[1] *Shao A, Lin D, Wang L et al.* **Oxidative Stress at the Crossroads of Aging, Stroke and Depression**. Aging and disease 2020; 11:1537-1566.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33269106
ABSTRACT
Epidemiologic studies have shown that in the aging society, a person dies from stroke every 3 minutes and 42 seconds, and vast numbers of people experience depression around the globe. The high prevalence and disability rates of stroke and depression introduce enormous challenges to public health. Accumulating evidence reveals that stroke is tightly associated with depression, and both diseases are linked to oxidative stress (OS). This review summarizes the mechanisms of OS and OS-mediated pathological processes, such as inflammation, apoptosis, and the microbial-gut-brain axis in stroke and depression. Pathological changes can lead to neuronal cell death, neurological deficits, and brain injury through DNA damage and the oxidation of lipids and proteins, which exacerbate the development of these two disorders. Additionally, aging accelerates the progression of stroke and depression by overactive OS and reduced antioxidant defenses. This review also discusses the efficacy and safety of several antioxidants and antidepressants in stroke and depression. Herein, we propose a crosstalk between OS, aging, stroke, and depression, and provide potential therapeutic strategies for the treatment of stroke and depression.

[2] *Trevillyan JM, Dart A, Paul E et al.* **Impact of rosuvastatin on atherosclerosis in people with HIV at moderate cardiovascular risk; a randomised, controlled trial**. Aids 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33252480
ABSTRACT
: People living with HIV-1 (PLHIV) are at increased risk for cardiovascular disease. OBJECTIVE: This study aimed to determine if PLHIV would benefit from starting statins at a lower threshold than currently recommended in the general population. DESIGN: A double-blind multicentre, randomised, placebo-controlled trial was performed. METHODS: Participants (n=88) with well controlled HIV, at moderate cardiovascular risk (Framingham score of 10-15%), and not recommended for statins were recruited from Australia and Switzerland. They were randomised 1:1 to rosuvastatin (n=44) 20mg daily, 10mg if co-administered with ritonavir/cobicistat-boosted antiretroviral therapy, or placebo (n=40) for 96 weeks. Assessments including fasting blood collection and carotid intima media thickness (CIMT) were performed at baseline, and weeks 48 and 96. The primary outcome was the change from baseline to week 96 in CIMT. (clinicaltrials.gov:NCT01813357) RESULTS:: Participants were predominantly male (82 (97·6%)); mean age 54 years (SD 6·0). At 96 weeks there was no difference in the progression of CIMT between the rosuvastatin (mean 0·004mm, SE 0·0036) and placebo (0·0062mm, SE 0·0039) arms (p value=0·684), leading to no difference in CIMT levels between groups at week 96 (rosuvastatin arm, 0·7232mm (SE 0·030); placebo arm 0·7785mm (SE 0·032), p=0·075).Adverse events were common (n=146) and predominantly in the rosuvastatin arm (108 [73·9%]). Participants on rosuvastatin were more likely to cease study medication due to an adverse event (7 [15.9%] vs 2 [5·0%], p=0.011). CONCLUSIONS: In PLHIV statins prescribed at a lower threshold than guidelines did not lead to improvements in CIMT but was associated with significant adverse events.

[3] *Jiao S, Huang J, Chen Y et al.* **Impacts of Glycemic Control on Intracranial Plaque in Patients with Type 2 Diabetes Mellitus: A Vessel Wall MRI Study**. AJNR. American journal of neuroradiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33272948

ABSTRACT

BACKGROUND AND PURPOSE: The relationship between glycemic control in patients with type 2 diabetes mellitus and intracranial atherosclerotic plaque features has remained understudied. This study aimed to investigate the association of type 2 diabetes mellitus and glycemic control with the characteristics of intracranial plaques using vessel wall MR imaging. MATERIALS AND METHODS: In total, 311 patients (217 [69.8%] men; mean age, 63.24 ± 11.44 years) with intracranial atherosclerotic plaques detected on vessel wall MR imaging were enrolled and divided into 3 groups according to type 2 diabetes mellitus and glycemic control statuses: the non-type 2 diabetes mellitus group, the type 2 diabetes mellitus with good glycemic control group, and the type 2 diabetes mellitus with poor glycemic control group. The imaging features of intracranial plaque were analyzed and compared among the groups. The clinical risk factors for atherosclerosis were also analyzed using logistic regression analysis. RESULTS: The plaque length and thickness were significantly higher in the type 2 diabetes mellitus with poor glycemic control group than in the non-type 2 diabetes mellitus group. The prevalence of strongly enhanced plaques was significantly higher in the type 2 diabetes mellitus with poor glycemic control group than in the non-type 2 diabetes mellitus and type 2 diabetes mellitus with good glycemic control groups (92.9%, 63.4%, and 72.7%, respectively; $P < .001$). Multivariate logistic regression analysis showed a significant association of poor glycemic control with the plaque length (OR = 1.966; 95% CI, 1.170-3.303; $P = .011$), plaque thickness (OR = 1.981; 95% CI, 1.174-3.340; $P = .010$), and strongly enhanced plaque (OR = 5.448; 95% CI, 2.385-12.444; $P < .001$). CONCLUSIONS: Poor glycemic control, compared with the history of diabetes, might have a greater impact on the burden and vulnerability of intracranial atherosclerotic plaques.

[4] *Ramhormozi P, Ansari JM, Simorgh S et al.* **Simvastatin accelerates the healing process of burn wound in Wistar rats through Akt/mTOR signaling pathway**. Ann Anat 2020:151652.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33278579

ABSTRACT

Statins, apart from cholesterol-lowering properties, have wound healing effects. Hereby, we aimed to assess the impact of Simvastatin (SMV), one of the most commonly used statins, on Akt/mTOR signaling pathway during burn wound healing process. After creating a second-degree burn on the dorsal area of adult male Wistar rats (n = 60), they were randomly divided into the control, SMV, vehicle of Simvastatin (SMV-Veh), Rapamycin (RM), vehicle of Rapamycin (RM-Veh), and combined SMV and RM (SMV + RM) groups. The animals were sacrificed on the 7(th) and 14(th) post-burn days and wound tissue samples were collected for histologic, immunohistochemical, quantitative real-time polymerase chain reaction (qRT-PCR), and western blot investigations. Rapamycin (RM) was also used to treat animals as an mTOR inhibitor. Topical administration of SMV resulted in a faster healing rate, elevated collagen deposition, and increased myofibroblast population compared to other experimental groups. Moreover, qRT-PCR findings showed that the wounds treated with SMV alone had the highest expression levels of CD31, VEGF, Akt, mTOR, and p70S6K after 7 and 14 days of burn model ($p < 0.001$). According to western blot findings, daily topical treatment with SMV further increased protein levels of P-Akt(Thr308), P-mTOR(Ser2448), and P-p70S6K(Thr389) compared with

other treatments, at both follow-up time points ($p < 0.001$). In contrast, inhibition of Akt/mTOR signaling pathway by RM reduced SMV-induced wound healing process. Seemingly, SMV promotes burn wound healing, at least in part, through activating Akt/mTOR signaling pathway, suggesting topically applied SMV as an alternative therapeutic approach for managing burn wound healing.

[5] *El Khoudary SR, Chen X, Nasr A et al.* **HDL (High-Density Lipoprotein) Subclasses, Lipid Content, and Function Trajectories Across the Menopause Transition: SWAN-HDL Study**. Arteriosclerosis, thrombosis, and vascular biology 2020:Atvbaha120315355.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33267661

ABSTRACT

OBJECTIVE: The cardioprotective capacity of HDL (high-density lipoprotein) cholesterol postmenopause has been challenged. HDL subclasses, lipid contents, and function might be better predictors of cardiovascular risk than HDL cholesterol. Changes in these measures have not been characterized over the menopause transition (MT) with respect to timing relative to the final menstrual period. Approach and Results: Four hundred seventy-one women with HDL particle (HDL-P) subclasses (nuclear magnetic resonance spectroscopy total, large, medium, and small HDL-P and HDL size), HDL lipid content (HDL phospholipids and triglycerides), and HDL function (cholesterol efflux capacity [HDL-CEC]) measured for a maximum of 5 time points across the MT were included. HDL cholesterol and total HDL-P increased across the MT. Within the 1 to 2 years bracketing the final menstrual period, large HDL-P and HDL size declined while small HDL-P and HDL-triglyceride increased. Although overall HDL-CEC increased across the MT, HDL-CEC per HDL-P declined. Higher concentrations of total, large, and medium HDL-P and greater HDL size were associated with greater HDL-CEC while of small HDL-P were associated with lower HDL-CEC. Associations of large HDL-P and HDL size with HDL-CEC varied significantly across the MT such that higher large HDL-P concentrations and greater HDL size were associated with lower HDL-CEC within the 1 to 2 years around the final menstrual period. CONCLUSIONS: Although HDL cholesterol increased over the MT, HDL subclasses and lipid content showed adverse changes. While overall HDL-CEC increased, HDL-CEC per HDL-P declined, consistent with reduced function per particle. Large HDL-P may become less efficient in promoting HDL-CEC during the MT.

[6] *Van Doren L, Nguyen N, Garzia C et al.* **Lipid Receptor GPR31 (G-Protein-Coupled Receptor 31) Regulates Platelet Reactivity and Thrombosis Without Affecting Hemostasis**. Arteriosclerosis, thrombosis, and vascular biology 2021; 41:e33-e45.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33267659

ABSTRACT

OBJECTIVE: 12-LOX (12-lipoxygenase) produces a number of bioactive lipids including 12(S)-HETE that are involved in inflammation and platelet reactivity. The GPR31 (G-protein-coupled receptor 31) is the proposed receptor of 12(S)-HETE; however, it is not known whether the 12(S)-HETE-GPR31 signaling axis serves to enhance or inhibit platelet activity. Approach and Results: Using pepducin technology and biochemical approaches, we provide evidence that 12(S)-HETE-GPR31 signals through Gi to enhance PAR (protease-activated receptor)-4-mediated platelet activation and arterial thrombosis using both human platelets and mouse carotid artery injury models. 12(S)-HETE suppressed AC (adenylyl cyclase) activity through GPR31 and resulted in Rap1 (Ras-related protein 1) and p38 activation and low but detectable calcium flux but did not induce platelet aggregation. A

GPR31 third intracellular (i3) loop-derived pepducin, GPR310 (G-protein-coupled receptor 310), significantly inhibited platelet aggregation in response to thrombin, collagen, and PAR4 agonist, AYPGKF, in human and mouse platelets but relative sparing of PAR1 agonist SFLLRN in human platelets. GPR310 treatment gave a highly significant 80% protection (P=0.0018) against ferric chloride-induced carotid artery injury in mice by extending occlusion time, without any effect on tail bleeding. PAR4-mediated dense granule secretion and calcium flux were both attenuated by GPR310. Consistent with these results, GPR310 inhibited 12(S)-HETE-mediated and PAR4-mediated Rap1-GTP and RASA3 translocation to the plasma membrane and attenuated PAR4-Akt and ERK activation. GPR310 caused a right shift in thrombin-mediated human platelet aggregation, comparable to the effects of inhibition of the Gi-coupled P2Y(12) receptor. Co-immunoprecipitation studies revealed that GPR31 and PAR4 form a heterodimeric complex in recombinant systems. CONCLUSIONS: The 12-LOX product 12(S)-HETE stimulates GPR31-Gi-signaling pathways, which enhance thrombin-PAR4 platelet activation and arterial thrombosis in human platelets and mouse models. Suppression of this bioactive lipid pathway, as exemplified by a GPR31 pepducin antagonist, may provide beneficial protective effects against platelet aggregation and arterial thrombosis with minimal effect on hemostasis.

[7] *Garrahy E, Heal C, Hespe CM et al.* **Familial hypercholesterolaemia and cascade testing in general practice: Lessons from COVID-19**. Australian journal of general practice 2020; 49:859-860.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33254219
ABSTRACT

[8] *Golforoush P, Yellon DM, Davidson SM*. **Mouse models of atherosclerosis and their suitability for the study of myocardial infarction**. Basic research in cardiology 2020; 115:73.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33258000
ABSTRACT
Atherosclerotic plaques impair vascular function and can lead to arterial obstruction and tissue ischaemia. Rupture of an atherosclerotic plaque within a coronary artery can result in an acute myocardial infarction, which is responsible for significant morbidity and mortality worldwide. Prompt reperfusion can salvage some of the ischaemic territory, but ischaemia and reperfusion (IR) still causes substantial injury and is, therefore, a therapeutic target for further infarct limitation. Numerous cardioprotective strategies have been identified that can limit IR injury in animal models, but none have yet been translated effectively to patients. This disconnect prompts an urgent re-examination of the experimental models used to study IR. Since coronary atherosclerosis is the most prevalent morbidity in this patient population, and impairs coronary vessel function, it is potentially a major confounder in cardioprotective studies. Surprisingly, most studies suggest that atherosclerosis does not have a major impact on cardioprotection in mouse models. However, a major limitation of atherosclerotic animal models is that the plaques usually manifest in the aorta and proximal great vessels, and rarely in the coronary vessels. In this review, we examine the commonly used mouse models of atherosclerosis and their effect on coronary artery function and infarct size. We conclude that none of the commonly used strains of mice are ideal for this purpose; however, more recently developed mouse models of atherosclerosis fulfil the requirement for coronary artery lesions, plaque rupture and lipoprotein patterns resembling the human profile, and may enable the identification of therapeutic interventions more applicable in the clinical setting.

[9] *Chan HC, Ke LY, Lu HT et al.* **An Increased Plasma Level of ApoCIII-Rich Electronegative High-Density Lipoprotein May Contribute to Cognitive Impairment in Alzheimer's Disease**. Biomedicines 2020; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33256187

ABSTRACT

High-density lipoprotein (HDL) plays a vital role in lipid metabolism and anti-inflammatory activities; a dysfunctional HDL impairs cholesterol efflux pathways. To understand HDL's role in patients with Alzheimer's disease (AD), we analyzed the chemical properties and function. HDL from AD patients (AD-HDL) was separated into five subfractions, H1-H5, using fast-protein liquid chromatography equipped with an anion-exchange column. Subfraction H5, defined as the most electronegative HDL, was increased 5.5-fold in AD-HDL (23.48 ± 17.83%) in comparison with the control HDL (4.24 ± 3.22%). By liquid chromatography mass spectrometry (LC/MS(E)), AD-HDL showed that the level of apolipoprotein (apo)CIII was elevated but sphingosine-1-phosphate (S1P)-associated apoM and anti-oxidative paraoxonase 1 (PON1) were reduced. AD-HDL showed a lower cholesterol efflux capacity that was associated with the post-translational oxidation of apoAI. Exposure of murine macrophage cell line, RAW 264.7, to AD-HDL induced a vibrant expression of ganglioside GM1 in colocalization with apoCIII on lipid rafts alongside a concomitant increase of tumor necrosis factor-α (TNF-α) detectable in the cultured medium. In conclusion, AD-HDL had a higher proportion of H5, an apoCIII-rich electronegative HDL subfraction. The associated increase in pro-inflammatory (apoCIII, TNF-α) components might favor Amyloid β assembly and neural inflammation. A compromised cholesterol efflux capacity of AD-HDL may also contribute to cognitive impairment.

[10] *Kassahun-Yimer W, Valle KA, Oshunbade AA et al.* **Joint modelling of longitudinal lipids and time to coronary heart disease in the Jackson Heart Study**. BMC Med Res Methodol 2020; 20:294.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33272219

ABSTRACT

BACKGROUND: Multiple longitudinal responses together with time-to-event outcome are common in biomedical studies. There are several instances where the longitudinal responses are correlated with each other and at the same time each longitudinal response is associated with the survival outcome. The main purpose of this study is to present and explore a joint modeling approach for multiple correlated longitudinal responses and a survival outcome. The method will be illustrated using the Jackson Heart Study (JHS), which is one of the largest cardiovascular studies among African Americans. METHODS: Four longitudinal responses, i.e., total cholesterol (TC), high density lipoprotein (HDL) cholesterol, triglyceride (TG) and inflammation measured by high-sensitivity C-reactive protein (hsCRP); and time-to-coronary heart disease (CHD) were considered from the JHS. The repeated lipid and hsCRP measurements from a given subject overtime are likely correlated with each other and could influence the subject's risk for CHD. A joint modeling framework is considered. To deal with the high dimensionality due to the multiple longitudinal profiles, we use a pairwise bivariate model fitting approach that was developed in the context of multivariate Gaussian random effects models. The method is further explored through simulations. RESULTS: The proposed model performed well in terms of bias and relative efficiency. The JHS data analysis showed that lipid and hsCRP trajectories could exhibit interdependence in their joint evolution and have impact on CHD

risk. CONCLUSIONS: We applied a unified and flexible joint modeling approach to analyze multiple correlated longitudinal responses and survival outcome. The method accounts for the correlation among the longitudinal responses as well as the association between each longitudinal response and the survival outcome at once. This helps to explore how the combination of multiple longitudinal trajectories could be related to the survival process.

[11] *Zhao X, Ma X, Luo X et al.* **Efficacy and safety of bempedoic acid alone or combining with other lipid-lowering therapies in hypercholesterolemic patients: a meta-analysis of randomized controlled trials**. BMC pharmacology & toxicology 2020; 21:86.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33276805
ABSTRACT
BACKGROUND: Bempedoic acid is a new drug that reduces cholesterol synthesis via inhibiting ATP citrate lyase. It remains unclear whether the combination of bempedoic acid and other lipid-lowering drugs is better than these drugs alone. This study systematically reviewed the efficacy and safety of bempedoic acid monotherapy or combination togethers in hypercholesterolemic patients. METHODS: Randomized controlled trials were searched across Medline, Embase, Cochrane library, web of science, etc. The net change scores [least squares mean (LSM) percentage change] in LDL-C level were meta-analyzed using weighted mean difference. The reductions in other lipids including total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (ApoB) and high sensitivity C reactive protein (hsCRP) were also assessed. Odds ratio (OR) of the incidence of adverse events (AEs) were calculated to evaluate the safety of bempedoic acid. RESULTS: A total of 13 trials (4858 participates) were included. Pooled data showed that the combination togethers resulted in greater reductions in LDL-C level than monotherapies (bempedoic acid + statin vs. statin: LSM difference (%), -18.37, 95% CI, -20.16 to -16.57, I(2) = 0; bempedoic acid + ezetimibe vs. ezetimibe: LSM difference (%), -18.89, 95% CI, -29.66 to -8.13, I(2) = 87%). But the difference in efficacy between bempedoic acid and ezetimibe was not obvious. Meta-regression analysis showed the treatment duration was a source of heterogeneity (adj R(2) = 16.92, 95% CI, 0.04 to 0.72). Furthermore, the background therapy of statin before screening decreased the efficacy of bempedoic acid. In addition, bempedoic acid also resulted in a significant reduction in TC, non-HDL-C, ApoB and hsCRP level. The OR of muscle-related AEs by the combination of bempedoic acid and statin was 1.29 (95% CI, 1.00 to 1.67, I(2) = 0) when compared with statin alone. CONCLUSION: This study showed the efficacy of combination togethers were similar but stronger than these drugs alone. Of note, a trend of high risk of muscle-related AEs by the combination of bempedoic acid and statin was observed, though it is not statistically significant, such risk is needed to be confirmed by more trials, because it is important for us to determine which is the better combinative administration for statin-intolerant patients.

[12] *Otte C, Chae WR, Nowacki J et al.* **Simvastatin add-on to escitalopram in patients with comorbid obesity and major depression (SIMCODE): study protocol of a multicentre, randomised, double-blind, placebo-controlled trial**. BMJ open 2020; 10:e040119.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33262189
ABSTRACT
INTRODUCTION: Major depressive disorder (MDD) and obesity are both common disorders associated with significant burden of disease worldwide. Importantly, MDD and obesity often co-

occur, with each disorder increasing the risk for developing the other by about 50%-60%. Statins are among the most prescribed medications with well-established safety and efficacy. Statins are recommended in primary prevention of cardiovascular disease, which has been linked to both MDD and obesity. Moreover, statins are promising candidates to treat MDD because a meta-analysis of pilot randomised controlled trials has found antidepressive effects of statins as adjunct therapy to antidepressants. However, no study so far has tested the antidepressive potential of statins in patients with MDD and comorbid obesity. Importantly, this is a difficult-to-treat population that often exhibits a chronic course of MDD and is more likely to be treatment resistant. Thus, in this confirmatory randomised controlled trial, we will determine whether add-on simvastatin to standard antidepressant medication with escitalopram is more efficacious than add-on placebo over 12 weeks in 160 patients with MDD and comorbid obesity. METHODS AND ANALYSIS: This is a protocol for a randomised, placebo-controlled, double-blind multicentre trial with parallel-group design (phase II). One hundred and sixty patients with MDD and comorbid obesity will be randomised 1:1 to simvastatin or placebo as add-on to standard antidepressant medication with escitalopram. The primary outcome is change in the Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to week 12. Secondary outcomes include MADRS response (defined as 50% MADRS score reduction from baseline), MADRS remission (defined as MADRS score <10), mean change in patients' self-reported Beck Depression Inventory (BDI-II) and mean change in high-density lipoprotein, low-density lipoprotein and total cholesterol from baseline to week 12. ETHICS AND DISSEMINATION: This protocol has been approved by the ethics committee of the federal state of Berlin (Ethik-Kommission des Landes Berlin, reference: 19/0226-EK 11) and by the relevant federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), reference: 4043387). Study findings will be published in peer-reviewed journals and will be presented at (inter)national conferences. TRIAL REGISTRATION NUMBERS: NCT04301271, DRKS00021119, EudraCT 2018-002947-27.

[13] *Dilba K, van Dijk AC, Crombag G et al.* **Association between Intraplaque Hemorrhage and Vascular Remodeling in Carotid Arteries: The Plaque at RISK (PARISK) Study**. Cerebrovasc Dis 2020:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33271533
ABSTRACT
INTRODUCTION: Vascular remodeling is a compensatory enlargement of the vessel wall in response to atherosclerotic plaque growth. We aimed to investigate the association between intraplaque hemorrhage (IPH), vascular remodeling, and luminal dimensions in recently symptomatic patients with mild to moderate carotid artery stenosis in which the differences in plaque size were taken into account. MATERIALS AND METHODS: We assessed vessel dimensions on MRI of the symptomatic carotid artery in 164 patients from the Plaque At RISK study. This study included patients with recent ischemic neurological event and ipsilateral carotid artery stenosis <70%. The cross section with the largest wall area (WA) in the internal carotid artery (ICA) was selected for analysis. On this cross section, the following parameters were determined: WA, total vessel area (TVA), and lumen area (LA). Vascular remodeling was quantified as the remodeling ratio (RR) and was calculated as TVA at this position divided by the TVA in an unaffected distal portion of the ipsilateral ICA. Adjustment for WA was performed to correct for plaque size. RESULTS: Plaques with IPH had a larger WA (0.56 vs. 0.46 cm2; $p < 0.001$), a smaller LA (0.17 vs. 0.22 cm2; $p = 0.03$), and a higher RR (2.0 vs. 1.9; $p = 0.03$) than plaques without IPH. After adjustment for WA, plaques containing IPH had a smaller LA (B

= -0.052, p = 0.01) than plaques without IPH, but the RR was not different. CONCLUSION: After correcting for plaque size, plaques containing IPH had a smaller LA than plaques without IPH. However, RR was not different.

[14] *Sun LQ, Liu JY, He Y et al.* **Evolution of blood lipids and risk factors of dyslipidemia among people living with human immunodeficiency virus who had received first-line antiretroviral regimens for 3 years in Shenzhen**. Chinese medical journal 2020; 133:2808-2815.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33273329

ABSTRACT

BACKGROUND: Lipid abnormalities are prevalent among people living with human immunodeficiency virus (HIV) (PLWH) and contribute to increasing risk of cardiovascular events. This study aims to investigate the incidence of dyslipidemia and its risk factors in PLWH after receiving different first-line free antiretroviral regimens. METHODS: PLWH who sought care at the Third People's Hospital of Shenzhen from January 2014 to December 2018 were included, and the baseline characteristics and clinical data during the follow-up were collected, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The risk factors of dyslipidemia after antiretroviral therapy were analyzed with the generalized estimating equation model. RESULTS: Among the 7623 PLWH included, the mean levels of TC, HDL-C and LDL-C were 4.23±0.85 mmol/L, 1.27±0.29 mmol/L and 2.54±0.65 mmol/L, respectively, and the median TG was 1.17 (IQR: 0.85-1.68) mmol/L. Compared with that in PLWH receiving tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) + ritonavir-boosted lopinavir (LPV/r), zidovudine (AZT) + 3TC + efavirenz (EFV), and AZT + 3TC + LPV/r, the incidence of dyslipidemia was lower in PLWH receiving TDF + 3TC + EFV. In multivariate analysis, we found that the risks of elevations of TG, TC, and LDL-C were higher with TDF + 3TC + LPV/r (TG: odds ratio [OR] = 2.82, 95% confidence interval [CI]: 2.55-3.11, P<0.001; TC: OR=1.24, 95% CI: 1.14-1.35, P<0.001; LDL: OR=1.06, 95% CI: 1.00-1.12, P=0.041), AZT + 3TC + EFV (TG: OR=1.41, 95% CI: 1.28-1.55, P<0.001; TC: OR=1.43, 95% CI: 1.31-1.56, P<0.001; LDL: OR=1.18, 95% CI: 1.12-1.25, P<0.001), and AZT + 3TC + LPV/r (TG: OR=3.08, 95% CI: 2.65-3.59, P<0.001; TC: OR=2.40, 95% CI: 1.96-2.94, P<0.001; LDL: OR=1.52, 95% CI: 1.37-1.69, P<0.001) than with TDF + 3TC + EFV, while treatment with TDF + 3TC + LPV/r was less likely to restore HDL-C levels compared with TDF + 3TC + EFV (OR=0.95, 95% CI: 0.92-0.97, P<0.001). In addition to antiretroviral regimens, antiretroviral therapy duration, older age, overweight, obesity and other traditional factors were also important risk factors for dyslipidemia. CONCLUSION: The incidence of dyslipidemia varies with different antiretroviral regimens, with TDF + 3TC + EFV having lower risk for dyslipidemia than the other first-line free antiretroviral regimens in China.

[15] *Hoogeveen RC, Ballantyne CM*. **Residual Cardiovascular Risk at Low LDL: Remnants, Lipoprotein(a), and Inflammation**. Clinical chemistry 2021; 67:143-153.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33257928

ABSTRACT

BACKGROUND: Current guidelines target low-density lipoprotein cholesterol (LDL-C) concentrations to reduce atherosclerotic cardiovascular disease (ASCVD) risk, and yet clinical trials demonstrate persistent residual ASCVD risk despite aggressive LDL-C lowering. CONTENT: Non-LDL-C lipid parameters, most notably triglycerides, triglyceride-rich lipoproteins (TGRLs), and lipoprotein(a), and

C-reactive protein as a measure of inflammation are increasingly recognized as associated with residual risk after LDL-C lowering. Eicosapentaenoic acid in statin-treated patients with high triglycerides reduced both triglycerides and ASCVD events. Reducing TGRLs is believed to have beneficial effects on inflammation and atherosclerosis. High lipoprotein(a) concentrations increase ASCVD risk even in individuals with LDL-C < 70 mg/dL. Although statins do not generally lower lipoprotein(a), proprotein convertase subtilisin/kexin type 9 inhibitors reduce lipoprotein(a) and cardiovascular outcomes, and newer approaches are in development. Persistent increases in C-reactive protein after intensive lipid therapy have been consistently associated with increased risk for ASCVD events. SUMMARY: We review the evidence that biochemical assays to measure TGRLs, lipoprotein(a), and C-reactive protein are associated with residual risk in patients treated to low concentrations of LDL-C. Growing evidence supports a causal role for TGRLs, lipoprotein(a), and inflammation in ASCVD; novel therapies that target TGRLs, lipoprotein(a), and inflammation are in development to reduce residual ASCVD risk.

[16] *Aguilar-Galarza A, García-Gasca T, Mejía C et al.* **"Evening chronotype associates with increased triglyceride levels in young adults in two independent populations"**. Clinical nutrition (Edinburgh, Scotland) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33277074
ABSTRACT
BACKGROUND & AIMS: Evening chronotype has been linked with obesity, diabetes and metabolic syndrome (MetS) in middle-aged and older adults. However, few studies have analyzed this association in young adults. The aim of this study was to assess potential associations between individual chronotype and cardiometabolic outcomes in young adults of two independent populations from Europe and America. METHODS: Total population comprised 2 223 young adults (18-29 years old), 525 from Spain (Europe) and 1 698 from Mexico (America). Anthropometric, body composition and biochemical analyses were performed. Circadian preference was determined using the Morningness-Eveningness Questionnaire (MEQ). RESULTS: In these two young adult populations, a higher metabolic risk was found in those individuals with evening chronotypes, whereas those with neither or morning chronotypes showed lower cardiometabolic risk. Evening chronotypes showed lipid alterations with increased levels of triglycerides in both populations, VLDL-c in Spaniards and total cholesterol and LDL-c in Mexicans. Among the Mexican population, evening chronotypes showed higher MetS risk and more obesity traits than the other two chronotypes; no significant differences for the same comparison were found among the equivalent Spanish chronotypes. Evening chronotypes showed lower carbohydrates and higher fat intake in Spaniards, while they had lower fiber intake in Mexicans. The associations between MEQ score and cardiometabolic risk were independent of the dietary characteristics. Lifestyle factors differed among chronotypes with more smokers and habitual drinkers among evening chronotypes than in neither or morning chronotypes ($P < 0.05$). CONCLUSIONS: This study performed in two American and European independent populations shows that even in apparently healthy young adults, evening chronotypes have increased cardiometabolic risk and lipid alterations as compared to neither or morning chronotypes.

[17] *Gallo A, Perregaux J, Bruckert E*. **Advances in the management of statin myopathy**. Current opinion in endocrinology, diabetes, and obesity 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33278129

ABSTRACT
PURPOSE OF REVIEW: Statins are highly effective therapies for reducing low-density lipoprotein cholesterol and preventing cardiovascular events. However, many patients taking statins experience statin-associated muscle symptoms. In the current manuscript, we review algorithms to define statin intolerance and approaches to optimize cardiovascular risk reduction and reduce the nocebo effect among individuals reporting statin-associated muscle pain. RECENT FINDINGS: Patients with statin intolerance have a higher cardiovascular event risk. These data underscore the need to apply clinical strategies that improve treatment utilization and adherence of patients experiencing statin-related side effects. Recent data have shown that the nocebo effect is frequent with statin therapy. This may be explained by the high frequency of muscle symptoms in the general population and media misinformation. When statins even at a low dosage are not tolerated other therapies can be used such as fibrate, ezetimibe nutraceuticals and antiPCSK9 antibodies. Recent data have identified other alternative therapeutic strategies such as bempedoic acid. SUMMARY: There are multiple strategies for the management of statin-intolerance, both pharmacological and nonpharmacological. Patient involvement in the justification of statin treatment indication and therapeutic choice is the first step to overcome misbelief and reduce nocebo effect.

[18] *Lan NSR, Burns K, Bell DA, Watts GF*. **Best practice for treating dyslipidaemia in patients with diabetes based on current international guidelines**. Current opinion in endocrinology, diabetes, and obesity 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33278128
ABSTRACT
PURPOSE OF REVIEW: Dyslipidaemia is a major modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD) in type 2 diabetes. We provide an in-context overview of recent trials of lipid-lowering pharmacotherapies and of recommendations from international guidelines for managing dyslipidaemia in patients with diabetes. RECENT FINDINGS: Clinical trials have demonstrated that patients with diabetes derive greater benefits from ezetimibe and proprotein convertase subtilisin-kexin type 9 inhibitors owing to the higher absolute ASCVD risk compared with patients without diabetes. Pure eicosapentaenoic acid ethyl ester therapy should be considered in high risk patients with diabetes and hypertriglyceridaemia who have well controlled low-density lipoprotein cholesterol on statin therapy. International guidelines from USA, Canada and Europe have been updated to support a more intensive approach to treating dyslipidaemia in diabetes. SUMMARY: Dyslipidaemia should be identified and treated intensively as part of overall diabetes management to reduce ASCVD risk. Although lifestyle modifications and statin therapy remain the cornerstone of management, add-on therapies should be strongly considered depending on the absolute risk of ASCVD and the degree of dyslipidaemia.

[19] *Mohamed F, Seedat F, Raal FJ*. **Novel therapies for familial hypercholesterolemia**. Current opinion in endocrinology, diabetes, and obesity 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33278127
ABSTRACT
PURPOSE FOR REVIEW: Familial hypercholesterolemia is a genetic disorder of defective clearance and subsequent increase in serum LDL cholesterol (LDL-C) with a resultant increased risk of premature atherosclerotic cardiovascular disease. Despite treatment with traditional lipid-lowering

therapies (LLT), most patients with familial hypercholesterolemia are unable to achieve target LDL-C. We review current and future novel therapeutic options available for familial hypercholesterolemia. RECENT FINDINGS: The use of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors are effective in lowering LDL-C in patients with familial hypercholesterolemia, with a reduction in LDL-C of 60% in heterozygous familial hypercholesterolemia (HeFH) and up to 35% in homozygous familial hypercholesterolemia (HoFH). Inclisiran, another novel agent, is a small-interfering ribonucleic acid that reduces hepatic production of PCSK9 to provide a prolonged and sustained reduction in LDL-C of nearly 50% in HeFH. However, both agents require LDL receptor (LDLR) activity. Evinacumab, a novel monoclonal antibody against angiopoetin-like 3 (ANGPTL3), reduces LDL-C by 50% independent of LDLR activity. SUMMARY: Achieving a target LDL-C in familial hypercholesterolemia can be challenging with standard LLT; however, novel therapeutic modalities show remarkable reductions in LDL-C allowing nearly all patients with HeFH and a significant proportion of patients with HoFH to achieve acceptable LDL-C levels.

[20] *Hernández-Reyes A, Vidal Á, Moreno-Ortega A et al.* **Waist Circumference as a Preventive Tool of Atherogenic Dyslipidemia and Obesity-Associated Cardiovascular Risk in Young Adults Males: A Cross-Sectional Pilot Study**. Diagnostics (Basel, Switzerland) 2020; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33276653

ABSTRACT

Although the correlation coefficient between body mass index (BMI) and poor lipid profile has been reported, representing a cardiovascular risk, the need to find new early detection markers is real. Waist circumference and markers of atherogenic dyslipidemia are not usually measured in medical review appointments. The present study aimed to investigate the relationship between central adiposity and cardiovascular risk. This was a cross-sectional pilot study of 57 young males (age: 35.9 ± 10.85, BMI: 32.4 ± 6.08) recruited from community settings and allocated to non-obese or obese attending to their waist circumference. Total cholesterol (TC), high-density lipoproteins (HDL-C), and low-density lipoproteins (LDL-C) cholesterol and triglycerides (TG) were measured from plasma samples. Patients with at least 100 cm of waist circumference had significantly increased TC, LDL-C, non-HDL-C, and triglycerides and lower levels of HDL-C. The three atherogenic ratios TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C were all optimal in non-obese patients. LDL-C/HDL-C and TG/HDL-C were significantly higher and over the limit when assessing for atherogenic dyslipidemia. The number of patients at risk for cardiovascular events increases 2.5 folds in obese compared to non-obese. Measurement of waist circumference could be adopted as a simpler valid alternative to BMI for health promotion, to alert those at risk of atherogenic dyslipidemia.

[21] *Jeong IK, Kim SR.* **Efficacy and Safety of Pitavastatin in a Real-World Setting: Observational Study Evaluating SaFety in Patient Treated with Pitavastatin in Korea (PROOF Study)**. Endocrinol Metab (Seoul) 2020; 35:882-891.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33261312

ABSTRACT

BACKGROUND: While randomized controlled trials provide useful information about drug safety and efficacy, they do not always reflect the observed results in the real world. The prospective, observational, non-comparative trial in South Korea was designed to evaluate the efficacy and safety of pitavastatin in clinical practice in 28,343 patients. METHODS: This study was conducted in 893

facilities in Korea from April 2, 2012 to April 1, 2017. This study was designed to administer 1, 2, or 4 mg pitavastatin to patients with hyperlipidemia at the age of 20 or older for at least 8 weeks. RESULTS: For 126 days of mean duration of administration of pitavastatin, the % change of low density lipoprotein cholesterol indicated a dose dependent reduction: -23.4%, -29.1%, and -35.2% in the 1, 2, and 4 mg groups, respectively in patients who have not been treated with lipid lowering medications prior to study. Only 1.74% (492/28,343) of pitavastatin-treated patients experienced adverse events, of which 0.43% (123/28,343) were adverse drug reactions. Less than 1% of patients experienced the grade 2 or more toxicity (Common Terminology Criteria for Adverse Events v4.03) in alanine aminotransferase, aspartate aminotransferase, serum creatinine, and serum creatine phosphokinase. Although there were no rhabdomyolysis in 28,343 patients, 0.04% of patients had been reported pitavastatin-related musculoskeletal disorders. CONCLUSION: Overall, this observational study showed that pitavastatin was well tolerated and effectively modified the lipid profile, reducing cardiovascular and cerebrovascular risk in Korean patients with hypercholesterolemia in the real world.

[22] *Martelli A, Citi V, Calderone V*. **Recent efforts in drug discovery on vascular inflammation and consequent atherosclerosis**. Expert opinion on drug discovery 2020:1-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33256484
ABSTRACT
Introduction: Preservation of vascular endothelium integrity and maintenance of its full functionality are fundamental aspects in order to avoid both cardiovascular and non-cardiovascular diseases. Areas covered: Although a massive endothelial disruption is a rare condition, caused by acute and uncontrolled inflammatory responses (e.g. the cytokine storm induced by SARS-CoV-2 infection), more frequently the vascular tree is the first target of slowly progressive inflammatory processes which affect the integrity of endothelium and its 'barrier' function, supporting the onset of atherosclerotic plaque and spreading inflammation. This endothelial dysfunction leads to decrease NO biosynthesis, impaired regulation of vascular tone, and increased platelet aggregation. Such chronic subclinic inflammation leads to macrophage infiltration in atherosclerotic lesions. Therefore, many efforts should be addressed to find useful approaches to preserve vascular endothelium from inflammation. In this review, the authors have evaluated the most recent strategies to counteract this pathological condition. Expert opinion: The therapeutic and nutraceutical approaches represent useful tools to treat or prevent different phases of vascular inflammation. In particular, the pharmacological approach should be used in advanced phases characterized by clinical signs of vascular disease, whilst the nutraceutical approach may represent a promising preventive strategy to preserve the integrity of the endothelial tissue.

[23] *Aung N, Khanji MY, Munroe PB, Petersen SE*. **Causal Inference for Genetic Obesity, Cardiometabolic Profile and COVID-19 Susceptibility: A Mendelian Randomization Study**. Frontiers in genetics 2020; 11:586308.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33262790
ABSTRACT
BACKGROUND: Cross-sectional observational studies have reported obesity and cardiometabolic co-morbidities as important predictors of coronavirus disease 2019 (COVID-19) hospitalization. The causal impact of these risk factors is unknown at present. METHODS: We conducted multivariable

logistic regression to evaluate the observational associations between obesity traits (body mass index [BMI], waist circumference [WC]), quantitative cardiometabolic parameters (systolic blood pressure [SBP], serum glucose, serum glycated hemoglobin [HbA1c], low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol and triglycerides [TG]) and SARS-CoV-2 positivity in the UK Biobank cohort. One-sample MR was performed by using the genetic risk scores of obesity and cardiometabolic traits constructed from independent datasets and the genotype and phenotype data from the UK Biobank. Two-sample MR was performed using the summary statistics from COVID-19 host genetics initiative. Cox proportional hazard models were fitted to assess the risk conferred by different genetic quintiles of causative exposure traits. RESULTS: The study comprised 1,211 European participants who were tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 387,079 participants who were either untested or tested negative between 16 March 2020 to 31 May 2020. Observationally, higher BMI, WC, HbA1c and lower HDL-cholesterol were associated with higher odds of COVID-19 infection. One-sample MR analyses found causal associations between higher genetically determined BMI and LDL cholesterol and increased risk of COVID-19 (odds ratio [OR]: 1.15, confidence interval [CI]: 1.05-1.26 and OR: 1.58, CI: 1.21-2.06, per 1 standard deviation increment in BMI and LDL cholesterol respectively). Two-sample MR produced concordant results. Cox models indicated that individuals in the higher genetic risk score quintiles of BMI and LDL were more predisposed to COVID-19 (hazard ratio [HR]: 1.24, CI: 1.03-1.49 and HR: 1.37, CI: 1.14-1.65, for the top vs the bottom quintile for BMI and LDL cholesterol, respectively). CONCLUSION: We identified causal associations between BMI, LDL cholesterol and susceptibility to COVID-19. In particular, individuals in higher genetic risk categories were predisposed to SARS-CoV-2 infection. These findings support the integration of BMI into the risk assessment of COVID-19 and allude to a potential role of lipid modification in the prevention and treatment.

[24] *González Roldán N, Duda KA*. **Editorial: Role of Lipids in the Dynamics of Allergic Airway Inflammation**. Frontiers in immunology 2020; 11:612297.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33250902
ABSTRACT

[25] *Yu J, Zhu R, Yu K et al.* **Galectin-9: A Suppressor of Atherosclerosis?** Frontiers in immunology 2020; 11:604265.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33250901
ABSTRACT
It is no longer controversial that atherosclerosis is a vascular wall chronic inflammatory disease mediated by cells of innate and adaptive immunity. Galectin-9 (Gal-9) seems to be a crucial regulator of T-cell immunity by inducing apoptosis in specific T-cell subpopulations associated with autoimmunity and inflammatory disease. Accumulating evidence showed that galectin-9 signaling via T-cell immunoglobulin mucin 3 (TIM-3) is concerned with different regulatory functions in autoimmunity, including direct depletion of pro-inflammatory T-cells, expanding the number of regulatory T cells, altering macrophages to an anti-inflammatory state and the induction of repressive myeloid-derived suppressor cells. In addition, anti-Tim-3-Ab administration increased atherosclerotic plaque formation by blocking Tim-3-galectin-9 interaction. Hence, we hypothesize that galectin-9 may be a novel therapy for atherosclerotic disease. Further researches are needed to investigate the precise effect of galectin-9 in the process of atherosclerosis.

[26] *Li G, Shang Z, Liu Y et al.* **The Diagnostic Values of Pretreatment Serum Inflammation Markers and Lipoprotein in Men With Total Prostate-Specific Antigen Between 4 and 10 ng/ml**. Frontiers in medicine 2020; 7:576812.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33251229

ABSTRACT

Background: The purpose of this study was to analyze the values of pretreatment serum inflammation markers, lipid, and lipoprotein for predicting the pathological results in men with total prostate-specific antigen between 4 and 10 ng/ml. Materials and method: A total of 611 eligible patients diagnosed with total prostate-specific antigen between 4 and 10 ng/ml and who received a transrectal ultrasound-guided prostate biopsy between January 2014 and December 2019 were included in our study. All the patients were divided into groups according to their pathological results and we collected the data of their pretreatment indicators of the blood routine and biochemistry. Results: The pathological results from prostate biopsies from 160 patients with prostate cancer and 451 patients with benign lesions. Age and total prostate-specific antigen values were significantly higher in patients with prostate cancer than those with benign lesions ($P < 0.05$). Red blood cell, platelet count, prealbumin, and triglyceride were significantly lower in patients with prostate cancer than those with benign lesions. Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte- monocyte ratio, and apolipoprotein B were lower and apolipoprotein A-I was higher in the prostate cancer group than in the benign lesions group but not significantly ($P > 0.05$). Multivariate logistic regression revealed that age and total prostate-specific antigen could be independent predictors for pathological results (OR, 1.064, 95%CI, 1.031-1.098, $P < 0.001$; OR, 1.232, 95%CI, 1.061-1.429, $P = 0.006$). Conclusion: Higher age and total prostate-specific antigen were closely related to the pathological results. Prospective studies conducted with a large number of patients are needed to evaluate the diagnostic value of non-invasively pretreatment serum inflammation markers and lipoprotein for predicting the pathological results in men with total prostate-specific antigen between 4 and 10 ng/ml.

[27] *Andreadou I, Tsoumani M, Vilahur G et al.* **PCSK9 in Myocardial Infarction and Cardioprotection: Importance of Lipid Metabolism and Inflammation**. Front Physiol 2020; 11:602497.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33262707

ABSTRACT

Extensive evidence from epidemiologic, genetic, and clinical intervention studies has indisputably shown that elevated low-density lipoprotein cholesterol (LDL-C) concentrations play a central role in the pathophysiology of atherosclerotic cardiovascular disease. Apart from LDL-C, also triglycerides independently modulate cardiovascular risk. Reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a therapeutic target for reducing plasma LDL-C, but it is also associated with a reduction in triglyceride levels potentially through modulation of the expression of free fatty acid transporters. Preclinical data indicate that PCSK9 is up-regulated in the ischaemic heart and decreasing PCSK9 expression impacts on infarct size, post infarct inflammation and remodeling as well as cardiac dysfunction following ischaemia/reperfusion. Clinical data support that notion in that PCSK9 inhibition is associated with reductions in the incidence of myocardial infarction, stroke, and coronary revascularization and an improvement of endothelial function in subjects with increased cardiovascular risk. The aim of the current review is to summarize the current knowledge on the

importance of free fatty acid metabolism on myocardial ischaemia/reperfusion injury and to provide an update on recent evidence on the role of hyperlipidemia and PCSK9 in myocardial infarction and cardioprotection.

[28] *Wang KW, Liang CL, Yeh LR et al.* **Simvastatin-Ezetimibe enhances growth factor expression and attenuates neuron loss in the hippocampus in a model of intracerebral hemorrhage**. Fundamental & clinical pharmacology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33278834
ABSTRACT
Intracerebral hemorrhage (ICH) is a common and severe neurological disorder associated with high morbidity and mortality rates. Despite extensive research into its pathology, there are no clinically-approved neuroprotective treatments for ICH. Increasing evidence has revealed that inflammatory responses mediate the pathophysiological processes of brain injury following ICH. Experimental ICH was induced by direct infusion of 100 μL fresh (non-heparinized) autologous whole blood into the right basal ganglia of Sprague-Dawley rats at a constant rate (10 μL/min). The simvastatin group was administered simvastatin (15 mg/kg) and the combination therapy group was administered simvastatin (10 mg/kg) and ezetimibe (10 mg/kg). Magnetic resonance imaging (MRI), the forelimb use asymmetry test, the Morris water maze test, and two biomarkers were used to evaluate the effect of simvastatin and combination therapy. MRI imaging revealed that combination therapy resulted in significantly reduced perihematomal edema. Biomarker analyses revealed that both treatments led to significantly reduced endothelial inflammatory responses. The forelimb use asymmetry test revealed that both treatment groups had significantly improved neurological outcomes. The Morris water maze test revealed improved neurological function after combined therapy, which also led to less neuronal loss in the hippocampal CA1 region. In conclusion, simvastatin-ezetimibe combination therapy can improve neurological function, attenuate the endothelial inflammatory response and lead to less neuronal loss in the hippocampal CA1 region in a rat model of ICH.

[29] *Kostara CE, Ferrannini E, Bairaktari ET et al.* **Early Signs of Atherogenic Features in the HDL Lipidomes of Normolipidemic Patients Newly Diagnosed with Type 2 Diabetes**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33266469
ABSTRACT
Cardiovascular disease (CVD) is the major cause of death in patients with type-2 diabetes mellitus (T2DM), although the factors that accelerate atherosclerosis in these patients are poorly understood. The identification of the altered quantity and quality of lipoproteins, closely related to atherogenesis, is limited in routine to a pattern of high triglycerides and low HDL-cholesterol (HDL-C) and in research as dysfunctional HDLs. We used the emerging NMR-based lipidomic technology to investigate compositional features of the HDLs of healthy individuals with normal coronary arteries, drug-naïve; recently diagnosed T2DM patients with normal coronary arteries; and patients with recent acute coronary syndrome. Patients with T2DM and normal serum lipid profiles even at diagnosis presented significant lipid alterations in HDL, characterized by higher triglycerides, lysophosphatidylcholine and saturated fatty acids; and lower cholesterol, phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, plasmalogens and polyunsaturated fatty acids, an atherogenic pattern that may be involved in the pathogenesis of atherosclerosis. These changes are qualitatively similar to those

found, more profoundly, in normolipidemic patients with established Coronary Heart Disease (CHD). We also conclude that NMR-based lipidomics offer a novel holistic exploratory approach for identifying and quantifying lipid species in biological matrixes in physiological processes and disease states or in disease biomarker discovery.

[30] *Stadler JT, Marsche G*. **Obesity-Related Changes in High-Density Lipoprotein Metabolism and Function**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33256096
ABSTRACT
In obese individuals, atherogenic dyslipidemia is a very common and important factor in the increased risk of cardiovascular disease. Adiposity-associated dyslipidemia is characterized by low high-density lipoprotein cholesterol (HDL-C) levels and an increase in triglyceride-rich lipoproteins. Several factors and mechanisms are involved in lowering HDL-C levels in the obese state and HDL quantity and quality is closely related to adiponectin levels and the bioactive lipid sphingosine-1-phosphate. Recent studies have shown that obesity profoundly alters HDL metabolism, resulting in altered HDL subclass distribution, composition, and function. Importantly, weight loss through gastric bypass surgery and Mediterranean diet, especially when enriched with virgin olive oil, is associated with increased HDL-C levels and significantly improved metrics of HDL function. A thorough understanding of the underlying mechanisms is crucial for a better understanding of the impact of obesity on lipoprotein metabolism and for the development of appropriate therapeutic approaches. The objective of this review article was to summarize the newly identified changes in the metabolism, composition, and function of HDL in obesity and to discuss possible pathophysiological consequences.

[31] *Wilson RB, Zhang R, Chen YJ et al.* **Two-Week Isocaloric Time-Restricted Feeding Decreases Liver Inflammation without Significant Weight Loss in Obese Mice with Non-Alcoholic Fatty Liver Disease**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33271781
ABSTRACT
Prolonged, isocaloric, time-restricted feeding (TRF) protocols can promote weight loss, improve metabolic dysregulation, and mitigate non-alcoholic fatty liver disease (NAFLD). In addition, 3-day, severe caloric restriction can improve liver metabolism and glucose homeostasis prior to significant weight loss. Thus, we hypothesized that short-term, isocaloric TRF would improve NAFLD and characteristics of metabolic syndrome in diet-induced obese male mice. After 26 weeks of ad libitum access to western diet, mice either continued feeding ad libitum or were provided with access to the same quantity of western diet for 8 h daily, over the course of two weeks. Remarkably, this short-term TRF protocol modestly decreased liver tissue inflammation in the absence of changes in body weight or epidydimal fat mass. There were no changes in hepatic lipid accumulation or other characteristics of NAFLD. We observed no changes in liver lipid metabolism-related gene expression, despite increased plasma free fatty acids and decreased plasma triglycerides in the TRF group. However, liver Grp78 and Txnip expression were decreased with TRF suggesting hepatic endoplasmic reticulum (ER) stress and activation of inflammatory pathways may have been diminished. We conclude that two-week, isocaloric TRF can potentially decrease liver inflammation, without significant weight loss or reductions in hepatic steatosis, in obese mice with NAFLD.

[32] *Balling M, Afzal S, Varbo A et al.* **VLDL Cholesterol Accounts for One-Half of the Risk of Myocardial Infarction Associated With apoB-Containing Lipoproteins**. Journal of the American College of Cardiology 2020; 76:2725-2735.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33272366

ABSTRACT

BACKGROUND: Plasma apolipoprotein B (apoB) is a composite measure of all apoB-containing lipoproteins causing atherosclerotic cardiovascular disease; however, it is unclear which fraction of risk is explained by cholesterol and triglycerides, respectively, in very low-density lipoproteins (VLDLs). OBJECTIVES: The authors tested the hypothesis that VLDL cholesterol and triglycerides each explain part of the myocardial infarction risk from apoB-containing lipoproteins. METHODS: Nested within 109,751 individuals from the Copenhagen General Population Study, the authors examined 25,480 subjects free of lipid-lowering therapy and myocardial infarction at study entry. All had measurements of plasma apoB (quantitating number of apoB-containing lipoproteins) and cholesterol and triglyceride content of VLDL, intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs). RESULTS: During a median 11 years of follow-up, 1,816 were diagnosed with myocardial infarction. Per 1-mmol/l higher levels, multivariable-adjusted hazard ratios for myocardial infarction were 2.07 (95% confidence interval [CI]: 1.81 to 2.36) for VLDL cholesterol, 1.19 (95% CI: 1.14 to 1.25) for VLDL triglycerides, 5.38 (95% CI: 3.73 to 7.75) for IDL cholesterol, and 1.86 (95% CI: 1.62 to 2.14) for LDL cholesterol. Per 1-g/l higher plasma apoB, the corresponding value was 2.21 (95% CI: 1.90 to 2.58). In a step-up Cox regression, risk factors for myocardial infarction entered by importance as VLDL cholesterol, systolic blood pressure, smoking, and IDL + LDL cholesterol, whereas VLDL triglycerides did not enter the model. VLDL cholesterol explained 50% and IDL + LDL cholesterol 29% of the risk of myocardial infarction from apoB-containing lipoproteins, whereas VLDL triglycerides did not explain risk. CONCLUSIONS: VLDL cholesterol explained one-half of the myocardial infarction risk from elevated apoB-containing lipoproteins, whereas VLDL triglycerides did not explain risk.

[33] *Castañer O, Pintó X, Subirana I et al.* **Remnant Cholesterol, Not LDL Cholesterol, Is Associated With Incident Cardiovascular Disease**. Journal of the American College of Cardiology 2020; 76:2712-2724.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33272365

ABSTRACT

BACKGROUND: Genetic, observational, and clinical intervention studies indicate that circulating levels of triglycerides and cholesterol transported in triglyceride-rich lipoproteins (remnant cholesterol) can predict cardiovascular events. OBJECTIVES: This study evaluated the association of triglycerides and remnant cholesterol (remnant-C) with major cardiovascular events in a cohort of older individuals at high cardiovascular risk. METHODS: This study determined the baseline lipid profile and searched for major adverse cardiovascular events (MACEs) in the high-risk primary prevention PREDIMED (Prevención con Dieta Mediterránea) trial population (mean age: 67 years; body mass index: 30 kg/m(2); 43% men; 48% with diabetes) after a median follow-up of 4.8 years. Unadjusted and adjusted Cox proportional hazard models were used to assess the association between lipid concentrations (either as continuous or categorical variables) and incident MACEs (N = 6,901; n cases = 263). RESULTS: In multivariable-adjusted analyses, triglycerides (hazard ratio

[HR]: 1.04; 95% confidence interval [CI]: 1.02 to 1.06, per 10 mg/dl [0.11 mmol/l]; p < 0.001), non-high-density lipoprotein cholesterol (HDL-C) (HR: 1.05; 95% CI: 1.01 to 1.10, per 10 mg/dl [0.26 mmol/l]; p = 0.026), and remnant-C (HR: 1.21; 95% CI: 1.10 to 1.33, per 10 mg/dl [0.26 mmol/l]; p < 0.001), but not low-density lipoprotein cholesterol (LDL-C) or HDL-C, were associated with MACEs. Atherogenic dyslipidemia (triglycerides >150 mg/dl [1.69 mmol/l] and HDL-C <40 mg/dl [1.03 mmol/l] in men or <50 mg/dl [1.29 mmol/l] in women) was also associated with MACEs (HR: 1.44; 95% CI: 1.04 to 2.00; p = 0.030). Remnant-C ≥30 mg/dl (0.78 mmol/l) differentiated subjects at a higher risk of MACEs compared with those at lower concentrations, regardless of whether LDL-C levels were on target at ≤100 mg/dl (2.59 mmol/l). CONCLUSIONS: In overweight or obese subjects at high cardiovascular risk, levels of triglycerides and remnant-C, but not LDL-C, were associated with cardiovascular outcomes independent of other risk factors.

[34] *Metzinger MP, Saldanha S, Gulati J et al.* **Effect of Anacetrapib on Cholesterol Efflux Capacity: A Substudy of the DEFINE Trial**. Journal of the American Heart Association 2020; 9:e018136.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33263263
ABSTRACT
Background Anacetrapib is the only cholesteryl ester transfer protein inhibitor proven to reduce coronary heart disease (CHD). However, its effects on reverse cholesterol transport have not been fully elucidated. Macrophage cholesterol efflux (CEC), the initial step of reverse cholesterol transport, is inversely associated with CHD and may be affected by sex as well as haptoglobin copy number variants among patients with diabetes mellitus. We investigated the effect of anacetrapib on CEC and whether this effect is modified by sex, diabetes mellitus, and haptoglobin polymorphism. Methods and Results A total of 574 participants with CHD were included from the DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib) trial. CEC was measured at baseline and 24-week follow-up using J774 macrophages, boron dipyrromethene difluoride-labeled cholesterol, and apolipoprotein B-depleted plasma. Haptoglobin copy number variant was determined using an ELISA assay. Anacetrapib increased CEC, adjusted for baseline CEC, risk factors, and changes in lipids/apolipoproteins (standard β, 0.23; 95% CI, 0.05-0.41). This CEC-raising effect was seen only in men (P interaction=0.002); no effect modification was seen by diabetes mellitus status. Among patients with diabetes mellitus, anacetrapib increased CEC in those with the normal 1-1 haptoglobin genotype (standard β, 0.42; 95% CI, 0.16-0.69) but not the dysfunctional 2-1/2-2 genotypes (P interaction=0.02). Conclusions Among patients with CHD, anacetrapib at a dose linked to improved CHD outcomes significantly increased CEC independent of changes in high-density lipoprotein cholesterol or other lipids, with effect modification by sex and a novel pharmacogenomic interaction by haptoglobin genotype, suggesting a putative mechanism for reduced risk requiring validation.

[35] *Munten S, Ménard L, Gagnon J et al.* **High-intensity interval exercise in the cold regulates acute and postprandial metabolism**. J Appl Physiol (1985) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33270513
ABSTRACT
High-Intensity Interval Exercise (HIIE) has been shown to be more effective than moderate-intensity exercise for increasing acute lipid oxidation and lowering blood lipids during exercise and

postprandially. Exercise in cold environments is also known to enhance lipid oxidation, however the immediate and long-term effects of HIIE exercise in cold are unknown. The purpose of this study was to examine the effects cold stress during HIIE on acute exercise metabolism and postprandial metabolism. Eleven recreationally active individuals (age: 23±3 years, weight: 80±9.7 kg, V̇O(2peak): 39.2±5.73 mL·kg(-1)·min(-1)) performed evening HIIE sessions (10x60s cycling, 90% V̇O(2peak) interspersed with 90s active recovery, 30% V̇O(2peak)) in thermoneutral (HIIE-TN, control; 21°C) and cold environments (HIIE-CO; 0°C), following a balanced crossover design. The following morning, participants consumed a high-fat meal. Indirect calorimetry was used to assess substrate oxidation, and venous blood samples were obtained to assess changes in noncellular metabolites. During acute exercise, lipid oxidation was 113% higher in HIIE-CO ($p=0.002$) without differences in V̇O(2) and EE ($p\geq0.162$) between conditions. Postprandial V̇O(2), lipid and CHO oxidation, plasma insulin and triglyceride concentrations were not different between conditions ($p>0.05$). Postprandial blood LDL-C levels were higher in HIIE-CO two hours after the meal ($p=0.003$). Postprandial glucose AUC was 49% higher in HIIE-CO vs HIIE-TN ($p=0.034$). Under matched energy expenditure conditions, HIIE demonstrated higher lipid oxidation rates during exercise in the cold; but only marginally influenced postprandial lipid metabolism the following morning. In conclusion, HIIE in the cold seemed to be less favorable for postprandial lipid and glycemic responses.

[36] *Takaeko Y, Kajikawa M, Kishimoto S et al.* **Low Levels of Low-Density Lipoprotein Cholesterol and Endothelial Function in Subjects without Lipid-Lowering Therapy**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33255270
ABSTRACT
An elevation of serum low-density lipoprotein cholesterol (LDL-C) levels has been associated with endothelial dysfunction in statin naïve subjects. However, there is no information on endothelial function in subjects with extremely low levels of LDL-C. The purpose of the present study was to determine the relationship of LDL-C levels, especially low levels of LDL-C, with endothelial function. Endothelial function assessed by flow-mediated vasodilation (FMD) measurement and LDL-C levels were evaluated in 7120 subjects without lipid-lowering therapy. We divided the subjects into five groups by LDL-C levels: <70 mg/dL, 70-99 mg/dL, 100-119 md/dL, 120-139 mg/dL, and ≥140 mg/dL. FMD values were significantly smaller in subjects with LDL-C levels of ≥140 mg/dL than in those with LDL-C levels of 70-99 mg/dL and 100-119 mg/dL ($p < 0.001$ and $p = 0.004$, respectively). The FMD values in the LDL-C of <70 mg/dL group were not significantly different from those in the other groups. To evaluate the relationship of extremely low LDL-C levels with endothelial function, we divided the subjects with LDL-C of <70 mg/dL into those with LDL-C levels of <50 mg/dL and 50-69 mg/dL. FMD values were similar in the LDL-C <50 mg/dL group and ≥50 mg/dL group in the propensity score-matched population ($p = 0.570$). A significant benefit was not found in subjects with low LDL-C levels from the aspect of endothelial function.

[37] *Burns H, Russell L, Cox ZL*. **Statin-induced rhabdomyolysis from azithromycin interaction in a patient with heterozygous SLCO1B1 polymorphism**. Journal of clinical pharmacy and therapeutics 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33277702
ABSTRACT

WHAT IS KNOWN AND OBJECTIVE: Unlike other macrolide antibiotics, azithromycin is considered safe to co-prescribe with simvastatin. We aim to elucidate the mechanism of a rare azithromycin-simvastatin interaction. CASE DESCRIPTION: We report a case of simvastatin-induced rhabdomyolysis caused by an azithromycin drug interaction in a patient with heterozygous SLCO1B1 loss-of-function polymorphism. We propose a dual-hit mechanism for this drug-drug-genome interaction. Azithromycin mildly inhibits simvastatin's CYP 3A4 hepatic metabolism, and the SLCO1B1 polymorphism reduces simvastatin hepatic uptake. The combination increases simvastatin serum concentrations significantly, inducing rhabdomyolysis. WHAT IS NEW AND CONCLUSION: Patients with statin-induced myopathy associated with non-classic CYP inhibitors should be considered for genetic testing and alternative statins with less risk of future interactions.

[38] *Mandal N, Grambergs R, Mondal K et al.* **Role of ceramides in the pathogenesis of diabetes mellitus and its complications**. Journal of diabetes and its complications 2020:107734.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33268241
ABSTRACT
Diabetes mellitus (DM) is a systemic metabolic disease that affects 463 million adults worldwide and is a leading cause of cardiovascular disease, blindness, nephropathy, peripheral neuropathy, and lower-limb amputation. Lipids have long been recognized as contributors to the pathogenesis and pathophysiology of DM and its complications, but recent discoveries have highlighted ceramides, a class of bioactive sphingolipids with cell signaling and second messenger capabilities, as particularly important contributors to insulin resistance and the underlying mechanisms of DM complications. Besides their association with insulin resistance and pathophysiology of type 2 diabetes, evidence is emerging that certain species of ceramides are mediators of cellular mechanisms involved in the initiation and progression of microvascular and macrovascular complications of DM. Advances in our understanding of these associations provide unique opportunities for exploring ceramide species as potential novel therapeutic targets and biomarkers. This review discusses the links between ceramides and the pathogenesis of DM and diabetic complications and identifies opportunities for novel discoveries and applications.

[39] *Zhang L, Hu M, Chen Y, Wang Y*. **Effects of atorvastatin and ticagrelor combination therapy on renal function and the levels of suppression of tumorigenicity 2 and interleukin-33 in patients with ST-segment elevation myocardial infarction**. J Int Med Res 2020; 48:300060520959502.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33275460
ABSTRACT
OBJECTIVE: We evaluated the effects of atorvastatin and ticagrelor combination therapy on renal function and the levels of suppression of tumorigenicity 2 (ST2) and interleukin 33 (IL-33) in patients with ST-segment elevation myocardial infarction (STEMI). METHODS: Eighty-four STEMI patients who underwent emergency percutaneous coronary intervention at our hospital from January 2015 to March 2018 were retrospectively analyzed and divided into a control group (n = 44) and an observation group (n = 40). The control group was treated with atorvastatin as routine STEMI treatment, whereas the observation group was concurrently administered ticagrelor. RESULTS: After treatment, significantly better outcomes were observed in the control group than in the observation group in terms of clinical indices, including chest pain relief, enzyme levels, duration of reperfusion-

associated arrhythmia, and depression of the ST segment. Both groups exhibited improvements in cardiac ultrasound indices, whereas the observation group showed lower left ventricular end-diastolic and end-systolic diameters and higher left ventricular ejection fractions than the control group. CONCLUSIONS: Atorvastatin and ticagrelor combination therapy is clinically effective and safe for STEMI patients as it reduces the degree of myocardial infarction, protects the heart and renal functions, improves inflammation, and reduces adverse cardiac event incidences.

[40] *Casula M, Gazzotti M, Bonaiti F et al.* **Reported muscle symptoms during statin treatment amongst Italian dyslipidaemic patients in the real-life setting: the PROSISA Study**. Journal of internal medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33259671
ABSTRACT
AIM: Statin-associated muscle symptoms (SAMS) are a major determinant of poor treatment adherence and/or discontinuation, but a definitive diagnosis of SAMS is challenging. The PROSISA study was an observational retrospective study aimed to assess the prevalence of reported SAMS in a cohort of dyslipidaemic patients. METHODS: Demographic/anamnestic data, biochemical values and occurrence of SAMS were collected by 23 Italian Lipid Clinics. Adjusted logistic regression was performed to estimate odds ratio (OR) and 95% confidence intervals for association between probability of reporting SAMS and several factors. RESULTS: Analyses were carried out on 16 717 statin-treated patients (mean ± SD, age 60.5 ± 12.0 years; 52.1% men). During statin therapy, 9.6% (N = 1599) of patients reported SAMS. Women and physically active subjects were more likely to report SAMS (OR 1.23 [1.10-1.37] and OR 1.35 [1.14-1.60], respectively), whist age ≥ 65 (OR 0.79 [0.70-0.89]), presence of type 2 diabetes mellitus (OR 0.62 [0.51-0.74]), use of concomitant nonstatin lipid-lowering drugs (OR 0.87 [0.76-0.99]), use of high-intensity statins (OR 0.79 [0.69-0.90]) and use of potential interacting drugs (OR 0.63 [0.48-0.84]) were associated with lower probability of reporting SAMS. Amongst patients reporting SAMS, 82.2% underwent dechallenge (treatment interruption) and/or rechallenge (change or restart of statin therapy), with reappearance of muscular symptoms in 38.4% (3.01% of the whole cohort). CONCLUSIONS: The reported prevalence of SAMS was 9.6% of the whole PROSISA cohort, but only a third of patients still reported SAMS after dechallenge/rechallenge. These results emphasize the need for a better management of SAMS to implement a more accurate diagnosis and treatment re-evaluation.

[41] *McCormick D, Bhatt DL, Bays HE et al.* **A regional analysis of payer and provider views on cholesterol management: PCSK9 inhibitors as an illustrative alignment model**. Journal of managed care & specialty pharmacy 2020; 26:1517-1528.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33251993
ABSTRACT
BACKGROUND: Multiple barriers exist for appropriate use of the proprotein convertase subtilisin/kexin type 9 enzyme inhibitors (PCSK9i) in patients with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolemia (FH) with inadequately controlled hypercholesterolemia despite standard therapies. Among these barriers, high payer rejection rates and inadequate prior authorization (PA) documentation by providers hinder optimal use of PCSK9i. OBJECTIVES: To (a) identify and discuss provider and payer discordances on barriers to authorization and use of PCSK9i based on clinical and real-world evidence and (b) align

understanding and application of clinical, cost, safety, and efficacy data of PCSK9i. METHODS: Local groups of 3 payers and 3 providers met in 6 separate locations across the United States through a collaborative project of AMCP and PRIME Education. Responses to selected pre- and postmeeting survey questions measured changes in attitudes and beliefs regarding treatment barriers, lipid thresholds for considering PCSK9i therapy, and tactics for improving PA processes. Statistical analysis of inter- and intragroup changes in attitudes were performed by Cox proportional hazards test and Fisher's exact test for < 5 variables. RESULTS: The majority of providers and payers (67%-78%) agreed that high patient copayments and inadequate PA documentation were significant barriers to PCSK9i usage. However, payers and providers differed on beliefs that current evidence does not support PCSK9i cost-effectiveness (6% providers, 56% payers; P = 0.003) and that PA presents excessive administrative burden (72% providers, 44% payers; P = 0.09) Average increases pre- to postmeeting were noted in provider beliefs that properly documented PA forms expedite access to PCSK9i (22%-50% increase) and current authorization criteria accurately distinguish patients who benefit most from PCSK9i (6%-22%). Payers decreased in their belief that current authorization criteria accurately distinguish benefiting patients (72%-50%). Providers and payers increased in their belief that PCSK9i are cost-effective (44%-61% and 28%-50%, respectively) and were more willing to consider PCSK9i at the low-density lipoprotein cholesterol threshold of > 70 mg/dL for patients with ASCVD (78%-83% and 44%-67%, respectively) or FH (22%-39% and 22%-33%). Payers were more agreeable to less stringent PA requirements for patients with FH (33%-72%, P = 0.019) and need for standardized PA requirements (50%-83%, P = 0.034); these considerations remained high (89%) among providers after the meeting. Most participants supported educational programs for patient treatment adherence (83%) and physician/staff PA processes (83%-94%). CONCLUSIONS: Provider and payer representatives in 6 distinct geographic locations provided recommendations to improve quality of care in patients eligible for PCSK9i. Participants also provided tactical recommendations for streamlining PA documentation processes and improving awareness of PCSK9i cost-effectiveness and clinical efficacy. The majority of participants supported development of universal, standardized patient eligibility criteria and PA forms. DISCLOSURES: The study reported in this article was part of a continuing education program funded by an independent educational grant awarded by Sanofi US and Regeneron Pharmaceuticals to PRIME Education. The grantor had no role in the study design, execution, analysis, or reporting. AMCP received grant funding from PRIME to assist in the study, as well as in writing the manuscript. McCormick, Bhatt, Bays, Taub, Caldwell, Guerin, Steinhoff, and Ahmad received an honorarium from PRIME for serving as faculty for the continuing education program. McCormick, Bhatt, Bays, Taub, Caldwell, Guerin, Steinhoff, and Ahmad were involved as participants in the study. Bhatt discloses the following relationships: Advisory board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice chair, ACC Accreditation Committee), Baim Institute

for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site co-investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded research: FlowCo, Merck, Novo Nordisk, Takeda. Bays' research site has received research grants from 89Bio, Acasti, Akcea, Allergan, Alon Medtech/Epitomee, Amarin, Amgen, AstraZeneca, Axsome, Boehringer Ingelheim, Civi, Eli Lilly, Esperion, Evidera, Gan and Lee, Home Access, Janssen, Johnson and Johnson, Lexicon, Matinas, Merck, Metavant, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, Selecta, TIMI, and Urovant. Bays has served as a consultant/advisor for 89Bio, Amarin, Esperion, Matinas, and Gelesis, and speaker for Esperion. McCormick, Caldwell, Guerin, Ahmad, Singh, Moreo, Carter, Heggen, and Sapir have nothing to disclose.

[42] *Čolak E, Pap D, Nikolić L, Vicković S*. **The impact of obesity to antioxidant defense parameters in adolescents with increased cardiovascular risk**. Journal of medical biochemistry 2020; 39:346-354.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33269023

ABSTRACT
BACKGROUND: The goal of this study was to assess the oxidative stress status through the values of antioxidant defense parameters: superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and total antioxidant status (TAS), as well as cardiovascular risk factors (total cholesterol, LDL-cholesterol, VLDL-cholesterol, non-HDL-cholesterol and triglycerides), anthropometric parameters (Body mass index-BMI, waist circumference-WC, hipp circumferemce-HC, waist-to-hipp ratio-WHR and inflammatory markers (high sensitive C-reactive protein) in a group of obese adolescents. METHODS: A total of 238 students of both sexes, age of 22.32 ± 1.85 yr. were included in the study. According to the values of BMI lower and higher than 25 kg/m2 and WC higher and lower than 94 cm (males)/80 cm (females) the tested group of students was divided into 2 subgroups: Group 1 (increased risk for CVD) and Group 2 (lower risk for CVD). RESULTS: Significantly reduced SOD and GPx with increased GR, TAS, inflammatory and lipoprotein parameters were obtained in Group 1 compared to Group 2. Significant positive association of hsCRP

(OR:1.41; 95%CI 1.08-1.83; P=0.007), TAS (OR:827.2; 95%CI 19.27-35498; P=0.007) and GR (OR:1.13; 95%CI 1.05-1.21; P=0.002) and negative association of GPx (OR:0.97; 95%CI 0.94-1.003; P=0.043) and HDL-cholesterol (OR:0.41; 95%CI 0.176-0.963; P=0.0014) with cardiovascular risk factors were found in obese students. According to the ROC analysis GR>44.8 U/L, TAS>1.35 mmol/L, hsCRP>1.71 mg/L and HDL-cholesterol <1.13 mmol/L have sufficient predictive ability for cardiovascular disease in obese students. CONCLUSIONS: Significant association of antioxidant defense parameters with anthropometric, lipid and inflammatory markers in obese students with increased cardiovascular risk suggest that screening of these parameters is necessary and highly recommended.

[43] *Vladimirov S, Zeljković A, Gojković T et al.* **Associations of cholesterol and vitamin D metabolites with the risk for development of high grade colorectal cancer**. Journal of medical biochemistry 2020; 39:318-327.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33269020
ABSTRACT
BACKGROUND: Vitamin D deficiency is repeatedly reported in colorectal cancer (CRC). Since cholesterol and vitamin D share common precursor 7-dehydrocholesterol (7-DHC), it would be important to explore the associations of key vitamin D metabolites and serum lipid parameters in patients with high and low grade CRC. The aim of this study was to analyze relationships between serum 25(OH)D3, 24,25(OH)2D3 and 7-DHC levels and serum lipids in patients with CRC, and to evaluate their potential for prediction of risk for development of high grade CRC. METHODS: We recruited 82 patients CRC and 77 controls. 7-DHC, 25(OH)D3 and 24,25(OH)2D3 were quantified by LC-MS/MS methods. RESULTS: 7-DHC, 25(OH)D3 and vitamin D metabolic ratio (VDMR) were significantly lower in CRC patients than in control group (P<0.001, P<0.010, P<0.050 and P<0.050, respectively). 25(OH)D3 levels were higher in patients with grade I CRC when compared to grade II (P<0.050). All vitamin D metabolites positively correlated with total cholesterol (TC) concentration in CRC patients. 25(OH)D3 was significant predictor of increased CRC risk (P<0.010). After adjustment for TC concentration, 25(OH)D3 lost its predictive abilities. However, 25(OH)D3 remained significant predictor of poorly differentiated type of cancer (P<0.050). CONCLUSIONS: We found significant positive association between vitamin D status and serum total cholesterol. Although low 25(OH)D3 was found to be a significant risk factor for CRC development, the obtained results primarily suggest profound impact of cholesterol level on vitamin D status in CRC. However, our results suggest that low 25(OH)D3 might independently contribute to development of poorly differentiated tumor.

[44] *Machado-Duque ME, Gaviria-Mendoza A, Machado-Alba JE*. **Real-World Effectiveness of Therapy With Rosuvastatin Combined With Fenofibric Acid in a Sample of Colombian Patients With Mixed Dyslipidemia**. J Prim Care Community Health 2020; 11:2150132720977733.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33251941
ABSTRACT
BACKGROUND: Ischemic heart disease is the leading cause of death in the world and is associated with dyslipidemia, high blood pressure, diabetes mellitus, and other factors. OBJECTIVE: To determine the clinical effectiveness on the lipid profile of the rosuvastatin + fenofibric acid combination in Colombian patients with high cardiovascular risk and mixed dyslipidemia. METHODS: Longitudinal observational study in a random sample of patients with a diagnosis of mixed dyslipidemia and

moderate, high, or very high cardiovascular risk who were treated with rosuvastatin + fenofibric acid. Anthropometric, clinical, laboratory, comorbidity, and pharmacological variables were identified. Effectiveness on the lipid profile was determined. RESULTS: A total of 386 patients were analyzed. They had a mean age of 60.8 ± 11.4 years, 53.1% were female, and 75.6% had high/very high cardiovascular risk. The initial evaluation showed a mean LDL cholesterol of 138.4 ± 67.1 mg/dL and triglycerides of 679.7 ± 573.6 mg/dL. At the end of follow-up, mean LDL cholesterol was 87.5 ± 41.2 mg/dL (reduced by 43.3%; P < .001), and triglycerides were 243.5 ± 170.5 mg/dL (reduced by 64.2%; P < .001). Only 35.4% (n = 73) of patients with very high risk reached the goal of metabolic control, compared to 61.6% (n = 53) with high risk and 55.4% (n = 46) with moderate risk. Belonging to the very high-risk group was associated with a lower probability of achieving the control goal (OR: 0.32; 95%CI: 0.192-0.539). CONCLUSION: The combination of rosuvastatin + fenofibric acid is an effective option in patients with mixed dyslipidemia and high cardiovascular risk, providing a therapeutic alternative for those conditions that require it.

[45] *Gergen AK, Kohtz PD, Halpern AL et al.* **Statins Inhibit Toll-Like Receptor 4-Mediated Growth of Human Esophageal Adenocarcinoma Cells**. J Surg Res 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33272595
ABSTRACT
BACKGROUND: Esophageal adenocarcinoma (EAC) is a lethal malignancy with poor prognosis. Pharmacologic inhibitors of inflammation, such as statins, have been shown to decrease the risk of development and progression of esophageal cancer, but the mechanism of this protection is unclear. The objective of this study was to elucidate the effect of statins on toll-like receptor 4-mediated-proliferation of human EAC cells and identify the mechanism responsible for these observed effects. METHODS: Human EAC cells (OE33 and FLO1) were treated with simvastatin or atorvastatin for increasing doses and time periods. Toll-like receptor 4 (TLR4) expression was assessed. Cells were pretreated with statin followed by lipopolysaccharide (LPS). Cell proliferation and expression of signaling proteins were evaluated. FLO1 cells were injected into the flank of nude mice. Mice received intraperitoneal injections of simvastatin, atorvastatin, or control solution and tumor volume was measured. RESULTS: OE33 and FLO1 cells demonstrated decreased TLR4 expression after treatment with simvastatin or atorvastatin for 8 h ($P < 0.05$). LPS increased proliferation, whereas pretreatment with statin abolished this response ($P < 0.05$). Statins decreased expression and activation of LPS-induced signaling proteins, including MyD88, TRAF6, Akt, and NF-κB ($P < 0.05$). Mice receiving daily statin injections demonstrated smaller tumors than control mice ($P < 0.001$ at day 33). CONCLUSIONS: Treatment of EAC cells with simvastatin or atorvastatin decreases TLR4-mediated proliferation and in vivo tumor growth. Decreased TLR4 expression and subsequent reduction in MyD88-dependent signaling could be a mechanism by which statins act to reduce tumor growth rates.

[46] *Zhou F, Hua Y, Ji X, Jia L.* **A systemic review into carotid plaque features as predictors of restenosis after carotid endarterectomy**. Journal of vascular surgery 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33253876
ABSTRACT
OBJECTIVE: Restenosis after carotid endarterectomy (CEA) limits its long-term efficacy for stroke prevention. Thus, it is of utmost importance to identify the factors that predispose a patient to

restenosis after CEA. This systemic review aims to survey the current literature regarding restenosis after CEA and discuss the predictive value of carotid plaque features. METHODS: A systemic review of studies on the predictive value of carotid plaque features for restenosis after CEA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed/MEDLINE and Embase databases were searched up to March 20, 2020. Two authors independently extracted the data and assessed the risk of bias with the Quality in Prognosis Studies (QUIPS) tool. Given the heterogeneity in the measurement of prognostic factors, types of CEA, and clinical outcomes, a qualitative synthesis was performed. RESULTS: Twenty-one articles with a sample size ranged from 11 to 1203 were included in this systematic review. Based on the presence of calcification in original carotid plaques, two progression patterns of restenosis were hypothesized: patients with calcified plaques may experience a temporary increase in intima-media thickness (IMT) followed by a decrease in IMT after CEA, while patients with non-calcified plaques may experience a gradual increase in IMT after CEA. Accordingly, patients with a high calcium score may have a high restenosis rate within six months after CEA and a low restenosis rate thereafter. Thus, the late restenosis rate in patients with uniformly echogenic plaques was lower than that in patients with uniformly echolucent plaques. Pathologically, a lipid-rich, inflammatory carotid plaque is associated with a decreased risk of restenosis within one year after CEA, mainly due to relatively mild reactive intimal hyperplasia at the surgical site and active inflammation in the remaining media and adventitia. Molecular predictors for restenosis included Mannose-binding lectin 2 genotype, preoperative C-reactive protein, serum homocysteine, apolipoprotein J, vitamin C, and telomere length of carotid plaques. CONCLUSIONS: This review demonstrated that carotid plaque features, including imaging features, cellular composition, and molecular features, are correlated with the risk of restenosis after CEA. A comprehensive evaluation of plaque characteristics may help stratify the risk of restenosis after CEA.

[47] *Vassy JL, Gaziano JM, Green RC et al.* **Effect of Pharmacogenetic Testing for Statin Myopathy Risk vs Usual Care on Blood Cholesterol: A Randomized Clinical Trial**. JAMA network open 2020; 3:e2027092.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33270123
ABSTRACT
IMPORTANCE: Nonadherence to statin guidelines is common. The solute carrier organic anion transporter family member 1B1 (SLCO1B1) genotype is associated with simvastatin myopathy risk and is proposed for clinical implementation. The unintended harms of using pharmacogenetic information to guide pharmacotherapy remain a concern for some stakeholders. OBJECTIVE: To determine the impact of delivering SLCO1B1 pharmacogenetic results to physicians on the effectiveness of atherosclerotic cardiovascular disease (ASCVD) prevention (measured by low-density lipoprotein cholesterol [LDL-C] levels) and concordance with prescribing guidelines for statin safety and effectiveness. DESIGN, SETTING, AND PARTICIPANTS: This randomized clinical trial was performed from December 2015 to July 2019 at 8 primary care practices in the Veterans Affairs Boston Healthcare System. Participants included statin-naive patients with elevated ASCVD risk. Data analysis was performed from October 2019 to September 2020. INTERVENTIONS: SLCO1B1 genotyping and results reporting to primary care physicians at baseline (intervention group) vs after 1 year (control group). MAIN OUTCOMES AND MEASURES: The primary outcome was the 1-year change in LDL-C level. The secondary outcomes were 1-year concordance with American College of

Cardiology-American Heart Association and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for statin therapy and statin-associated muscle symptoms (SAMS). RESULTS: Among 408 patients (mean [SD] age, 64.1 [7.8] years; 25 women [6.1%]), 193 were randomized to the intervention group and 215 were randomized to the control group. Overall, 120 participants (29%) had a SLCO1B1 genotype indicating increased simvastatin myopathy risk. Physicians offered statin therapy to 65 participants (33.7%) in the intervention group and 69 participants (32.1%) in the control group. Compared with patients whose physicians did not know their SLCO1B1 results at baseline, patients whose physicians received the results had noninferior reductions in LDL-C at 12 months (mean [SE] change in LDL-C, -1.1 [1.2] mg/dL in the intervention group and -2.2 [1.3] mg/dL in the control group; difference, -1.1 mg/dL; 90% CI, -4.1 to 1.8 mg/dL; P<.001 for noninferiority margin of 10 mg/dL). The proportion of patients with American College of Cardiology-American Heart Association guideline-concordant statin prescriptions in the intervention group was noninferior to that in the control group (12 patients [6.2%] vs 14 patients [6.5%]; difference, -0.003; 90% CI, -0.038 to 0.032; P<.001 for noninferiority margin of 15%). All patients in both groups were concordant with CPIC guidelines for safe statin prescribing. Physicians documented 2 and 3 cases of SAMS in the intervention and control groups, respectively, none of which was associated with a CPIC guideline-discordant prescription. Among patients with a decreased or poor SLCO1B1 transporter function genotype, simvastatin was prescribed to 1 patient in the control group but none in the intervention group. CONCLUSIONS AND RELEVANCE: Clinical testing and reporting of SLCO1B1 results for statin myopathy risk did not result in poorer ASCVD prevention in a routine primary care setting and may have been associated with physicians avoiding simvastatin prescriptions for patients at genetic risk for SAMS. Such an absence of harm should reassure stakeholders contemplating the clinical use of available pharmacogenetic results. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02871934.

[48] *Artunc F*. **Kidney-derived PCSK9-a new driver of hyperlipidemia in nephrotic syndrome?** Kidney international 2020; 98:1393-1395.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33276863
ABSTRACT
Increased plasma concentrations of proprotein convertase subtilisin/kexin type 9 or PCSK9, which reduces hepatic uptake of low-density lipoprotein by downregulation of the low-density lipoprotein receptor, have been reported in nephrotic patients and might contribute to hyperlipidemia in nephrotic syndrome. The results of the study by Molina-Jijon et al. found that renal PCSK9 expression was upregulated in the collecting duct of nephrotic patients and animals, suggesting that the kidney might be a major source for plasma PCSK9 in nephrotic syndrome.

[49] *Garcia E, Bennett DW, Connelly MA et al.* **The extended lipid panel assay: a clinically-deployed high-throughput nuclear magnetic resonance method for the simultaneous measurement of lipids and Apolipoprotein B**. Lipids in health and disease 2020; 19:247.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33261644
ABSTRACT
BACKGROUND: Standard lipid panel assays employing chemical/enzymatic methods measure total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), from which are calculated estimates of low-density lipoprotein cholesterol (LDL-C). These lipid measures are used

universally to guide management of atherosclerotic cardiovascular disease risk. Apolipoprotein B (apoB) is generally acknowledged to be superior to LDL-C for lipid-lowering therapeutic decision-making, but apoB immunoassays are performed relatively infrequently due to the added analytic cost. The aim of this study was to develop and validate the performance of a rapid, high-throughput, reagent-less assay producing an "Extended Lipid Panel" (ELP) that includes apoB, using the Vantera® nuclear magnetic resonance (NMR) analyzer platform already deployed clinically for lipoprotein particle and other testing. METHODS: Partial least squares regression models, using as input a defined region of proton NMR spectra of plasma or serum, were created to simultaneously quantify TC, TG, HDL-C, and apoB. Large training sets (n>~1000) of patient sera analyzed independently for lipids and apoB by chemical methods were employed to ensure prediction models reflect the wide lipid compositional diversity of the population. The analytical performance of the NMR ELP assay was comprehensively evaluated. RESULTS: Excellent agreement was demonstrated between chemically-measured and ELP assay values of TC, TG, HDL-C and apoB with correlation coefficients ranging from 0.980 to 0.997. Within-run precision studies measured using low, medium, and high level serum pools gave coefficients of variation for the 4 analytes ranging from 1.0 to 3.8% for the low, 1.0 to 1.7% for the medium, and 0.9 to 1.3% for the high pools. Corresponding values for within-lab precision over 20 days were 1.4 to 3.6%, 1.2 to 2.3%, and 1.0 to 1.9%, respectively. Independent testing at three sites over 5 days produced highly consistent assay results. No major interference was observed from 38 endogenous or exogenous substances tested. CONCLUSIONS: Extensive assay performance evaluations validate that the NMR ELP assay is efficient, robust, and substantially equivalent to standard chemistry assays for the clinical measurement of lipids and apoB. Routine reporting of apoB alongside standard lipid measures could facilitate more widespread utilization of apoB for clinical decision-making.

[50] *Benmimoun B, Papastefanaki F, Périchon B et al.* **An original infection model identifies host lipoprotein import as a route for blood-brain barrier crossing**. Nature communications 2020; 11:6106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33257684
ABSTRACT
Pathogens able to cross the blood-brain barrier (BBB) induce long-term neurological sequelae and death. Understanding how neurotropic pathogens bypass this strong physiological barrier is a prerequisite to devise therapeutic strategies. Here we propose an innovative model of infection in the developing Drosophila brain, combining whole brain explants with in vivo systemic infection. We find that several mammalian pathogens are able to cross the Drosophila BBB, including Group B Streptococcus (GBS). Amongst GBS surface components, lipoproteins, and in particular the B leucine-rich Blr, are important for BBB crossing and virulence in Drosophila. Further, we identify (V)LDL receptor LpR2, expressed in the BBB, as a host receptor for Blr, allowing GBS translocation through endocytosis. Finally, we show that Blr is required for BBB crossing and pathogenicity in a murine model of infection. Our results demonstrate the potential of Drosophila for studying BBB crossing by pathogens and identify a new mechanism by which pathogens exploit the machinery of host barriers to generate brain infection.

[51] *Crunkhorn S.* **Blocking PCSK9 enhances immune checkpoint therapy**. Nature reviews. Drug discovery 2021; 20:20.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33262511
ABSTRACT

[52] *Khadke S, Mandave P, Kuvalekar A et al.* **Synergistic Effect of Omega-3 Fatty Acids and Oral-Hypoglycemic Drug on Lipid Normalization through Modulation of Hepatic Gene Expression in High Fat Diet with Low Streptozotocin-Induced Diabetic Rats**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33261004
ABSTRACT
Type 2 diabetes mellitus, which an outcome of impaired insulin action and its secretion, is concomitantly associated with lipid abnormalities. The study was designed to evaluate the combinational effect of omega-3 fatty acids (flax and fish oil) and glibenclamide on abnormal lipid profiles, increased blood glucose, and impaired liver and kidney functions in a high fat diet with low streptozotocin (STZ)-induced diabetic rats, including its probable mechanism of action. The male Wistar rats (n = 48) were distributed into eight groups. All animal groups except the healthy received a high fat diet (HFD) for 90 days. Further, diabetes was developed by low dose STZ (35 mg/kg). Diabetic animals received, omega-3 fatty acids (500 mg/kg), along with glibenclamide (0.25 mg/kg). Both flax and fish oil intervention decreased ($p \leq 0.001$) serum triglycerides and very low density lipoprotein and elevated ($p \leq 0.001$) high density lipoprotein levels in diabetic rats. Total cholesterol and low-density lipoprotein level was decreased ($p \leq 0.001$) in fish oil-treated rats. However, it remained unaffected in the flax oil treatment group. Both flax and fish oil intervention downregulate the expression of fatty acid metabolism genes, transcription factors (sterol regulatory element-binding proteins-1c and nuclear factor-κβ), and their regulatory genes i.e., acetyl-coA carboxylase alpha, fatty acid synthase, and tumor necrosis factors-α. The peroxisome proliferator-activated receptor gamma gene expression was upregulated ($p \leq 0.001$) in the fish oil treatment group. Whereas, carnitine palmitoyltransferase 1 and fatty acid binding protein gene expression were upregulated ($p \leq 0.001$) in both flax and fish oil intervention group.

[53] *Pal A, Metherel AH, Fiabane L et al.* **Do Eicosapentaenoic Acid and Docosahexaenoic Acid Have the Potential to Compete against Each Other?** Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33276463
ABSTRACT
Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are n-3 polyunsaturated fatty acids (PUFAs) consumed in low abundance in the Western diet. Increased consumption of n-3 PUFAs may have beneficial effects for a wide range of physiological outcomes including chronic inflammation. However, considerable mechanistic gaps in knowledge exist about EPA versus DHA, which are often studied as a mixture. We suggest the novel hypothesis that EPA and DHA may compete against each other through overlapping mechanisms. First, EPA and DHA may compete for residency in membrane phospholipids and thereby differentially displace n-6 PUFAs, which are highly prevalent in the Western diet. This would influence biosynthesis of downstream metabolites of inflammation initiation and resolution. Second, EPA and DHA exert different effects on plasma membrane biophysical structure, creating an additional layer of competition between the fatty acids in controlling signaling. Third, DHA regulates membrane EPA levels by lowering its rate of conversion to EPA's elongation product n-3 docosapentaenoic acid. Collectively, we propose the critical need to

investigate molecular competition between EPA and DHA in health and disease, which would ultimately impact dietary recommendations and precision nutrition trials.

[54] *Sotos-Prieto M, Ruiz-Canela M, Song Y et al.* **The Effects of a Mediterranean Diet Intervention on Targeted Plasma Metabolic Biomarkers among US Firefighters: A Pilot Cluster-Randomized Trial**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33255353
ABSTRACT
Metabolomics is improving the understanding of the mechanisms of the health effects of diet. Previous research has identified several metabolites associated with the Mediterranean Diet (MedDiet), but knowledge about longitudinal changes in metabolic biomarkers after a MedDiet intervention is scarce. A subsample of 48 firefighters from a cluster-randomized trial at Indianapolis fire stations was randomly selected for the metabolomics study at 12 months of follow up (time point 1), where Group 1 (n = 24) continued for another 6 months in a self-sustained MedDiet intervention, and Group 2 (n = 24), the control group at that time, started with an active MedDiet intervention for 6 months (time point 2). A total of 225 metabolites were assessed at the two time points by using a targeted NMR platform. The MedDiet score improved slightly but changes were non-significant (intervention: 24.2 vs. 26.0 points and control group: 26.1 vs. 26.5 points). The MedDiet intervention led to favorable changes in biomarkers related to lipid metabolism, including lower LDL-C, ApoB/ApoA1 ratio, remnant cholesterol, M-VLDL-CE; and higher HDL-C, and better lipoprotein composition. This MedDiet intervention induces only modest changes in adherence to the MedDiet and consequently in metabolic biomarkers. Further research should confirm these results based on larger study samples in workplace interventions with powerful study designs.

[55] *Yu JS, Shin DH, Kim JS*. **Repurposing of Fluvastatin as an Anticancer Agent against Breast Cancer Stem Cells via Encapsulation in a Hyaluronan-Conjugated Liposome**. Pharmaceutics 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33255298
ABSTRACT
Fluvastatin (FLUVA), which is a common anti-hypercholesterolemia drug, exhibits potential anticancer activity as it suppresses the proliferation, angiogenesis, and metastasis of breast cancer cells via inhibiting 3-hydroxy-methyl glutaryl-coenzyme A (HMG-CoA) reductase. In this study, hyaluronan-conjugated FLUVA-encapsulating liposomes (HA-L-FLUVA) were evaluated for their anticancer efficacy in vitro and in vivo. The particle size, zeta potential, and encapsulation efficiency of HA-L-FLUVA were 158.36 ± 1.78 nm, -24.85 ± 6.26 mV, and 35%, respectively. Growth inhibition of breast cancer stem cells (BCSCs) by HA-L-FLUVA was more effective than that by free FLUVA. The half maximal inhibitory concentration (IC(50)) values of FLUVA, L-FLVUA, and HA-L-FLUVA were 0.16, 0.17, and 0.09 μM, respectively. The in vivo anticancer effect of HA-L-FLUVA in combination with doxorubicin (DOX) was more effective than that of free FLUVA, free DOX, and HA-L-FLUVA. The longest survival of mice was achieved by treatment with FLUVA (15 mg/kg) and HA-L-FLUVA (15 mg/kg) + DOX (3 mg/kg), followed by HA-L-FLUVA (15 mg/kg), Dulbecco's phosphate buffered saline, and DOX (3 mg/kg). No more than 10% body weight loss was observed in the mice injected with FLUVA, indicating that the drug was not toxic. Taken together, these results indicate that HA-L-

FLUVA could serve as an effective anticancer drug by inhibiting the growth of both breast cancer cells and cancer stem cells.

[56] *Zou Y, Sheng G, Yu M, Xie G*. **The association between triglycerides and ectopic fat obesity: An inverted U-shaped curve**. PloS one 2020; 15:e0243068.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33253312

ABSTRACT

BACKGROUND: Ectopic fat obesity and triglycerides are risk factors for diabetes and multiple cardiovascular diseases. However, there have been limited studies on the association between triglycerides and ectopic fat obesity. The purpose of this study was to explore the association between triglycerides and ectopic fat obesity. METHODS AND RESULTS: In this cross-sectional study, we retrospectively analyzed 15464 adult participants recruited by Murakami Memorial Hospital (8430 men and 7034 women, average age of 43.71 ± 8.90). All patients were divided into two groups according to the threshold used to diagnose hypertriglyceridemia. The logistic regression model was used to analyze the association between triglycerides and the risk of ectopic fat obesity, and the generalized additive model was used to identify the nonlinear association. In this study population, the prevalence of ectopic fat obesity was 17.73%. After adjusting other covariables, triglycerides were positively correlated with the risk of ectopic fat obesity (OR: 1.54, 95% CI:1.41-1.69, P<0.0001). Through smooth curve fitting, we found that there was an inverted U-shaped curve association between triglycerides and ectopic fat obesity. This association remained unchanged even if the adjusted covariables were removed from the model, and the inflection point of the curve was 3.98. When triglyceride levels were ≤3.98, triglycerides were positively correlated with the risk of ectopic fat obesity (OR:1.784, 95% CI:1.611-1.975, P<0.0001). When triglyceride levels were >3.98 (right side of the inflection point), there was a negative correlation (OR:0.519, 95% CI:0.333-0.810, P = 0.0039). CONCLUSIONS: Our research showed that there is a significant association between triglycerides and ectopic fat obesity. This relation is not a simple linear relationship but instead an inverted U-shaped curve association.

[57] *Cota BC, Suhett LG, Leite NN et al.* **Cardiometabolic risk and health behaviours in adolescents with normal-weight obesity: a systematic review**. Public health nutrition 2020:1-12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33256881

ABSTRACT

OBJECTIVE: To analyse the presence of cardiometabolic risk factors in adolescents with normal-weight obesity (NWO), as well as to investigate health behaviours related to the phenotype. DESIGN: The study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and the bibliographic search was carried out in the PubMed, Scielo and ScienceDirect databases. SETTING: School, university and population. PARTICIPANTS: Adolescents between 10 and 19 years old. RESULTS: A total of eight papers were included. Most studies have found a relationship between NWO and the presence of cardiometabolic risk factors, such as high waist circumference, unfavourable lipid and glycid profile. As for health behaviours, three of the eight studies included evaluated eating habits; however, the results were not conclusive. In addition, four studies analysed the practice of physical activity or physical fitness, which was lower in NWO. CONCLUSIONS: The available evidence indicates that NWO is related to the early development of cardiometabolic changes, physical inactivity and less physical fitness in adolescents.

The results also reveal the importance of early detection of the phenotype, as well as the need for further research on the associated factors to prevent future diseases. Registration (PROSPERO: CRD42020161204).

[58] *Tulbah AS*. **The potential of Atorvastatin for chronic lung diseases therapy**. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 2020; 28:1353-1363.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33250642
ABSTRACT
Atorvastatin (ATO) is of the statin class and is used as an orally administered lipid-lowering drug. ATO is a reversible synthetic competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase thus leading to a reduction in cholesterol synthesis. It has recently been demonstrated that ATO has different pharmacological actions, which are unrelated to its lipid-lowering effects and has the ability to treat chronic airway diseases. This paper reviews the potential of ATO as an anti-inflammatory, antioxidant, and anti-proliferative agent after oral or inhaled administration. This paper discusses the advantages and disadvantages of using ATO under conditions associated with those found in the airways. This treatment could potentially be used to support the formulating of ATO as an inhaler for the treatment of chronic respiratory diseases.

[59] *Sverre E, Peersen K, Perk J et al.* **Challenges in coronary heart disease prevention - experiences from a long-term follow-up study in Norway**. Scandinavian cardiovascular journal : SCJ 2020:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33274648
ABSTRACT
Objective. To determine longitudinal changes in lifestyle behaviour and lipid management in a chronic coronary heart disease (CHD) population. Design. A multi-centre cohort study consecutively included 1127 patients at baseline in 2014-2015, on average 16 months after a CHD event. Data were collected from hospital records, a questionnaire and clinical examination. Seven hundred and seven of 1021 eligible patients participated in a questionnaire-based follow-up in 2019. Data were analysed with univariate statistics. Results. After a mean follow-up of 4.7 years (SD 0.4) from baseline, the percentage of current smokers (15% versus 16%), obesity (23% versus 25%) and clinically significant symptoms of anxiety (21% versus 17%) and depression (13% versus 14%) remained unchanged, whereas the proportion with low physical activity increased from 53% to 58% ($p < .001$). The proportions with reduced physical activity level were similar in patients over and under 70 years of age. Most patients were still taking statins (94% versus 92%) and more patients used high-intensity statin (49% versus 54%, $p < .001$) and ezetimibe (5% versus 15%, $p < .001$) at follow-up. 73% reported ≥1 primary-care consultation(s) for CHD during the last year while 27% reported no such follow-up. There were more smokers among participants not attending primary-care consultations compared to those attending (19% versus 14%, $p = .026$). No differences were found for other risk factors. Conclusions. We found persistent suboptimal risk factor control in coronary outpatients during long-term follow-up. Closer follow-up and intensified risk management including lifestyle and psychological health are needed to improved secondary prevention and outcome of CHD. Trial registration: Registered at ClinicalTrials.gov: NCT02309255. Registered at 5 December 2014, registered retrospectively.

[60] *Barrios V, Escobar C, Gamarra J et al.* **[Management of patients with dyslipidaemia in Spain. The Cardio Right Care Control of cardiovascular risk project]**. Semergen / Sociedad Espanola de Medicina Rural y Generalista 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33268266
ABSTRACT
OBJECTIVE: To ascertain the opinion of physicians about diagnostic criteria, control targets, control rates, and therapeutic approach of patients with dyslipidaemia in Spain. METHODS: A specific questionnaire was created about diagnostic criteria, control targets, control rates, lipid lowering therapies, and therapeutic inertia in patients with dyslipidaemia. Physicians completed the questionnaire online during a 4-month period. RESULTS: A total of 959 questionnaires were collected from all over Spain. The most frequent scale to stratify cardiovascular risk is SCORE (54.9%), and guidelines from the European Society of Cardiology are the most common guidelines used (50.5%). The majority of patients are on primary prevention (57.7%), and 31.4% have a high-very high cardiovascular risk. More than 70% of investigators considered that the target among patients at very high risk and those in secondary prevention is an LDL cholesterol < 70 mg/dL. It is considered by 60.0% and 66.4% of investigators that their patients on primary and secondary prevention, respectively, achieve control targets. Statins are the most common lipid lowering drugs used, followed by ezetimibe. In the majority of cases, when a patient is not adequately controlled with statins, there is an increase in the dose or a change to another statin. Poor adherence to treatment and therapeutic inertia are the main reasons for poor LDL cholesterol control. CONCLUSIONS: The Cardio Right Care CVR Control project allows those aspects to be identified, as well as areas of improvement in patients with dyslipidaemia in Spain.

[61] *Zabihi M, Askarian F, Hekmatimoghaddam S et al.* **Combination of atorvastatin and gemfibrozil plus physical activity: an animal model of statin/fibrate-induced myopathy**. Somatosens Mot Res 2020:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33263458
ABSTRACT
INTRODUCTION: Drug-induced myopathy is among the most common causes of muscle disease. Lipid-lowering drugs, primarily the statins as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are a common cause of myopathy. Statin-fibrate combination potentially increases risk for myopathy and rhabdomyolysis. Blood levels of the enzymes creatine kinase (CK), aldolase and lactate dehydrogenase (LDH) increase during myopathy. Exercise may be a trigger for statin-associated muscle symptoms (SAMS). METHODS: In this study a model of myopathy induction was designed via combination of oral atorvastatin, gemfibrozil and exercise for ten days in rats. To maximise exercise, the rats were placed in a pool of water and allowed to swim before sinking in the last three days. Finally, the mean of swimming tolerance times and blood levels of creatine kinase, aldolase and lactate dehydrogenase were measured. RESULTS: The results showed a significantly ($p<0.05$) decreased swimming tolerance time and elevated enzyme levels in rats receiving atorvastatin (ATV) and gemfibrozil (GMF) plus exercise compared with those rats in other groups. This animal model can be used to evaluate the effects of medication on reduction of statin/fibrate-induced myopathy.

[62] *Xu J, Dai L, Zhang Y et al.* **Severity of Nonalcoholic Fatty Liver Disease and Risk of Future Ischemic Stroke Events**. Stroke 2021; 52:103-110.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33272125

ABSTRACT

BACKGROUND AND PURPOSE: We assessed prospectively whether nonalcoholic fatty liver disease (NAFLD) and its severity predict future ischemic stroke (IS) events in a community-based cohort. METHODS: From the Kailuan study, participants free of history of stroke, cancer, or myocardial infarction were enrolled after excluding alcohol abuse and other liver diseases. NAFLD was evaluated through ultrasonography. Participants with NAFLD were further stratified into mild, moderate, and severe groups. The outcome was the first occurrence of IS. The secondary outcomes included myocardial infarction and combined vascular events. We used Cox proportional hazards models to estimate hazard ratios and 95% CIs of incident IS according to presence and severity of NAFLD, adjusting for age, sex, physical activity, body mass index, smoker, history of hypertension, diabetes, hypercholesterolemia, lipid-lowering medication, HDL (high-density lipoprotein), triglyceride, hsCRP (high-sensitivity C-reactive protein), and fasting blood glucose. RESULTS: During a median of 10.34 years of follow-up, we documented 3490 incident stroke cases among 79 905 participants. NAFLD was found in 24 874 (31.18%) participants. Relative to participants without NAFLD at the baseline, those with NAFLD had a 16% higher risk (95% CI, 1.07-1.26) of developing ischemic stroke, after adjusted for confounding variables. The hazard ratios for patients with mild, moderate, and severe NAFLD were 1.15 (95% CI, 1.05-1.25), 1.19 (95% CI, 1.06-1.34), and 1.21 (95% CI, 1.08-1.50), respectively. CONCLUSIONS: The severity of NAFLD is associated with a higher risk of future ischemic stroke events.

[63] *Cao LX, Yang M, Liu Y et al.* **Chinese patient with cerebrotendinous xanthomatosis confirmed by genetic testing: A case report and literature review**. World journal of clinical cases 2020; 8:5446-5456.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33269283

ABSTRACT

BACKGROUND: Cerebrotendinous xanthomatosis (CTX) is a treatable autosomal recessive inherited metabolic disorder. It results from a deficiency of sterol 27-hydroxylase (CYP27A1), which is a mitochondrial cytochrome P450 enzyme that catalyzes the hydroxylation of cholesterol and modulates cholesterol homeostasis. Patients with CYP27A1 deficiency show symptoms related to excessive accumulation of cholesterol and cholestanol in lipophilic tissues such as the brain, eyes, tendons, and vessels, resulting in juvenile cataracts, tendon xanthoma, chronic diarrhea, cognitive impairment, ataxia, spastic paraplegia, and peripheral neuropathy. CTX is underdiagnosed as knowledge of the disorder is mainly based on case reports. CASE SUMMARY: A Chinese family with CTX consisting of one patient and four heterozygous carriers was studied. The patient is a 47-year-old male, who mainly had psychiatric signs but without some cardinal features of CTX such as cataracts, cerebellar ataxia, pyramidal signs and chronic diarrhea. There was a significant increase in the concentration of free fatty acid compared to normal range. Doppler ultrasound of the urinary system showed multiple left kidney stones, a right kidney cyst, and a hypoechoic area in the bladder, which could move with body position. Sagittal and axial magnetic resonance imaging (MRI) of the right ankle joint showed apparent enlargement of the right Achilles tendon and upper medial malleolus flexor tendon, abnormal thickening of the plantar fat, and a small amount of exudation

around the fascia in front of the Achilles tendon. Cerebral MRI suggested white matter (WM) demyelination and slight cerebral atrophy. The diagnosis was confirmed by targeted sequencing, which identified compound heterozygous mutations in exon 2 and intron 7 of the CYP27A1 gene (c.435G>T, c.1263+1G>A). Treatment for 3 wk with a combination of lipid-lowering and antipsychotic therapy improved his psychiatric symptoms and normalized the levels of serum free fatty acid. Sediments in the bladder disappeared after therapy. CONCLUSION: CYP27A1 genetic analysis should be the definitive method for CTX diagnosis. This case suggests that urinary system diseases may be neglected in CTX patients. The clinical, biological, radiological, and genetic characteristics of CTX are summarized to promote early diagnosis and treatment of this disease.