treatment goals, 17 patients (65%) have achieved an LDL-C level of <70 mg/dL, and 12 (46%) have reached a level of <55 mg/dL. No serious adverse reactions were documented, and only 2 patients discontinued the treatment (not due to muscle symptoms or CPK elevation). CONCLUSIONS: PCSK9i constitute a safe, tolerable, and effective treatment for hyperlipidemia in patients with markedly elevated CPK. While statin intolerance is a major cause for CPK elevation, concomitant etiologies for increased CPK values were rather common.

[4] *Henning RJ*. **Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity**. American journal of cardiovascular disease 2021; 11:504-529.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34548951

ABSTRACT

Two billion people worldwide older than 18 years of age, or approximately 30% of the world population, are overweight or obese. In addition, more than 43 million children under the age of 5 are overweight or obese. Among the population in the United States aged 20 and greater, 32.8 percent are overweight and 39.8 percent are obese. Blacks in the United States have the highest age-adjusted prevalence of obesity (49.6%), followed by Hispanics (44.8%), whites (42.2%) and Asians (17.4%). The impact of being overweight or obese on the US economy exceeds $1.7 trillion dollars,

which is equivalent to approximately eight percent of the nation's gross domestic product. Obesity causes chronic inflammation that contributes to atherosclerosis and causes >3.4 million deaths/year. The pathophysiologic mechanisms in obesity that contribute to inflammation and atherosclerosis include activation of adipokines/cytokines and increases in aldosterone in the circulation. The adipokines leptin, resistin, IL-6, and monocyte chemoattractant protein activate and chemoattract monocytes/macrophages into adipose tissue that promote visceral adipose and systemic tissue inflammation, oxidative stress, abnormal lipid metabolism, insulin resistance, endothelial dysfunction, and hypercoagulability that contribute to atherosclerosis. In addition in obesity, the adipokines/cytokines IL-1β, IL-18, and TNF are activated and cause endothelial cell dysfunction and hyperpermeability of vascular endothelial junctions. Increased aldosterone in the circulation not only expands the blood volume but also promotes platelet aggregation, vascular endothelial dysfunction, thrombosis, and fibrosis. In order to reduce obesity and obesity-induced inflammation, therapies including diet, medications, and bariatric surgery are discussed that should be considered in patients with BMIs>35-40 kg/m(2) if diet and lifestyle interventions fail to achieve weight loss. In addition, antihypertensive therapy, plasma lipid reduction and glucose lowering therapy should be prescribed in obese patients with hypertension, a 10-year CVD risk >7.5%, or prediabetes or diabetes.

[5] *Schiele F, Pérez de Isla L, Arca M, Vlachopoulos C*. **Is it Time for Single-Pill Combinations in Dyslipidemia?** American journal of cardiovascular drugs : drugs, devices, and other interventions 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34549371
ABSTRACT
Despite the availability of lipid-lowering therapies (LLTs) that are safe and effective, the overall rate of low-density lipoprotein cholesterol (LDL-C) control at a population level in real-life studies is low. Higher-intensity treatment, earlier intervention, and longer-term treatment have all been shown to improve outcomes. However, in clinical practice, actual exposure to LLT is a product of the duration and intensity of, and adherence to, the treatment. To increase exposure to LLTs, the European Society of Cardiology guidelines recommended a stepwise optimization of LLTs by increasing statin intensity to the maximally tolerated dose, with subsequent addition of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Evidence from randomized controlled trials performed in a range of patients suggested that adding ezetimibe to statins rather than doubling the statin dose resulted in significantly more patients at LDL-C goal and significantly fewer patients discontinuing treatment because of adverse events. In addition, data showed that combination treatments effectively increased exposure to LLT. Despite these data and recommendations, optimization of LLT is often limited to increasing statin dose. Therapeutic inertia and poor treatment adherence are significant and prevalent barriers to increasing treatment exposure. They are known to be influenced by pill burden and complexity of treatment. Single-pill combinations provide a strategic approach that supports the intensification of treatment without increasing pill burden or treatment complexity. Single-pill combinations, compared with free associations, have been shown to increase the adherence to LLT and the percentage of patients at LDL-C goal.

[6] *Sacheck JM, Huang Q, Van Rompay MI et al.* **Vitamin D supplementation and cardiometabolic risk factors among diverse schoolchildren: a randomized clinical trial**. The American journal of clinical nutrition 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550329

ABSTRACT

BACKGROUND: There remains a lack of evidence demonstrating a potential relationship between vitamin D and cardiometabolic risk among children. OBJECTIVE: We examined the effect of three different doses of vitamin D on cardiometabolic risk factors among children at risk for deficiency. DESIGN: Racially diverse schoolchildren aged 8-15 years were randomized in a double-blind fashion to supplementation with 600, 1000, or 2000 IU/day for 6 months. Changes in high density lipoprotein cholesterol (HDLc), triglycerides, low-density lipoprotein cholesterol (LDLc), total cholesterol and blood glucose over 6 months and at 12-months (6 months post-supplementation) were assessed. Subgroup analyses were also performed by weight status and race. RESULTS: Among 604 children, 40.9% were vitamin D inadequate at baseline (<20 ng/mL; mean 22.0 ± 6.8 ng/mL), 46.4% were overweight/obese, and 60.9% had one or more sub-optimal blood lipids or glucose. Over 6 months, serum 25(OH)D increased in all three dose groups from baseline (mean change 4.4 ± 0.6, 5.7 ± 0.7, and 10.7 ± 0.6 ng/ml for 600, 1000, and 2000 IU/day, respectively; $P < 0.001$). While HDLc and triglycerides increased in the 600 IU group ($P = 0.002$ and $P = 0.02$), LDLc and total cholesterol decreased across dose groups. At 6-months post-supplementation, HDLc remained elevated in the 600 and 1000 IU groups ($P < 0.001$ and $P = 0.02$) while triglycerides remained elevated in the 1000 and 2000 IU groups ($P = 0.04$ and $P = 0.006$). The suppression of LDLc and total cholesterol persisted in the 2000 IU group only ($P = 0.04$ and $P < 0.001$). There were no significant changes in blood glucose and similar responses were observed overall by weight status and racial groups across doses. CONCLUSIONS: Vitamin D supplementation demonstrated generally positive effects on HDLc, LDLc and cholesterol, especially at the lower dose of 600 IU, with several significant changes persisting during the post-supplementation period. Increases in triglycerides across dose groups may be due to natural changes during adolescence warranting further study. TRIAL REGISTRATION: ClinicalTrials.gov, NCT01537809.

[7] *Wu B, Wang Y, Li W et al.* **The effect of rosuvastatin on cardiogenic cerebral infarction**. American journal of translational research 2021; 13:9444-9450.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34540064

ABSTRACT

OBJECTIVE: To investigate the effect of rosuvastatin on cardiogenic cerebral infarction and its related effects on patients' neurological function, lipid levels, inflammatory factor levels, and oxidative stress status. METHODS: 300 patients with cardiogenic cerebral infarction were recruited as the study cohort and randomly divided into an observation group and a control group. Routine treatment, including urinary kallikrein injections and bayaspirin tablets were given to the patients in the control group for one month. Rosuvastatin was given once a day in addition to the treatment the control group received to the patients in the observation group, also for one month. The two groups' treatment efficacies were compared. Also, the two groups' NIHSS and mRS scores, lipid and inflammatory factor levels, and their oxidative stress statuses were also compared. RESULTS: The total effective rate in the observation group was significantly higher than it was in the control group (74.0% vs 84.7%, P=0.023). The NIHSS and mRS scores in the observation group were significantly lower than they were in the control group (all P<0.001). Compared with their levels after the treatment in the control group, the cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels in the observation group were significantly decreased and the high-density lipoprotein

cholesterol (HDL-C) was significantly increased (all P<0.001). Moreover, after the treatment, the inflammatory factors, such as the tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) levels, and the oxidative stress status, such as the oxidatively modified low density lipoprotein (ox-LDL) levels, were significantly lower than they were in the control group, but the superoxide dimutase (SOD) levels were significantly higher. CONCLUSIONS: Rosuvastatin remarkably improves the treatment efficacy and neurological function in cardiogenic cerebral infarction patients, and is associated with the improvement of the lipid levels, the inflammatory response, and the oxidative stress status.

[8] *Pokora-Rodak A, Krzowska-Firych J, Tomasiewicz K*. **Concentration of LDLR, degree of hepatic fibrosis and hepatic steatosis in patients with chronic hepatitis B infection treated with tenofovir disoproxil fumarate**. Ann Agric Environ Med 2021; 28:458-462.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34558270
ABSTRACT
INTRODUCTION: Epidemiological data indicate that one-third of the world's population have serological markers of hepatitis B virus infection. Hepatic steatosis is often observed in patients with chronic liver diseases. The exact mechanisms of hepatic steatosis progression and the efficacy of antiviral therapy in patients with CHB and hepatic steatosis are not yet fully understood. OBJECTIVE: The aim of the study was to investigate the LDLR concentration and degree of hepatic fibrosis and hepatic steatosis in patients with chronic hepatitis B infection during tenofovir disoproxil fumarate therapy. MATERIAL AND METHODS: The study group consisted of 54 patients with CHB. The LDLR concentration, assessment of the degree of hepatic fibrosis, hepatic steatosis, total cholesterol, low density lipoprotein, high density lipoprotein and triglyceride concentrations, were assessed at the beginning of therapy, 6 months later, and 12 months after commencement of therapy. The control group consisted of 18 healthy individuals. RESULTS: The mean LDLR concentration in the studied groups was statistically significantly lower (p<0.05) than in the controls. The antiviral therapy based on TDF had no influence on the LDLR concentration and HBsAg level. CONCLUSIONS: The results indicate a statistically significant lower(p<0.05) concentration of LDLR in patients with chronic hepatitis B infection. Negative correlations between HBsAg level and LDLR concentration in patients with chronic HBV, at all stages of the study may indicate, that HBsAg protects hepatocytes from LDL accumulation.

[9] *Jang YH, Choi KH, Song YB et al.* **Effects of Statin Intensity on Long-Term Outcomes after Coronary Artery Bypass Grafting**. The Annals of thoracic surgery 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34555373
ABSTRACT
BACKGROUND: The current study sought to investigate the association between statin intensity and long-term clinical outcomes according to initial clinical presentation following CABG. METHODS: A total of 6,531 patients who underwent CABG were finally included in this study, and the study population was classified into four groups according to statin intensity (no or low[atorvastatin<10mg,n=731], lower-moderate[atorvastatin 10mg equivalent,n=2310], higher-moderate [atorvastatin 20mg equivalent,n=2404], and high-intensity [atorvastatin≥40mg equivalent, n=1086]). The primary endpoint was MACCE at 5-years. Multivariable Cox and inverse-probability-weighting methods were performed to adjust for baseline differences. RESULTS: At least moderate-

intensity statin use was associated with significantly lower risk of 5-year MACCE compared with no or low-intensity statin use(HR 0.694,95%CI:0.493-0.977,p=0.036). Among patients who were taken at-least moderate-intensity statin, both higher moderate-intensity(HR:0.622,95%CI:0.479-0.807,p<0.001) and high-intensity statin(HR:0.613,95%CI:0.421-0.894,p=0.011) groups showed significantly lower risks of MACCE than lower-moderate intensity statin group at 5-years after CABG. There was no significant difference in the risk of MACCE between higher-moderate intensity and high-intensity statin groups(HR:0.987,95%CI:0.661-1.475,p=0.950). Multivariable Cox and inverse-probability-weighting methods yielded similar results. In subgroup analysis, compared with the use of a lower-moderate intensity statin, the use of a higher-moderate or high-intensity statin(equivalent dose with atorvastatin≥20mg) was associated with a significantly lower risk of MACCE among CABG patients who presented with ACS, but not in those who presented with stable ischemic heart disease(interaction-p=0.001). CONCLUSIONS: The use of a lower-moderate intensity statin(atorvastatin 10mg equivalent) was associated with relatively poorer long-term clinical outcomes than the use of higher-moderate or high-intensity statin, especially in ACS patients following CABG.

[10] *Ferrari F, Santos RD*. **Physical Activity and HDL-C: Are There Gender Differences in the Dose-response Effect?** Arquivos brasileiros de cardiologia 2021; 117:501-502.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550235
ABSTRACT

[11] *Fayad ZA, Robson PM*. **Bringing Color to Atherosclerotic Plaque Calcification With (18)F-Sodium Fluoride Positron Emission Tomography Imaging**. Arteriosclerosis, thrombosis, and vascular biology 2021; 41:2585-2587.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550711
ABSTRACT

[12] *Dobiasova M*. **Correspondence to: "Atherogenic index of plasma and the risk of rapid progression of coronary atherosclerosis beyond traditional risk factors"**. Atherosclerosis 2021; 335:148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34563338
ABSTRACT

[13] *Lind L*. **The metabolomic profile of carotid artery intima-media thickness and echogenicity**. Atherosclerosis 2021; 335:142-147.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34556332
ABSTRACT
BACKGROUND AND AIMS: Nuclear magnetic resonance (NMR)-based metabolomics analyses have defined the lipoprotein profile of carotid artery intima-media thickness (IMT) in detail. In this study, the aim was to use multi-modal mass spectroscopy (MS) to relate multiple metabolites from different chemical classes to IMT and also to the echogenicity of the intima-media complex (IM-GSM). METHOD: Multi-modal MS with 791 annotated non-xenobiotic metabolites was measured in two different population-based samples (PIVUS at age 80, n = 586 and POEM at age 50, n = 495) in which also carotid IMT and IM-GSM have been assessed by ultrasound. RESULTS: Four metabolites were significantly (false discovery rate, FDR<0.05) related to IMT in a meta-analysis of POEM and

PIVUS. The top finding was adenosine 3',5'-cyclic monophosphate (cAMP), being inversely related to IMT. Fifty metabolites were significantly related to IM-GSM in a meta-analysis of POEM and PIVUS. The top findings were branched-chained amino acids (BCAA), fructosyllysine, metabolonic lactone sulfate, a ceramide together with some sphingomyelins and phosphatidylcholines. All these top findings represented inverse relationships. Two metabolites identified by lasso regression in PIVUS increased discrimination of an echolucent IM-GSM by 3.3% in POEM compared to traditional cardiovascular risk factors (p = 0.020). CONCLUSIONS: IMT, especially IM-GSM, was related to multiple metabolites from different chemical classes. Although such metabolites improved the discrimination of an echolucent IM-GSM, it remains to be investigated if any of those metabolites are involved in the pathogenesis of carotid arteriopathy.

[14] *Paquette M, Bernard S, Baass A*. **Hemoglobin concentration, hematocrit and red blood cell count predict major adverse cardiovascular events in patients with familial hypercholesterolemia**. Atherosclerosis 2021; 335:41-46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34547589

ABSTRACT

BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is a genetic disease associated with an important risk of premature and recurrent atherosclerotic cardiovascular disease (ASCVD). Red blood cell (RBC) parameters such as cell count and hematocrit (HCT) have previously been associated with ASCVD risk in the general population. However, little is known concerning their effect in FH. The aim of the present study is to investigate the effect of the different RBC parameters on the incidence of major adverse cardiovascular events (MACE) in FH patients. METHODS: In this prospective cohort study, genetically-confirmed FH patients aged between 18 and 65 years and without history of a prior ASCVD event were included. MACE included myocardial infarction, stroke, coronary revascularization, unstable angina or cardiovascular death. RESULTS: A total of 482 subjects (6217 person-years of follow-up) were included in the analysis. Hemoglobin (HB), RBC count, and HCT were significant predictors of MACE risk (HR 1.04 (95% CI 1.01-1.06) p = 0.001, HR 2.69 (95% CI 1.49-4.86) p = 0.001, and HR 1.16 (95% CI 1.08-1.26) p < 0.0001, respectively) and these associations remained significant when adjusted for traditional cardiovascular risk factors. In addition, the frequency of recurrent MACE was 4-fold and 7-fold higher in the group above vs below the median for HB (p = 0.002) and RBC count (p = 0.001), respectively. CONCLUSIONS: HB, RBC count and HCT were significant predictors of incident and recurring MACE in FH patients. These parameters could therefore be used to further refine the ASCVD risk prediction in this vulnerable population.

[15] *Poredoš P, Cevc M, Blinc A*. **Characteristics of atherosclerosis in femoropopliteal artery and its clinical relevance**. Atherosclerosis 2021; 335:31-40.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34547588

ABSTRACT

Atherosclerosis is a systemic disease with different faces. Despite identical or similar pathogenetic mechanisms, atherosclerotic lesions and their clinical manifestations vary in different parts of the vascular system. Peripheral arterial disease (PAD) represents one of the most frequent clinical manifestations of atherosclerosis with predominant location in the superficial femoral artery (SFA). Morphological characteristics of atherosclerotic plaques in peripheral arteries differ from lesions in the

coronary and carotid arteries. Plaques in SFA have more fibrotic components, less lipids and inflammatory cells, which makes them more stable and less prone to rupture. Factors that determine the different structure of plaques in SFA compared to coronary arteries include hemodynamic forces, vasa vasorum and calcification. Low shear stress in SFA in the adductor canal is one of the factors which determines frequent atherosclerotic lesions in this region. Lower lipid content and fewer inflammatory cells explain higher stability of SFA plaques. The specific structure of SFA plaques may require preventive and therapeutic measures, which to some extent differ from prevention of coronary atherosclerosis and may include inhibition of fibrotic proliferation in SFA plaques and calcification. Revascularization of PAD differs from procedures used in coronary arteries and requires specific technical expertise and devices.

[16] *Scicchitano P, Milo M, Mallamaci R et al.* **Inclisiran in lipid management: A Literature overview and future perspectives**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021; 143:112227.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34563953
ABSTRACT
Primary and secondary prevention protocols aim at reducing the plasma levels of lipids - with particular reference to low-density lipoprotein cholesterol (LDL-C) plasma concentrations - in order to improve the overall survival and reduce the occurrence of major adverse cardiovascular events. The use of statins has been widely considered as the first-line approach in lipids management as they can dramatically impact on the cardiovascular risk profile of individuals. The introduction of ezetimibe and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors overcame the adverse effects of statins and ameliorate the achievement of the target lipids levels. Indeed, advances in therapies promote the use of specific molecules - i.e. short strands of RNA named small-interfering RNAs (siRNAs) - to suppress the transcription of genes related to lipids metabolism. Recently, the inclisiran has been developed: this is a siRNA able to block the mRNA of the PCSK9 gene. About 50% reduction in low-density lipoprotein cholesterol levels have been observed in randomized controlled trials with inclisiran. The aim of this review was to summarize the literature regarding inclisiran and its possible role in the general management of patients with lipid disorders and/or in primary/secondary prevention protocols.

[17] *Panbehkar-Jouybari M, Mollahosseini M, Salehi-Abargouei A et al.* **The Mediterranean diet and dietary approach to stop hypertension (DASH)-style diet are differently associated with lipid profile in a large sample of Iranian adults: a cross-sectional study of Shahedieh cohort**. BMC endocrine disorders 2021; 21:192.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34548048
ABSTRACT
BACKGROUND: The association between the Mediterranean diet (MED) or dietary approach to stop hypertension (DASH) and cardiovascular disease (CVD) risk factors is well-documented. Nevertheless, a consistent relationship with the Middle East population has yet to be known. Thus, we aimed to investigate the association between DASH/MED and blood lipids in Iranian adults. METHODS: Four thousand seven hundred forty participants, aged 35-70 years (mean: 50.0) participated in the Shahedieh cohort study in Yazd, Iran, were followed from 2016 until now. Participants provided dietary and blood lipid data through a validated semi-quantitative food

frequency questionnaire, and blood samples were taken after a fasted state. We used binary logistic regression to examine the association between DASH/MED scores and blood lipids. RESULTS: In the participants who ingested a DASH-like diet the third vs. the first tertile of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) levels, and LDL/HDL (high-density lipoprotein) ratio reduced significantly (P < 0.01). While in the participants who ingested the MED-like diet the HDL level increased significantly(52.8 ± 12. 3 vs. 51.6 ± 11.6, P < 0.01). In Binary logistic regression, higher adherence to the DASH diet showed 19 % lower odds of high TC level (OR: 0.81; 95 %CI: 0.69-0.95) and 18 % lower odds of high LDL/HDL ratio (OR: 0.82; 95 %CI: 0.70-0.96). Besides, high adherence to the MED diet was associated with lower odds of LDL/HDL ratio (OR: 0.85; 95 %CI: 0.72-0.99). CONCLUSIONS: Our findings suggest that TC, TG, LDL, LDL/HDL ratio, and HDL improved in participants who ingested a DASH-like diet and the LDL/HDL ratio improved in participants who ingested MED-like diet and, subsequently they might have a protective effect on CVDs risk. Further epidemiological studies are needed to confirm our findings.

[18] *Wu YQ, Hu YY, Li GN*. **Rare novel LPL mutations are associated with neonatal onset lipoprotein lipase (LPL) deficiency in two cases**. BMC pediatrics 2021; 21:414.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34544385
ABSTRACT
BACKGROUND: Lipoprotein lipase (LPL) deficiency is a monogenic lipid metabolism disorder biochemically characterized by hypertriglyceridemia (HTG) inherited in an autosomal recessive manner. Neonatal onset LPL deficiency is rare. The purpose of this study was to clarify the clinical features of neonatal LPL deficiency and to analyze the genetic characteristics of LPL gene. METHODS: In order to reach a definite molecular diagnose, metabolic diseases-related genes were sequenced through gene capture and next generation sequencing. Meanwhile, the clinical characteristics and follow-up results of the two newborns were collected and analyzed. RESULTS: Three different mutations in the LPL gene were identified in the two newborns including a novel compound heterozygous mutation (c.347G > C and c.472 T > G) and a reported homozygous mutation (c.836 T > G) was identified. Interestingly, both the two neonatal onset LPL deficiency patients presented with suffered recurrent infection in the hyperlipidemia stage, which was not usually found in childhood or adulthood onset LPL deficiency patients. CONCLUSION: The two novel mutaitons, c.347G > C and c.472 T > G, identified in this study were novel, which expanded the LPL gene mutation spectrum. In addition, suffered recurrent infection in the hyperlipidemia stage implied a certain correlation between immune deficiency and lipid metabolism abnormality. This observation further supplemented and expanded the clinical manifestations of LPL deficiency.

[19] *Libby P*. **Inflammation during the life cycle of the atherosclerotic plaque**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550337
ABSTRACT
Inflammation orchestrates each stage of the life cycle of atherosclerotic plaques. Indeed, inflammatory mediators likely link many traditional and emerging risk factors with atherogenesis. Atheroma initiation involves endothelial activation with recruitment of leukocytes to the arterial intima, where they interact with lipoproteins or their derivatives that have accumulated in this layer. The prolonged and usually clinically silent progression of atherosclerosis involves periods of smoldering

inflammation, punctuated by episodes of acute activation that may arise from inflammatory mediators released from sites of extravascular injury or infection or from subclinical disruptions of the plaque. Smooth muscle cells and infiltrating leukocytes can proliferate but also undergo various forms of cell death that typically lead to formation of a lipid-rich "necrotic" core within the evolving intimal lesion. Extracellular matrix synthesized by smooth muscle cells can form a fibrous cap that overlies the lesion's core. Thus, during progression of atheroma, cells not only procreate but perish. Inflammatory mediators participate in both processes. The ultimate clinical complication of atherosclerotic plaques involves disruption that provokes thrombosis, either by fracture of the plaque's fibrous cap or superficial erosion. The consequent clots can cause acute ischemic syndromes if they embarrass perfusion. Incorporation of the thrombi can promote plaque healing and progressive intimal thickening that can aggravate stenosis and further limit downstream blood flow. Inflammatory mediators regulate many aspects of both plaque disruption and the healing process. Thus, inflammatory processes contribute to all phases of the lifecycle of atherosclerotic plaques, and represent ripe targets for mitigating the disease.

[20] *Waring OJ, Skenteris NT, Biessen EAL, Donners M*. **Two-faced Janus: The dual role of macrophages in atherosclerotic calcification**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550346

ABSTRACT

Calcification is an independent predictor of atherosclerosis-related cardiovascular events. Microcalcification is linked to inflamed, unstable lesions, in comparison to the fibrotic stable plaque phenotype generally associated with advanced calcification. This paradox relates to recognition that calcification presents in a wide spectrum of manifestations that differentially impact plaque's fate. Macrophages, the main inflammatory cells in atherosclerotic plaque, have a multifaceted role in disease progression. They crucially control the mineralisation process, from microcalcification to the osteoid metaplasia of bone-like tissue. It is a bilateral interaction, that weighs heavily on the overall plaque fate, but remains rather unexplored. This review highlights current knowledge about macrophage phenotypic changes in relation to, and interaction with the calcifying environment. On the one hand, macrophage-led inflammation kickstarts microcalcification through a multitude of interlinked mechanisms, which in turn stimulates phenotypic changes in vascular cell types to drive microcalcification. Macrophages may also modulate the expression/activity of calcification inhibitors and inducers, or eliminate hydroxyapatite nucleation points. Contrarily, direct exposure of macrophages to an early calcifying milieu impacts macrophage phenotype, with repercussions for plaque progression and/or stability. Macrophages surrounding macrocalcification deposits show a more reparative phenotype, modulating extracellular matrix, and expressing osteoclast genes. This phenotypic shift favours gradual displacement of the pro-inflammatory hubs; the lipid necrotic core, by macrocalcification. Parallels to bone metabolism may explain many of these changes to macrophage phenotype, with advanced-calcification able to show homeostatic osteoid metaplasia. As the targeted treatment of vascular calcification developing in atherosclerosis is thus far severely lacking, it is crucial to better understand its mechanisms of development.

[21] *Brousseau ME, Clairmont KB, Spraggon G et al.* **Identification of a PCSK9-LDLR disruptor peptide with in vivo function**. Cell chemical biology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34547225

ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates plasma low-density lipoprotein cholesterol (LDL-C) levels by promoting hepatic LDL receptor (LDLR) degradation. Therapeutic antibodies that disrupt PCSK9-LDLR binding reduce LDL-C concentrations and cardiovascular disease risk. The epidermal growth factor precursor homology domain A (EGF-A) of the LDLR serves as a primary contact with PCSK9 via a flat interface, presenting a challenge for identifying small molecule PCSK9-LDLR disruptors. We employ an affinity-based screen of 10(13)in vitro-translated macrocyclic peptides to identify high-affinity PCSK9 ligands that utilize a unique, induced-fit pocket and partially disrupt the PCSK9-LDLR interaction. Structure-based design led to molecules with enhanced function and pharmacokinetic properties (e.g., (13)PCSK9i). In mice, (13)PCSK9i reduces plasma cholesterol levels and increases hepatic LDLR density in a dose-dependent manner. (13)PCSK9i functions by a unique, allosteric mechanism and is the smallest molecule identified to date with in vivo PCSK9-LDLR disruptor function.

[22] *Song Y, Liu J, Zhao K et al.* **Cholesterol-induced toxicity: An integrated view of the role of cholesterol in multiple diseases**. Cell Metab 2021; 33:1911-1925.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34562355
ABSTRACT
High levels of cholesterol are generally considered to be associated with atherosclerosis. In the past two decades, however, a number of studies have shown that excess cholesterol accumulation in various tissues and organs plays a critical role in the pathogenesis of multiple diseases. Here, we summarize the effects of excess cholesterol on disease pathogenesis, including liver diseases, diabetes, chronic kidney disease, Alzheimer's disease, osteoporosis, osteoarthritis, pituitary-thyroid axis dysfunction, immune disorders, and COVID-19, while proposing that excess cholesterol-induced toxicity is ubiquitous. We believe this concept will help broaden the appreciation of the toxic effect of excess cholesterol, and thus potentially expand the therapeutic use of cholesterol-lowering medications.

[23] *Pavlović J, Greenland P, Franco OH et al.* **Recommendations and Associated Levels of Evidence for Statin Use in Primary Prevention of Cardiovascular Disease: A Comparison at Population Level of the American Heart Association/American College of Cardiology/Multisociety, US Preventive Services Task Force, Department of Veterans Affairs/Department of Defense, Canadian Cardiovascular Society, and European Society of Cardiology/European Atherosclerosis Society Clinical Practice Guidelines**. Circulation. Cardiovascular quality and outcomes 2021; 14:e007183.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34546786
ABSTRACT
BACKGROUND: Despite using identical evidence to support practice guidelines for lipid-lowering treatment in primary prevention of cardiovascular disease (CVD), it is unclear to what extent the 2018 American Heart Association/American College of Cardiology/Multisociety, 2016 US Preventive Services Task Force (USPSTF), 2020 Department of Veterans Affairs/Department of Defense, 2021 Canadian Cardiovascular Society, and 2019 European Society of Cardiology/European Atherosclerosis Society guidelines differ in grading and assigning levels of evidence and classes of recommendations (LOE/class) at a population level. METHODS: We included 7262 participants, aged

45 to 75 years, without history of CVD from the prospective population-based Rotterdam Study. Per guideline, proportions of the population recommended statin therapy by LOE/class, sensitivity and specificity for CVD events, and numbers needed to treat at 10 years were calculated. RESULTS: Mean age was 61.1 (SD 6.9) years; 58.2% were women. American Heart Association/American College of Cardiology/Multisociety, USPSTF, Department of Veterans Affairs/Department of Defense, Canadian Cardiovascular Society, and European Society of Cardiology/European Atherosclerosis Society strongly recommended statin initiation in respective 59.4%, 40.2%, 45.2%, 73.7%, and 42.1% of the eligible population based on high-quality evidence. Sensitivity for CVD events for treatment recommendations supported with strong LOE/class was 86.3% for American Heart Association/American College of Cardiology/Multisociety (IA or IB), 69.4% for USPSTF (USPSTF-B), 74.5% for Department of Veterans Affairs/Department of Defense (strong for), 93.3% for Canadian Cardiovascular Society (strong), and 66.6% for European Society of Cardiology/European Atherosclerosis Society (IA). Specificity was highest for the USPSTF at 45.3% and lowest for European Society of Cardiology/European Atherosclerosis Society at 10.0%. Estimated numbers needed to treat at 10 years for those with the strongest LOE/class were ranging from 20 to 26 for moderate-intensity and 12 to 16 for high-intensity statins. CONCLUSIONS: Sensitivity, specificity, and numbers needed to treat at 10 years for assigned LOE/class varied greatly among 5 CVD prevention guidelines. The level of variability seems to be driven by differences in how the evidence is graded and translated into LOE/class underlying the treatment recommendations by different professional societies. Efforts towards harmonizing evidence grading systems for clinical guidelines in primary prevention of CVD may reduce ambiguity and reinforce updated evidence-based recommendations.

[24] *Zhang X, Lv Z, Zhang J et al.* **Association between Serum Free Fatty Acids to HDL-Cholesterol Ratio and Nonalcoholic Fatty Liver Disease: a Cross-Sectional Study**. Clinical laboratory 2021; 67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34542962

ABSTRACT

BACKGROUND: This cross-sectional study aimed to investigate the association between serum free fatty acids and high-density lipoprotein-cholesterol ratio (FHR) and nonalcoholic fatty liver disease (NAFLD) in a Chinese population. METHODS: A total of 760 NAFLD subjects and 379 healthy controls who took their annual health checkups were enrolled during 2019. Fasting blood samples were obtained from the population. NAFLD was diagnosed based on hepatic ultrasound examination. RESULTS: Serum FHR (*100) in NAFLD subjects was significantly higher than that in controls. We found that the serum FHR in NAFLD participants was positively correlated with BMI, DBP, WBC, HGB, ALT, AST, GGT, TG, FPG, UA, and hsCRP. Univariate and multivariate logistic regression analysis showed that FHR was independently associated with the presence of NAFLD. The area under curve (AUC) of the receiver operating characteristic (ROC) curve of FHR for NAFLD was 0.781 with the 95% confidence interval from 0.753 to 0.810. The optimal cutoff point of FHR for predicting NAFLD was 41.14 with 78.8% sensitivity and 77.3%, respectively. CONCLUSIONS: FHR was significantly associated with NAFLD and may serve as an effective indicator in NAFLD patients.

[25] *Nishikido T, Ray KK*. **The power of lipid registries for cardiovascular disease prevention**. Current opinion in lipidology 2021; 32:342-348.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34561312

ABSTRACT
PURPOSE OF REVIEW: Lipid registry-based research is a valuable tool for assessing current lipid management in patients at risk of cardiovascular disease (CVD). Results of several registries are useful for improving clinical practice highlight gaps between guidelines and their implementation and potential impact on population health. We summarize recent clinical studies based on lipid registries. RECENT FINDINGS: Current guidelines for lipid management recommend high-intensity statins and concomitant therapies such as ezetimibe and proprotein convertase subtilisin-kexin type 9 inhibitors for high-risk patients. However, recent observational studies show that the majority of patients received inadequate lipid-lowering therapy (LLT), and the low-density lipoprotein-cholesterol (LDL-C) goal attainment rates are still unsatisfactory. SUMMARY: There is a clear gap between lipid guidelines and lipid management in clinical practice. Clinical studies based on registry databases represent real-world conditions, as opposed to clinical trials. Contemporary registry data reveal that only half of the patients received high-intensity statins, and less than half achieve the LDL-C <70 mg/dL in secondary prevention. In addition, the major reasons for insufficient therapy have been shown to be not only side effects of LLT, but poor adherence by patients to medication regimens and low use of combination therapies by physicians. The real-world evidence from lipid registries clarifies gaps, areas for focus for implementation, to improve CVD prevention.

[26] *Thompson GR*. **Use of apheresis in the age of new therapies for familial hypercholesterolaemia**. Current opinion in lipidology 2021; 32:363-369.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34561311

ABSTRACT
PURPOSE OF REVIEW: Lipoprotein apheresis has been first line therapy for homozygous familial hypercholesterolaemia (FH) and other severe and refractory forms of dyslpidaemia for over 40 years but the recent advent of novel and potent LDL-lowering compounds necessitates a reappraisal of its role. RECENT FINDINGS: During the past decade a substantial amount of evidence has accumulated describing the effect of LDL-lowering with apheresis and conventional drug therapy upon the cardiovascular outcomes associated with homozygous and statin-refractory heterozygous FH. This has necessitated re-defining the target levels of LDL cholesterol needed to arrest progression of atherosclerosis in these situations. At the same time, evidence has accrued regarding the pathogenicity of raised levels of lipoprotein (a) and the promising role of apheresis in mitigating the adverse effects of the latter. The latest advance in treatment has been the introduction of three classes of novel and potent LDL-lowering compounds in the shape of inhibitors of Propertin convertase subtilisin kexin 9 (PCSK9), microsomal triglyceride transfer protein and angiopoietin-like 3. SUMMARY: These recent developments raise the question of whether these compounds will be used as adjuvants to bolster lipoprotein apheresis in FH homozygotes or whether they will render it obsolete, as is already occurring with PCSK9 inhibitors in FH heterozygotes.

[27] *Vergès B, Hassid J, Rouland A et al.* **Liraglutide reduces plasma PCSK9 in patients with type 2 diabetes not treated with statins**. Diabetes Metab 2021:101284.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34551355

ABSTRACT
AIM: Dyslipidaemia in type 2 diabetes mellitus (T2DM), which increases cardiovascular risk, includes abnormal metabolism of low-density lipoproteins (LDL). Our group has recently shown that liraglutide

increases LDL catabolism in patients with T2DM and that it reduces the expression of PCSK9 (a major inhibitor of LDL-receptor expression) in vitro and in mice. This prompted us to study the effect of liraglutide on plasma PCSK9 level in patients with T2DM. METHODS: We studied prospectively 82 patients with T2DM (51 without statins, 31 with statins). Plasma PCSK9 and plasma lipids were measured before and six months after the initiation of a treatment with liraglutide at a dose of 1.2 mg/day. RESULTS: Plasma PCSK9 was significantly reduced by liraglutide treatment (214.9 ± 56.4 vs 244.5 ± 99.2 ng/ml, P = 0.024) in patients not on statins, but not in patients treated with statins (301.1 ± 91.5 vs 281.2 ± 96.9 ng/ml, P = 0.41). In patients not on statins, a very significant 17% decrease in plasma PCSK9 was observed in patients with baseline haemoglobin A1c (HbA1c) < 10 % (n=33; mean = -45.0 ng/ml, P = 0.013), when it was not observed in patients with baseline HbA1c ≥ 10 % (n=18; mean = +5.2 ng/ml, P = 0.75). In multivariate analysis, baseline HbA1c was an independent factor associated with plasma PCSK9 reduction, in patients not on statins. CONCLUSION: Treatment with liraglutide induces a significant reduction of plasma PCSK9 in patients with T2DM not on statins. This is in line with the acceleration of LDL catabolism that has been observed with liraglutide. However, this decrease in plasma PCSK9 is significantly influenced by glycaemic control and is not observed in patients with poorly controlled T2DM.

[28] *Siddiqui MK, Smith G, St Jean P et al.* **Diabetes status modifies the long-term effect of lipoprotein-associated phospholipase A2 on major coronary events**. Diabetologia 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34562103

ABSTRACT

AIMS/HYPOTHESIS: Lipoprotein-associated phospholipase A2 (Lp-PLA2) activity has an independent prognostic association with major coronary events (MCE). However, no study has investigated whether type 2 diabetes status modifies the effect of Lp-PLA2 activity or inhibition on the risk of MCE. We investigate the interaction between diabetes status and Lp-PLA2 activity with risk of MCE. Subsequently, we test the resulting hypothesis that diabetes status will play a role in modifying the efficacy of an Lp-PLA2 inhibitor. METHODS: A retrospective cohort study design was utilised in two study populations. Discovery analyses were performed in the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) cohort based in Scotland, UK. Participants were categorised by type 2 diabetes control status: poorly controlled (HbA(1c) ≥ 48 mmol/mol or ≥6.5%) and well-controlled (HbA(1c) < 48 mmol/mol or <6.5%) diabetes (n = 7420). In a secondary analysis of the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial of Lp-PLA2 inhibitor (darapladib) efficacy, 15,828 participants were stratified post hoc by type 2 diabetes diagnosis status (diabetes or no diabetes) at time of recruitment. Lp-PLA2 activity was then divided into population-specific quartiles. MCE were determined from linked medical records in GoDARTS and trial records in STABILITY. First, the interaction between diabetes control status and Lp-PLA2 activity on the outcome of MCE was explored in GoDARTS. The effect was replicated in the placebo arm of STABILITY. The effect of Lp-PLA2 on MCE was then examined in models stratified by diabetes status. This helped determine participants at higher risk. Finally, the effect of Lp-PLA2 inhibition was assessed in STABILITY in the higher risk group. Cox proportional hazards models adjusted for confounders were used to assess associations. RESULTS: In GoDARTS, a significant interaction between increased Lp-PLA2 activity (continuous and quartile divided) and diabetes control status was observed in the prediction of MCE (p < 0.0001). These effects were replicated in the placebo arm of STABILITY (p < 0.0001). In GoDARTS, stratified analyses showed that, among

individuals with poorly controlled diabetes, the hazards of MCE for those with high (Q4) Lp-PLA2 activity was 1.19 compared with individuals with lower (Q1-3) Lp-PLA2 activity (95% CI 1.11, 1.38; p<0.0001) and 1.35 (95% CI 1.16, 1.57; p<0.0001) when compared with those with the lowest activity (Q1). Those in the higher risk group were identified as individuals with the highest Lp-PLA2 activity (Q4) and poorly controlled diabetes or diabetes. Based on these observations in untreated populations, we hypothesised that the Lp-PLA2 inhibitor would have more benefit in this higher risk group. In this risk group, Lp-PLA2 inhibitor use was associated with a 33% reduction in MCE compared with placebo (HR 0.67 [95% CI 0.50, 0.90]; p=0.008). In contrast, Lp-PLA2 inhibitor showed no efficacy in individuals with low activity, regardless of diabetes status, or among those with no baseline diabetes and high Lp-PLA2 activity. CONCLUSIONS/INTERPRETATION: These results support the hypothesis that diabetes status modifies the association between Lp-PLA2 activity and MCE. These results suggest that cardiovascular morbidity and mortality associated with Lp-PLA2 activity is especially important in patients with type 2 diabetes, particularly those with worse glycaemic control. Further investigation of the effects of Lp-PLA2 inhibition in diabetes appears warranted. DATA AVAILABILITY: STABILITY trial data are available from clinicaltrials.gov repository through the GlaxoSmithKline clinical study register https://clinicaltrials.gov/ct2/show/NCT00799903 . GoDARTS datasets generated during and/or analysed during the current study are available following request to the GoDARTS Access Managements Group https://godarts.org/scientific-community/ .

[29] *Safouris A, Magoufis G, Tsivgoulis G*. **Emerging agents for the treatment and prevention of stroke: progress in clinical trials**. Expert opinion on investigational drugs 2021; 30:1025-1035. **PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=34555978

ABSTRACT

INTRODUCTION: Recent years have witnessed unprecedented progress in stroke care, but unmet needs persist regarding the efficacy of acute treatment and secondary prevention. Novel approaches are being tested to enhance the efficacy of thrombolysis or provide neuroprotection in non-thrombolized patients. AREAS COVERED: The current review highlights pharmaceutical agents under evaluation in clinical trials concerning the acute, subacute, and chronic phase post-stroke. We examine the evidence in favor of tenecteplase as an alternative thrombolytic drug to alteplase, nerinetide as a promising neuroprotective agent, and glibenclamide for reducing edema in malignant hemispheric infarction. We discuss the use of ticagrelor and the promising novel category of factor XI inhibitors in the subacute phase after stroke. We offer our insights on combined rivaroxaban and antiplatelet therapy, PCSK-9 inhibitors, and other non-statin hypolipidemic agents, as well as novel antidiabetic agents that have been shown to reduce cardiovascular events in the long-term. EXPERT OPINION: Current approaches in stroke treatment and stroke prevention have already transformed stroke care from a linear one-for-all treatment paradigm to a more individualized approach that targets specific patient subgroups with novel pharmaceutical agents. This tendency enriches the therapeutic armamentarium with novel agents developed for specific stroke subgroups. ABBREVIATIONS: IVT: intravenous thrombolysis; RCTs: randomized-controlled clinical trials; TNK: Tenecteplase; COVID-19: Coronavirus 2019 Disease; EXTEND-IA TNK: The Tenecteplase versus Alteplase Before Endovascular Therapy for Ischemic Stroke trial; AIS: acute ischemic stroke; NNT: number needed to treat; MT: mechanical thrombectomy; sICH: symptomatic intracranial hemorrhage; mRS: modified Rankin Scale; AHA/ASA: American Heart Association/American Stroke Association; ESO: European Stroke Organization; NA-1: Nerinetide; ENACT: Evaluating Neuroprotection in

Aneurysm Coiling Therapy; CTA: CT angiography; TIA: transient ischemic attack; CHANCE: Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events; LOF: loss-of-function; PRINCE: Platelet Reactivity in Acute Nondisabling Cerebrovascular Events; THALES: Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA [acetylsalicylic acid] for Prevention of Stroke and Death; CHANCE-2: Clopidogrel With Aspirin in High-risk Patients With Acute Non-disabling Cerebrovascular Events II; FXI: Factor XI; PACIFIC-STROKE: Program of Anticoagulation via Inhibition of FXIa by the Oral Compound BAY 2433334-NonCardioembolic Stroke study; COMPASS: Cardiovascular Outcomes for People Using Anticoagulation Strategies; CANTOS-ICAD: Combination Antithrombotic Treatment for Prevention of Recurrent Ischemic Stroke in Intracranial Atherosclerotic Disease; SAMMPRIS: Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis; WASID: Warfarin-Aspirin Symptomatic Intracranial Disease; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels; LDL-C: low-density lipoprotein cholesterol; TST: Treat Stroke to Target; IMPROVE-IT: Improved Reduction of Outcomes: Vytorin Efficacy International Trial; PCSK9: proprotein convertase subtilisin-kexin type 9; FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; CLEAR: Cholesterol Lowering via Bempedoic acid, an ACL-inhibiting Regimen; REDUCE-IT: Reduction of Cardiovascular Events With EPA Intervention Trial; STRENGTH: Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT: Veterans Affairs Diabetes Trial; GLP-1R: Glucagon-like peptide-1 receptor; SGLT2: sodium-glucose cotransporter 2; CONVINCE: COlchicine for preventioN of Vascular Inflammation in Non-CardioEmbolic stroke; PROBE: Prospective Randomized Open-label Blinded Endpoint assessment.

[30] *Zhang X, Wang D, Tian Y et al.* **Risk Factors for Atorvastatin as a Monotherapy for Chronic Subdural Hematoma: A Retrospective Multifactor Analysis**. Frontiers in aging neuroscience 2021; 13:726592.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34539386

ABSTRACT

Chronic subdural hematoma (CSDH) is a common form of intracranial hemorrhage in the aging population. We aimed to investigate the predictive factors for atorvastatin efficacy as a monotherapy for moderate CSDH. We retrospectively reviewed the medical records of patients who were diagnosed with moderate CSDH and received atorvastatin monotherapy between February 5, 2014, and November 7, 2015, in multiple neurosurgical departments. Univariate, multivariate and receiver operating characteristic curve analyses were performed to identify the potential significant factors indicative of the good therapeutic efficacy or poor therapeutic efficacy of atorvastatin for mild CSDH, such as age, sex, history of injury, Markwalder grading scale-Glasgow Coma Scale (MGS-GCS), Activities of Daily Life-the Barthel Index scale (ADL-BI), American Society of Anesthesiologists Physical Status classification system (ASA-PS), blood cell counts, serum levels and computed tomography findings. A total of 89 patients (75 men and 14 women) aged 24-88 years (mean age 61.95 ± 15.30 years) were followed-up for 24 weeks. Computed tomography findings at admission showed mixed-density hematoma in 22 patients, isodense hematoma in 13 patients, high-density hematoma in 26 patients, and low-density hematoma in 28 patients. In total, 3, 80, and 6 patients had

MGS-GCS grades of 0, 1, and 2, respectively. The efficacy rate at 6 months was 87.6% (78/89). Eleven patients were switched to surgery due to a worsened neurological condition, of whom 8, 1, 1, and 1 had high-density, low-density, isodense and mixed-density hematomas, respectively. These patients were switched to surgery over a range of 2-27 days, with a median interval of 12 days after the medication treatment. Univariate and multivariate analyses, confirmed by ROC curves, revealed that high-density hematoma, basal cistern compression, and hematoma volume to be independent risk factors for the efficacy of atorvastatin monotherapy in patients with moderate CSDH. Atorvastatin is an effective monotherapy for the treatment of mild CSDH. High-density hematoma, basal cistern compression, and hematoma volume are independent predictors of the efficacy of atorvastatin as a non-surgical treatment. The results suggested that ADL-BI was more sensitive than the MGS-GCS and ASA-PS for determining patient outcomes in our moderate CSDH cohort.

[31] *Mohamed SH, Hassaan MMM, Ibrahim BA, Sabbah NA*. **PCSK9 E670G (rs505151) Variant and Coronary Artery Disease Risk Among Diabetics**. Genetic testing and molecular biomarkers 2021; 25:615-623.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550777
ABSTRACT
Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme in the family of proprotein convertases implicated in lipid metabolism and is a significant genetic risk factor in cardiovascular diseases among various populations. Aim of the Study: This study explored the correlation between the alleles of the rs505151 (E670G) locus of the PCSK9 gene and its expression levels with coronary artery disease (CAD) risk in Egyptian patients with type 2 diabetes mellitus (T2DM). Subjects and Methods: A case-control study was performed on 112 lean subjects compared to 100 T2DM patients without CAD and 84 T2DM patients with CAD to investigate the relationships among PCSK9 expression levels, the E670G (rs505151) gene variant, lipid concentrations, and CAD risk in an Egyptian diabetic population. A restriction fragment length polymorphism-polymerase chain reaction (PCR) assay was used to assess the gene polymorphism, and PCSK9 mRNA expression was determined by quantitative real-time PCR. Results: The prevalence of the E670G (rs505151) AG genotype in diabetics with CAD was significantly greater than the other two groups. The PCSK9 gene expression levels in diabetics with CAD were significantly greater than the other two groups. G allele carriers (AG+GG) had a higher relative PCSK9 expression than A allele carriers. Conclusion: PCSK9 relative expression levels and the E670G (rs505151) AG genotype are CAD risk factors among Egyptian diabetics and are linked positively to the atherogenic index of plasma.

[32] *Horn CL, Morales AL, Savard C et al.* **Role of Cholesterol-Associated Steatohepatitis in the Development of NASH**. Hepatology communications 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34558856
ABSTRACT
The rising prevalence of nonalcoholic fatty liver disease (NAFLD) and NAFLD-related cirrhosis in the United States and globally highlights the need to better understand the mechanisms causing progression of hepatic steatosis to fibrosing steatohepatitis and cirrhosis in a small proportion of patients with NAFLD. Accumulating evidence suggests that lipotoxicity mediated by hepatic free cholesterol (FC) overload is a mechanistic driver for necroinflammation and fibrosis, characteristic of nonalcoholic steatohepatitis (NASH), in many animal models and also in some patients with NASH.

Diet, lifestyle, obesity, key genetic polymorphisms, and hyperinsulinemia secondary to insulin resistance are pivotal drivers leading to aberrant cholesterol signaling, which leads to accumulation of FC within hepatocytes. FC overload in hepatocytes can lead to ER stress, mitochondrial dysfunction, development of toxic oxysterols, and cholesterol crystallization in lipid droplets, which in turn lead to hepatocyte apoptosis, necrosis, or pyroptosis. Activation of Kupffer cells and hepatic stellate cells by hepatocyte signaling and cholesterol loading contributes to this inflammation and leads to hepatic fibrosis. Cholesterol accumulation in hepatocytes can be readily prevented or reversed by statins. Observational studies suggest that use of statins in NASH not only decreases the substantially increased cardiovascular risk, but may ameliorate liver pathology. Conclusion: Hepatic FC loading may result in cholesterol-associated steatohepatitis and play an important role in the development and progression of NASH. Statins appear to provide significant benefit in preventing progression to NASH and NASH-cirrhosis. Randomized controlled trials are needed to demonstrate whether statins or statin/ezetimibe combination can effectively reverse steatohepatitis and liver fibrosis in patients with NASH.

[33] *Davoodi L, Jafarpour H, Oladi Z et al.* **Atorvastatin therapy in COVID-19 adult inpatients: A double-blind, randomized controlled trial**. International journal of cardiology. Heart & vasculature 2021; 36:100875.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34541293
ABSTRACT
INTRODUCTION: Efficacious therapies are urgently required to tackle the coronavirus disease 2019 (COVID-19). This trial aims to evaluate the effects of atorvastatin in comparison with standard care for adults hospitalized with COVID-19. METHODS: We conducted a randomized controlled clinical trial on adults hospitalized with COVID-19. Patients were randomized into a treatment group receiving atorvastatin + lopinavir/ritonavir or a control group receiving lopinavir/ritonavir alone. The primary outcome of the trial was the duration of hospitalization. The secondary outcomes were the need for interferon or immunoglobulin, receipt of invasive mechanical ventilation, and O2 saturation (O2sat), and level of C-reactive protein (CRP) which were assessed at the onset of admission and on the 6th day of treatment. RESULTS: Forty patients were allocated and enrolled in the study with a 1 to 1 ratio in atorvastatin + lopinavir/ritonavir and lopinavir/ritonavir groups. Clinical and demographic characteristics were similar between the two groups. CRP level was significantly decreased in the lopinavir/ritonavir + atorvastatin group ($P < 0.0001$, Cohen's $d = 0.865$) so that there was a significant difference in CRP level on the 6th day between the two groups ($P = 0.01$). Nevertheless, there was no significant difference in O2sat on day 6. Although the duration of hospitalization in the lopinavir/ritonavir + atorvastatin group was significantly reduced compared to the control group ($P = 0.012$), there was no significant difference in the invasive mechanical ventilation reception and the need for interferon and immunoglobulin. CONCLUSION: Atorvastatin + lopinavir/ritonavir may be more effective than lopinavir/ritonavir in treating COVID-19 adult hospitalized patients.

[34] *Verdickt S, Van der Schueren B, Vangoitsenhoven R et al.* **Belgian data of ODYSSEY APPRISE: stringent LDL-c targets are in reach when using all available tools**. Int J Clin Pract 2021:e14916.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34551183
ABSTRACT

BACKGROUND: As lipid targets became more stringent in the latest ESC/EAS guidelines, many patients on statin monotherapy are left above their risk-based target, increasing the need for lipid-lowering therapies. The results of the ODYSSEY APPRISE study were recently published by Gaudet et al In this trial, alirocumab (a PCSK9 inhibitor) was investigated in high cardiovascular risk patients in a real-life setting. OBJECTIVE: We aim at analysing the characteristics, safety and efficacy of alirocumab in the Belgian population of the ODYSSEY APPRISE trial and, based on literature research, we aim to evaluate the importance and the need for the add-on, non-statin lipid-lowering therapy in clinical practice. METHODS AND RESULTS: ODYSSEY APPRISE is a multicentric, prospective, single-arm, Phase 3b open-label trial. A total of 68 Belgian patients were enrolled, 63 patients had heterozygous familial hypercholesterolaemia (HeFH). Baseline mean LDL-c was 188.7 mg/dL (SD ± 51.8). At week 12, 65 patients had an evaluable efficacy end point with a mean LDL-c reduction of 59.9% from baseline. The overall incidence of treatment-emergent adverse events (TEAEs) was 75.0%. The most frequent TEAE was back pain (10.3%), nasopharyngitis (10.3%) and injection site erythema (8.8%). Based on the literature, a majority of patients do not reach their risk-based lipid target despite statin therapy alone. CONCLUSION: In a real-life setting, alirocumab is both well-tolerated, safe and very effective in reducing LDL-c in this Belgian cohort. In clinical practice, more patients should be initiated on the add-on, non-statin lipid-lowering therapy in order to reach their risk-based lipid target.

[35] *Wittlinger T, Schwaab B, Völler H et al.* **Efficacy of Lipid-Lowering Therapy during Cardiac Rehabilitation in Patients with Diabetes Mellitus and Coronary Heart Disease**. Journal of cardiovascular development and disease 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34564123

ABSTRACT

BACKGROUND: Cardiac rehabilitation (CR) in patients with coronary heart disease (CHD) increases adherence to a healthy lifestyle and to secondary preventive medication. A notable example of such medication is lipid-lowering therapy (LLT). LLT during CR improves quality of life and prognosis, and thus is particularly relevant for patients with diabetes mellitus, which is a major risk factor for CHD. DESIGN: A prospective, multicenter registry study with patients from six rehabilitation centers in Germany. METHODS: During CR, 1100 patients with a minimum age of 18 years and CHD documented by coronary angiography were included in a LLT registry. RESULTS: In 369 patients (33.9%), diabetes mellitus was diagnosed. Diabetic patients were older (65.5 ± 9.0 vs. 62.2 ± 10.9 years, $p < 0.001$) than nondiabetic patients and were more likely to be obese (BMI: 30.2 ± 5.2 kg/m(2) vs. 27.8 ± 4.2 kg/m(2), $p < 0.001$). Analysis indicated that diabetic patients were more likely to show LDL cholesterol levels below 55 mg/dL than patients without diabetes at the start of CR (Odds Ratio (OR) 1.9; 95% CI 1.3 to 2.9) until 3 months of follow-up (OR 1.9; 95% CI 1.2 to 2.9). During 12 months of follow-up, overall and LDL cholesterol levels decreased within the first 3 months and remained at the lower level thereafter ($p < 0.001$), irrespective of prevalent diabetes. At the end of the follow-up period, LDL cholesterol did not differ significantly between patients with or without diabetes mellitus ($p = 0.413$). CONCLUSION: Within 3 months after CR, total and LDL cholesterol were significantly reduced, irrespective of prevalent diabetes mellitus. In addition, CHD patients with diabetes responded faster to LTT than nondiabetic patients, suggesting that diabetic patients benefit more from LLT treatment during CR.

[36] *Sun H, Wang J, Liu S et al.* **Discovery of Novel Small Molecule Inhibitors Disrupting the PCSK9-LDLR Interaction**. J Chem Inf Model 2021; 61:5269-5279.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34553597

ABSTRACT

Proprotein convertase subtilisin kexin 9 (PCSK9) has been identified as a reliable therapeutic target for hypercholesterolemia and coronary artery heart diseases since the monoclonal antibodies of PCSK9 have launched. Disrupting the protein-protein interaction (PPI) between PCSK9 and the low-density lipoprotein receptor (LDLR) has been considered as a promising approach for developing PCSK9 inhibitors. However, PPIs have been traditionally considered difficult to target by small molecules since the PPI surface is usually large, flat, featureless, and without a "pocket" or "groove" for ligand binding. The PCSK9-LDLR PPI interface is such a typical case. In this study, a potential binding pocket was generated on the PCSK9-LDLR PPI surface of PCSK9 through induced-fit docking. On the basis of this induced binding pocket, virtual screening, molecular dynamics (MD) simulation, and biological evaluations have been applied for the identification of novel small molecule inhibitors of PCSK9-LDLR PPI. Among the selected compounds, compound 13 exhibited certain PCSK9-LDLR PPI inhibitory activity (IC(50): 7.57 ± 1.40 μM). The direct binding affinity between 13 and PCSK9 was determined with a K(D) value of 2.50 ± 0.73 μM. The LDLR uptake function could be also restored to a certain extent by 13 in HepG2 cells. This well-characterized hit compound will facilitate the further development of novel small molecule inhibitors of PCSK9-LDLR PPI.

[37] *Marinelli C, Zingone F, Lupo MG et al.* **Serum Levels of PCSK9 Are Increased in Patients With Active Ulcerative Colitis Representing a Potential Biomarker of Disease Activity: A Cross-sectional Study**. J Clin Gastroenterol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34560758

ABSTRACT

BACKGROUND/GOAL: Ulcerative colitis (UC) is characterized by chronic inflammation and progressive course, with potential extraintestinal complications including cardiovascular mortality. Serum proprotein convertase subtilisin/kexin type 9 (PCSK9) levels have been recently recognized as biomarkers of low-grade inflammation and cardiovascular disease. The aim of our study was to evaluate PCSK9 levels in patients with UC and different degrees of disease activity. METHODS: We prospectively recruited consecutive patients with UC attending our center at the University Hospital of Padua. Demographics, clinical characteristics, and biochemical data, including PCSK9, high sensitivity C-reactive protein, and fecal calprotectin, were recorded. Moreover, endoscopic procedures were performed in all subjects. RESULTS: We included 112 patients with UC (mean age=52.62±12.84 y; 52.62% males). Patients with UC and abnormal fecal calprotectin (≥250 μg/g) and/or C-reactive protein (≥3 mg/L) had greater levels of PCSK9 compared with UC patients with normal fecal calprotectin and high sensitivity C-reactive protein (P=0.03 and 0.005, respectively). Higher endoscopic scores in UC were characterized by greater levels of PCSK9 (P=0.03). Furthermore, we found a positive correlation between PCSK9 levels and fecal calprotectin (r=0.18, P=0.04), endoscopic Mayo Score (r=0.25, P=0.007), and UC-Riley Index (r=0.22, P=0.01). We also found a positive correlation between PCSK9 levels and both total and low-density lipoprotein cholesterol values (P<0.05). CONCLUSIONS: Serum PCSK9 levels are increased in patients with biochemical and endoscopic evidence of active disease in UC. Further longitudinal studies are

necessary to evaluate the role of PCSK9 as a potential biomarker of disease activity and cardiovascular risk in UC.

[38] *Park K, Vishnevetskaya K, Vaidyanathan J et al.* **Pediatric Drug Development Studies for Familial Hypercholesterolemia Submitted to the US Food and Drug Administration Between 2007 and 2020**. Journal of clinical pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34562277
ABSTRACT
Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder of lipoprotein metabolism that leads to an increased risk of developing atherosclerosis and coronary artery disease. Hypercholesterolemia in pediatric patients is typically due to FH. Treatment of pediatric FH is achieved through lifestyle modifications, lipid-modifying pharmacotherapy, and/or apheresis. The primary objective of this review is to describe the characteristics of clinical trials conducted in pediatric patients with FH with data submitted to the US Food and Drug Administration from 2007 to 2020. Of 10 trials with 8 products in pediatric FH submitted to the Food and Drug Administration, 1 product was studied in both the heterozygous and the homozygous phenotypes, 5 were studied for heterozygous hypercholesterolemia only, and 2 were studied for homozygous familial hypercholesterolemia only. Most of the trials included pediatric patients ≥10 years of age and older. Clinical trial characteristics including the primary efficacy end points between pediatric and adult trials were mostly identical. Many lipid-lowering drugs with novel mechanisms of action have been recently approved or are currently being studied. In summary, the drug treatment of hypercholesterolemia in pediatric patients is expanding beyond the use of statins, and now involves multiple mechanisms of action involving cholesterol metabolism. As younger pediatric patients are diagnosed and treated for heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia, optimizing the doses of these agents and safety studies specific to younger pediatric patients will be necessary.

[39] *Delluc A, Ghanima W, Kovacs MJ et al.* **Statins for venous event reduction in patients with venous thromboembolism: A multicenter randomized controlled pilot trial assessing feasibility**. Journal of thrombosis and haemostasis : JTH 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34564938
ABSTRACT
BACKGROUND: Statins may reduce the risk for recurrent venous thromboembolism (VTE); however, no randomized trials have explored this hypothesis. We performed a pilot randomized trial to determine feasibility of recruitment for a larger trial of secondary VTE prevention with rosuvastatin. METHODS: Patients with a newly diagnosed symptomatic proximal deep vein thrombosis and/or pulmonary embolism, receiving standard anticoagulation, were randomly allocated to adjuvant rosuvastatin 20 mg once daily for 180 days or no rosuvastatin for 6 months. RESULTS: Between November 2016 and December 2019, 3391 patients were assessed for eligibility in six centers. Of these patients, 1347 (39.7%) were eligible and approached for participation in the trial and 312 (23.1%) were randomized. The mean rate of randomization was 8.2 ± 4.3 patients per month. During follow-up, five recurrent VTE events were observed, three (1.9%) in the rosuvastatin group (two pulmonary embolism, one deep vein thrombosis), and two (1.3%) in the control group (two pulmonary embolism; P = 0.68). One major arterial event occurred in the rosuvastatin arm and none in the control arm (0.6% vs. 0%, P = 0.50). CONCLUSION: This pilot trial supports the feasibility of a larger

scale randomized controlled trial to determine the efficacy of adjuvant rosuvastatin for the secondary prevention of VTE.

[40] *Yoon YH, Ahn JM, Kang DY et al.* **Association of Lipoprotein(a) With Recurrent Ischemic Events Following Percutaneous Coronary Intervention**. JACC Cardiovasc Interv 2021; 14:2059-2068.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34556280
ABSTRACT
OBJECTIVES: This study evaluated the association between elevated levels of lipoprotein(a) [Lp(a)] and risk of recurrent ischemic events in patients who underwent percutaneous coronary intervention (PCI). BACKGROUND: Elevated levels of Lp(a) have been identified as an independent, possibly causal, risk factor for atherosclerotic cardiovascular disease in a general population study. METHODS: A prospective single-center registry was used to identify 12,064 patients with baseline Lp(a) measurements who underwent PCI between 2003 and 2013. The primary outcomes were a composite of cardiovascular death, spontaneous myocardial infarction, and ischemic stroke. RESULTS: From the registry, 3,747 (31.1%) patients had high Lp(a) (>30 mg/dL) and 8,317 (68.9%) patients had low Lp(a) (≤30 mg/dL). During a median follow-up of 7.4 years, primary outcomes occurred in 1,490 patients, and the incidence rates of primary outcomes were 2.0 per 100 person-years in the high-Lp(a) group and 1.6 per 100 person-years in the low-Lp(a) group (adjusted hazard ratio [aHR]: 1.17; 95% confidence interval [CI]: 1.05-1.30; P = 0.004). Increased risk of recurrent ischemic cardiovascular events in the high-Lp(a) group was consistent in various subgroups including patients receiving statin treatment at discharge (aHR: 1.18; 95% CI: 1.03-1.34; P = 0.011). In addition, the risk of repeated revascularization was significantly higher in the high-Lp(a) group (aHR: 1.13; 95% CI: 1.02-1.25; P = 0.022). CONCLUSIONS: Elevated levels of Lp(a) were significantly associated with the recurrent ischemic events in patients who underwent PCI. This study provides a rationale for outcome trials to test Lp(a)-lowering therapy for secondary prevention in patients undergoing PCI.

[41] *Slomski A*. **Guidelines for Lipid-Lowering Therapy Intensification Rarely Followed**. Jama 2021; 326:800.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34547090
ABSTRACT

[42] *Navar AM, Fonarow GC*. **Transforming the Paradigm for Lipid Lowering**. JAMA cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34550298
ABSTRACT

[43] *Goyal S, Tanigawa Y, Zhang W et al.* **APOC3 genetic variation, serum triglycerides, and risk of coronary artery disease in Asian Indians, Europeans, and other ethnic groups**. Lipids in health and disease 2021; 20:113.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34548093
ABSTRACT

BACKGROUND: Hypertriglyceridemia has emerged as a critical coronary artery disease (CAD) risk factor. Rare loss-of-function (LoF) variants in apolipoprotein C-III have been reported to reduce triglycerides (TG) and are cardioprotective in American Indians and Europeans. However, there is a lack of data in other Europeans and non-Europeans. Also, whether genetically increased plasma TG due to ApoC-III is causally associated with increased CAD risk is still unclear and inconsistent. The objectives of this study were to verify the cardioprotective role of earlier reported six LoF variants of APOC3 in South Asians and other multi-ethnic cohorts and to evaluate the causal association of TG raising common variants for increasing CAD risk. METHODS: We performed gene-centric and Mendelian randomization analyses and evaluated the role of genetic variation encompassing APOC3 for affecting circulating TG and the risk for developing CAD. RESULTS: One rare LoF variant (rs138326449) with a 37% reduction in TG was associated with lowered risk for CAD in Europeans ($p = 0.007$), but we could not confirm this association in Asian Indians ($p = 0.641$). Our data could not validate the cardioprotective role of other five LoF variants analysed. A common variant rs5128 in the APOC3 was strongly associated with elevated TG levels showing a p-value $2.8 \times 10(-424)$. Measures of plasma ApoC-III in a small subset of Sikhs revealed a 37% increase in ApoC-III concentrations among homozygous mutant carriers than the wild-type carriers of rs5128. A genetically instrumented per 1SD increment of plasma TG level of 15 mg/dL would cause a mild increase (3%) in the risk for CAD ($p = 0.042$). CONCLUSIONS: Our results highlight the challenges of inclusion of rare variant information in clinical risk assessment and the generalizability of implementation of ApoC-III inhibition for treating atherosclerotic disease. More studies would be needed to confirm whether genetically raised TG and ApoC-III concentrations would increase CAD risk.

[44] *Schmidt AF, Hunt NB, Gordillo-Marañón M et al.* **Cholesteryl ester transfer protein (CETP) as a drug target for cardiovascular disease**. Nature communications 2021; 12:5640.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34561430

ABSTRACT

Development of cholesteryl ester transfer protein (CETP) inhibitors for coronary heart disease (CHD) has yet to deliver licensed medicines. To distinguish compound from drug target failure, we compared evidence from clinical trials and drug target Mendelian randomization of CETP protein concentration, comparing this to Mendelian randomization of proprotein convertase subtilisin/kexin type 9 (PCSK9). We show that previous failures of CETP inhibitors are likely compound related, as illustrated by significant degrees of between-compound heterogeneity in effects on lipids, blood pressure, and clinical outcomes observed in trials. On-target CETP inhibition, assessed through Mendelian randomization, is expected to reduce the risk of CHD, heart failure, diabetes, and chronic kidney disease, while increasing the risk of age-related macular degeneration. In contrast, lower PCSK9 concentration is anticipated to decrease the risk of CHD, heart failure, atrial fibrillation, chronic kidney disease, multiple sclerosis, and stroke, while potentially increasing the risk of Alzheimer's disease and asthma. Due to distinct effects on lipoprotein metabolite profiles, joint inhibition of CETP and PCSK9 may provide added benefit. In conclusion, we provide genetic evidence that CETP is an effective target for CHD prevention but with a potential on-target adverse effect on age-related macular degeneration.

[45] *Burlutskaya AV, Tril VE, Polischuk LV, Pokrovskii VM*. **Dyslipidemia in pediatrician's practice**. Reviews in cardiovascular medicine 2021; 22:817-834.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34565080

ABSTRACT

Atherosclerosis ranks first among cardiovascular system diseases. It is the "disease of the century", and more than 50% of people with circulatory pathology die of it. The clinical manifestation of atherosclerosis is observed at the middle and older ages, but it is known that the pathological process develops much earlier. There has been a clear trend in theoretical and practical cardiology in recent years to study the earliest atherogenic markers. Epidemiological, clinical, and morphological studies have proved the presence in children and adolescents of sexual, endogenous, exogenous, primary, and potentiating risk factors contributing to an early formation of a pathogenic foundation for atherosclerotic cardiovascular diseases. Disorders of lipid metabolism - dyslipidemias are attributed to the most significant risk factor for atherosclerotic cardiovascular diseases. The DLP prevalence in the pediatric population is extremely high. According to the results of conducted global studies, lipid metabolism disorders occur in more than 70% of children and adolescents. It causes the need for timely diagnostic, therapeutic and preventive measures. The need to extrapolate the risk factor concept to childhood age is justified by several reasons, the main of which include the broadest spread of atherosclerosis that has become a global pandemic, genetic determinism, and low variability of the lipid spectrum of blood serum: the levels of lipids and lipoproteins discovered in childhood are stable throughout life and have an independent prognostic value. That is why the most practical significance is inherent to the study of lipid and lipoprotein metabolism, starting in the early periods of lipid and lipoprotein ontogenesis. Since risk factors can be identified at the preclinical stage of the atherosclerotic process, dyslipidemia phenotyping will facilitate identifying children and adolescents at risk of developing cardiovascular pathologies in the future. The study objective is to examine the pathophysiological aspects of lipid and lipoprotein metabolism and examine DLP epidemiology - as the leading atherosclerotic cardiovascular disease risk factor in children and adolescents, DLP classification, modern approaches to DLP diagnosis and management.

[46] *Galiero R, Caturano A, Vetrano E et al.* **Pathophysiological mechanisms and clinical evidence of relationship between Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease**. Reviews in cardiovascular medicine 2021; 22:755-768.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34565074

ABSTRACT

Evidence suggests a close connection between Nonalcoholic Fatty Liver Disease (NAFLD) and increased cardiovascular (CV) risk. Several cross-sectional studies report that NAFLD is related to preclinical atherosclerotic damage, and to coronary, cerebral and peripheral vascular events. Similar results have been showed by prospective studies and also by meta-analyzes on observational studies. The pathophysiological mechanisms of NAFLD are related to insulin resistance, which causes a dysfunction in adipokine production, especially adiponectin, from adipose tissue. A proinflammatory state and an increase in oxidative stress, due to increased reacting oxygen species (ROS) formation with consequent oxidation of free fatty acids and increased de novo lipogenesis with accumulation of triglycerides, are observed. These mechanisms may have an impact on atherosclerotic plaque formation and progression, and they can lead to increased cardiovascular risk in subjects with NAFLD. This review extensively discusses and comments current and developing NAFLD therapies and their possible impact on cardiovascular outcome.

[47] *Alketbi EH, Hamdy R, El-Kabalawy A et al.* **Lipid-based therapies against SARS-CoV-2 infection**. Rev Med Virol 2021; 31:1-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34546604
ABSTRACT
Viruses have evolved to manipulate host lipid metabolism to benefit their replication cycle. Enveloped viruses, including coronaviruses, use host lipids in various stages of the viral life cycle, particularly in the formation of replication compartments and envelopes. Host lipids are utilised by the virus in receptor binding, viral fusion and entry, as well as viral replication. Association of dyslipidaemia with the pathological development of Covid-19 raises the possibility that exploitation of host lipid metabolism might have therapeutic benefit against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this review, promising host lipid targets are discussed along with potential inhibitors. In addition, specific host lipids are involved in the inflammatory responses due to viral infection, so lipid supplementation represents another potential strategy to counteract the severity of viral infection. Furthermore, switching the lipid metabolism through a ketogenic diet is another potential way of limiting the effects of viral infection. Taken together, restricting the access of host lipids to the virus, either by using lipid inhibitors or supplementation with exogenous lipids, might significantly limit SARS-CoV-2 infection and/or severity.

[48] *Qi L, Zhang Q, Zheng Z et al.* **Treatment of Chinese Patients with Hypertriglyceridemia with a Pharmaceutical-Grade Preparation of Highly Purified Omega-3 Polyunsaturated Fatty Acid Ethyl Esters: Main Results of a Randomized, Double-Blind, Controlled Trial**. Vascular health and risk management 2021; 17:571-580.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34552329
ABSTRACT
INTRODUCTION: The lipid-modifying potential of omega-3 polyunsaturated fatty acids in Chinese patients is under-researched. We conducted a multicenter, randomized, placebo-controlled, double-blind, parallel-group study of twice-daily treatment with OMACOR (OM3EE), a prescription-only formulation of highly purified ethyl esters of omega-3 polyunsaturated fatty acids in Chinese adult patients (≥18 years) who had elevated baseline fasting serum triglycerides (TG). METHODS: Patients were stratified according to the severity of their hypertriglyceridemia (severe HTG, with baseline TG ≥500 and <1000 mg/dL or moderate HTG, with baseline TG >200 and <500 mg/dL) or use of statins. Patients randomized to OM3EE therapy received 2 g/day for 4 weeks, then 4 g/day for 8 weeks. The primary efficacy endpoint was the percentage change in fasting serum TG between baseline and the end of treatment in patients with severe HTG. The study was concluded after a planned interim analysis demonstrated a significant TG-lowering effect of OM3EE in that contingent (p=0.0019). RESULTS: The mean TG end-of-treatment effect of OM3EE was -29.46% (standard deviation 40.60%) in the severe HTG contingent compared with +0.26% (standard deviation 54.68%) in the placebo group. Corresponding changes were -12.12% and -23.25% in the moderate HTG and combination cohorts (vs +55.45% and +6.24% in relevant placebo groups). A dose-dependent reduction in TG was evident in all patient contingents. Safety and tolerability of OM3EE were in line with previous experience. DISCUSSION: These data indicate that OMACOR therapy at a dose of 2-4 g/day is an effective treatment for Chinese patients with raised TG levels and is well tolerated.

[49] *Masson W, Lobo M, Barbagelata L et al.* **Effects of lipid-lowering therapy on major adverse limb events in patients with peripheral arterial disease: A meta-analysis of randomized clinical trials**. Vascular 2021:17085381211043952.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34541946

ABSTRACT
OBJECTIVE: Patients with peripheral artery disease (PAD) are at increased risk of major adverse limb events (MALE). Furthermore, MALE have several clinical implications and a poor prognosis, so prevention is a fundamental issue. The main objective of the present meta-analysis of randomized clinical trials is to evaluate the effect of different lipid-lowering therapies on MALE incidence in patients with PAD. METHODS: A meta-analysis of randomized studies that evaluated the use of lipid-lowering therapy in patients with PAD and reported MALE was performed, after searching the PubMed/MEDLINE, Embase, ScieLO, Google Scholar, and Cochrane Controlled Trials databases. A fixed- or random-effects model was used. RESULTS: Five randomized clinical trials including 11,603 patients were identified and considered eligible for the analyses (5903 subjects were allocated to receive lipid-lowering therapy, while 5700 subjects were allocated to the respective placebo/control arms). The present meta-analysis revealed that lipid-lowering therapy was associated with a lower incidence of MALE (OR: 0.76, 95% confidence interval: 0.66-0.87; I2: 28%) compared to placebo/control groups. The sensitivity analysis shows that the results are robust. CONCLUSION: This study demonstrated that the use of lipid-lowering therapy compared with the placebo/control arms was associated with a marked reduction in the risk of MALE. Physicians involved in the monitoring and treatment of patients with PAD must work hard to ensure adequate lipid-lowering medication in these patients.