[1] *Liu P, Gao Q, Guan L et al.* **Atorvastatin attenuates surgery-induced BBB disruption and cognitive impairment partly by suppressing NF-κB pathway and NLRP3 inflammasome activation in aged mice**. Acta biochimica et biophysica Sinica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33674828

ABSTRACT

In clinic, perioperative neurocognitive disorder is becoming a common complication of surgery in old patients. Neuroinflammation and blood-brain barrier (BBB) disruption are important contributors for cognitive impairment. Atorvastatin, as a strong HMG-CoA reductase inhibitor, has been widely used in clinic. However, it remains unclear whether atorvastatin could prevent anesthesia and surgery-induced BBB disruption and cognitive injury by its anti-inflammatory property. In this study, aged C57BL/6J mice were used to address this question. Initially, the mice were subject to atorvastatin treatment for 7 days (10 mg/kg). After a simple laparotomy under 1.5% isoflurane anesthesia, Morris water maze was performed to assess spatial learning and memory. Western blot analysis, immunohistochemistry, and enzyme-linked immunosorbent assay were used to examine the inflammatory response, BBB integrity, and cell apoptosis. Terminal-deoxynucleotidyl transferase mediated nick end labeling assay was used to assess cell apoptosis. The fluorescein sodium and transmission electron microscopy were used to detect the permeability and structure of BBB. The results showed that anesthesia and surgery significantly injured hippocampal-dependent learning and memory, which was ameliorated by atorvastatin. Atorvastatin could also reverse the surgery-induced increase of systemic and hippocampal cytokines, including IL-1β, TNF-α, and IL-6, accompanied by inhibiting the nuclear factor kappa-B (NF-κB) pathway and Nucleotide-Binding Oligomerization Domain, or Leucine Rich Repeat and Pyrin Domain Containing 3 (NLRP3) inflammasome activation, as well as hippocampal neuronal apoptosis. In addition, surgery triggered an increase of BBB permeability, paralleled by a decrease of the ZO-1, occludin, and Claudin 5 proteins in the hippocampus. However, atorvastatin treatment could protect the BBB integrity from the impact of surgery, by up-regulating the expressions of ZO-1, occludin, and Claudin 5. These findings suggest that atorvastatin exhibits neuroprotective effects on cognition in aged mice undergoing surgery.

[2] *Armitage NH, Kramer MK, Nelson MS et al.* **Effectiveness of Lifestyle Interventions in an Active Duty Air Force Population**. Am J Health Promot 2021:890117121997308.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33657870

ABSTRACT

PURPOSE: To examine the effectiveness of 3 lifestyle intervention programs in an active duty military population. DESIGN: Experimental design with stratified random assignment to 1 of 3 intervention groups. Measures were taken at baseline, 3 months and 6 months. SETTING: A Military Treatment Facility in the western U.S. SUBJECTS/INTERVENTION: 122 active duty service members were enrolled and randomly assigned to 1 of 3 lifestyle intervention programs: the Diabetes Prevention Program-Group Lifestyle Balance (DPP-GLB), the Better Body Better Life (BBBL) program or the Fitness Improvement Program (FIP). MEASURES: weight, abdominal circumference, lipid and HbA1c levels, physical activity, and well-being as measured by the RAND SF-36 questionnaire. ANALYSIS: Statistical analyses were performed to assess changes over time. RESULTS: 83 participants completed the study (BBBL N = 23, FIP N = 30, DPP-GLB N = 30). The DPP-GLB participants had statistically significant decreases in weight (-3.1 pounds, p = .01) and abdominal circumference (-0.9 inches; p = .01) over time. HbA1c was also significantly lower in this group at 6 months compared to

baseline (p = .036). There were no statistically significant changes in weight, abdominal circumference, or HbA1c in the FIP or BBBL groups. No significant changes were observed in lipids in any of the groups. CONCLUSION: Results from this study indicate that the DPP-GLB program may be effective in reducing weight, abdominal circumference, and HbA1c in an active duty U.S. military population.

[3] *Al-Mrabeh A*. **β-Cell Dysfunction, Hepatic Lipid Metabolism, and Cardiovascular Health in Type 2 Diabetes: New Directions of Research and Novel Therapeutic Strategies**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33672162
ABSTRACT
Cardiovascular disease (CVD) remains a major problem for people with type 2 diabetes mellitus (T2DM), and dyslipidemia is one of the main drivers for both metabolic diseases. In this review, the major pathophysiological and molecular mechanisms of β-cell dysfunction and recovery in T2DM are discussed in the context of abnormal hepatic lipid metabolism and cardiovascular health. (i) In normal health, continuous exposure of the pancreas to nutrient stimulus increases the demand on β-cells. In the long term, this will not only stress β-cells and decrease their insulin secretory capacity, but also will blunt the cellular response to insulin. (ii) At the pre-diabetes stage, β-cells compensate for insulin resistance through hypersecretion of insulin. This increases the metabolic burden on the stressed β-cells and changes hepatic lipoprotein metabolism and adipose tissue function. (iii) If this lipotoxic hyperinsulinemic environment is not removed, β-cells start to lose function, and CVD risk rises due to lower lipoprotein clearance. (iv) Once developed, T2DM can be reversed by weight loss, a process described recently as remission. However, the precise mechanism(s) by which calorie restriction causes normalization of lipoprotein metabolism and restores β-cell function are not fully established. Understanding the pathophysiological and molecular basis of β-cell failure and recovery during remission is critical to reduce β-cell burden and loss of function. The aim of this review is to highlight the link between lipoprotein export and lipid-driven β-cell dysfunction in T2DM and how this is related to cardiovascular health. A second aim is to understand the mechanisms of β-cell recovery after weight loss, and to explore new areas of research for developing more targeted future therapies to prevent T2DM and the associated CVD events.

[4] *Kauerova S, Bartuskova H, Muffova B et al.* **Statins Directly Influence the Polarization of Adipose Tissue Macrophages: A Role in Chronic Inflammation**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669779
ABSTRACT
Statins represent one of the most widely used classes of drugs in current medicine. In addition to a substantial decrease in atherogenic low density lipoprotein (LDL) particle concentrations, several large trials have documented their potent anti-inflammatory activity. Based on our preliminary data, we showed that statins are able to decrease the proportion of pro-inflammatory macrophages (CD14+16+CD36high) in visceral adipose tissue in humans. In the present study including 118 healthy individuals (living kidney donors), a very close relationship between the pro-inflammatory macrophage proportion and LDL cholesterol levels was found. This was confirmed after adjustment for the most important risk factors. The effect of statins on the proportion of pro-inflammatory macrophages was also confirmed in an experimental model of the Prague hereditary

hypercholesterolemia rat. A direct anti-inflammatory effect of fluvastatin on human macrophage polarization in vitro was documented. Based on modifying the LDL cholesterol concentrations, statins are suggested to decrease the cholesterol inflow through the lipid raft of macrophages in adipose tissue and hypercholesterolemia to enhance the pro-inflammatory macrophage phenotype polarization. On the contrary, due to their opposite effect, statins respond with anti-inflammatory activity, affecting the whole organism.

[5] *Ren G, Zhou Q, Lu M, Wang H*. **Rosuvastatin corrects oxidative stress and inflammation induced by LPS to attenuate cardiac injury by inhibiting the NLRP3/TLR4 pathway**. Canadian journal of physiology and pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33641435
ABSTRACT
The aim of the current study was to evaluate whether rosuvastatin was effective in attenuating cardiac injury in lipopolysaccharide(LPS)-challenged mice and H9C2 cells and identify the underlying mechanisms, focusing on the NLRP3/TLR4 pathway. Cardiac injury, cardiac function, apoptosis, oxidative stress, inflammatory response and the NLRP3/TLR4 pathway were evaluated in both in vivo and in vitro studies. LPS-induced cardiomyocytes injury was markedly attenuated by rosuvastatin treatment. Apoptosis was clearly ameliorated in myocardial tissue and H9C2 cells cotreated with rosuvastatin. In addition, excessive oxidative stress was present, as indicated by increases in MDA content, NADPH activity and ROS production and decreased SOD activity after LPS challenge. Rosuvastatin improved all the indicators of oxidative stress, with a similar effect to NAC(ROS scavenger). Notably, LPS-exposed H9C2 cells and mice showed significant NLRP3 and TLR4/NF-κB pathway activation. Administration of rosuvastatin reduced the increases in expression of NLRP3, ASC, pro-caspase-1, TLR4, and p65 and decreased the contents of TNF-α, IL-1β, IL-18 and IL-6, with a similar effect as MCC950 (NLRP3 inhibitor). In conclusion, inhibition of the inflammatory response and oxidative stress contributes to cardioprotection of rosuvastatin on cardiac injury induced by LPS, and the effect of rosuvastatin was achieved by inactivation of the NF-κB/NLRP3 pathway.

[6] *Lefort C, Cani PD*. **The Liver under the Spotlight: Bile Acids and Oxysterols as Pivotal Actors Controlling Metabolism**. Cells 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669184
ABSTRACT
Among the myriad of molecules produced by the liver, both bile acids and their precursors, the oxysterols are becoming pivotal bioactive lipids which have been underestimated for a long time. Their actions are ranging from regulation of energy homeostasis (i.e., glucose and lipid metabolism) to inflammation and immunity, thereby opening the avenue to new treatments to tackle metabolic disorders associated with obesity (e.g., type 2 diabetes and hepatic steatosis) and inflammatory diseases. Here, we review the biosynthesis of these endocrine factors including their interconnection with the gut microbiota and their impact on host homeostasis as well as their attractive potential for the development of therapeutic strategies for metabolic disorders.

[7] *Tiemann J, Lindenkamp C, Plümers R et al.* **Statins as a Therapeutic Approach for the Treatment of Pseudoxanthoma Elasticum Patients: Evaluation of the Spectrum Efficacy of Atorvastatin In Vitro**. Cells 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669724
ABSTRACT
Pseudoxanthoma elasticum (PXE) is an autosomal recessive disorder caused by mutations in the ATP-binding cassette sub-family C member 6 gene. Our previous studies revealed that PXE might be associated with premature aging. Treatment with statins showed positive effects not only for PXE but also for other diseases associated with premature aging like Hutchinson-Gilford progeria syndrome. Nevertheless, the molecular mechanisms in the case of PXE remain unclear. Thus, this study was performed to evaluate the efficiency of atorvastatin by analyzing key characteristics of the PXE phenotype in primary human dermal fibroblasts of PXE patients. Our data indicate that an atorvastatin treatment has a positive effect, especially on factors associated with cholesterol biosynthesis and prenylation processes, whereas the effect on age- and calcification-related factors was less pronounced.

[8] *Kanagalingam T, Lazarte J, Wong DKH, Hegele RA*. **Liver Injury Associated With Ezetimibe Monotherapy**. CJC Open 2021; 3:195-197.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33644733
ABSTRACT
Statin intolerance, primarily myalgia, is not uncommon in patients treated for elevated low-density lipoprotein cholesterol. Nonstatin drugs, such as ezetimibe, can spare patients from statin exposure, while still reducing low-density lipoprotein cholesterol. Ezetimibe is generally very well tolerated, although gastrointestinal and musculoskeletal symptoms have been occasionally reported. We describe an extremely rare case of an ezetimibe-associated liver injury who required protracted treatment with prednisone and azathioprine. Ezetimibe-associated liver injury should be suspected with development of hepatic abnormalities concurrent with the timing of ezetimibe treatment and in the absence of other possible precipitating factors.

[9] *Hosseinpour-Niazi S, Bakhshi B, Mirmiran P, Azizi F*. **Socioeconomic and lifestyle factors modifies the association between nut consumption and metabolic syndrome incidence**. Clinical nutrition (Edinburgh, Scotland) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33642144
ABSTRACT
BACKGROUND & AIMS: The aim of this study was to evaluate the association of nut consumption and its various types with metabolic syndrome (MetS) risk and to investigate whether lifestyle factors (physical activity and smoking status) and socioeconomic status (education and occupation) modulate the association of nut consumption and the risk of MetS. METHODS: We prospectively studied 1915 participants of the Tehran Lipid and Glucose study, among whom 591 were diagnosed with MetS during 8.9 years of follow-up. Nut consumption and its various types were assessed using a validated semi-quantitative food frequency questionnaire. Multivariable adjusted Cox regression was used to estimate Hazard Ratios (HRs) for MetS events across tertiles of nut consumption and its various types. Regarding interaction between nut consumption and physical activity levels, education levels, and smoking status on the risk of MetS, using joint classification, the effect modification of

lifestyle factors and socioeconomic status on the association between nut consumption (<median and ≥ median) and risk of MetS was assessed by Cox regression. RESULTS: Nut consumption was inversely associated with MetS risk in multivariable-adjusted models. The highest tertiles of the constituents of nuts including fiber, polyphenol, MUFA and PUFA reduced MetS risk compared with the lowest tertiles, after adjustment for confounders. Among various types of nuts, the multivariable-adjusted HRs of MetS were 0.78 (0.63-0.96) for walnuts, and 0.77 (0.63-0.94) for pistachios, compared with the lowest intake. Among adult population, consuming nuts higher than the median and having moderate to high physical activity levels resulted in significant reduction in the MetS risk (HRs: 0.74, CI: 0.55-0.98 for moderate and HRs: 0.63, CI: 0.47-0.86 for high physical activity level). Participants who did not smoke had lower risk of MetS regardless of their amount of nuts consumption (HRs: 0.67, CI: 0.47-0.94 for intakes < median and HRs: 0.71, CI: 0.53-0.93 for intakes ≥ median). Stratification based on education status resulted in reduction in the risk of MetS in participants consuming nuts ≥ median in both educated and not-educated group (HRs: 0.81, CI: 0.66-0.98 for the non-educated group and HRs: 0.63, CI: 0.47-0.84 for the educated group). CONCLUSIONS: Incorporating nuts, especially walnuts, into dietary patterns reduced the risk of MetS, especially among individuals with more physical activity levels.

[10] *Huh KY, Lee SW, Lee SB et al.* **Pharmacokinetic Interaction Among Ezetimibe, Rosuvastatin, and Telmisartan**. Clinical pharmacology in drug development 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33647189

ABSTRACT

To evaluate the pharmacokinetic interactions among rosuvastatin, ezetimibe, and telmisartan, a randomized, open-label, 3-period, 6-sequence crossover study was conducted in healthy subjects. Subjects received one of the following treatments once daily for 7 days in each period with a 1-week washout: a fixed-dose combination of ezetimibe/rosuvastatin 10/20 mg, telmisartan 80 mg, combination therapy of ezetimibe/rosuvastatin 10/20 mg, or telmisartan 80 mg. Blood samples were collected up to 24 hours postdose at steady state. Geometric mean ratios (GMRs) and their 90% confidence intervals (CIs) of the combination therapy to monotherapy for the maximum plasma concentration (C(max,ss)), and the area under the time-concentration curve within a dosing interval at steady state (AUC(tau,ss)) were estimated. Among the 36 randomized subjects, 31 subjects completed the study. The GMRs and 90%CIs of C(max,ss) and AUC(tau,ss) of total ezetimibe were not significantly altered. The C(max,ss) of free ezetimibe was increased (GMR, 1.85; 90%CI, 1.56-2.19) but not for the AUC(tau,ss) (GMR, 1.16; 90%CI, 1.06-1.26). Similarly, the C(max,ss) of rosuvastatin was increased (GMR, 2.13; 90%CI, 1.88-2.43) without a change in the AUC(tau,ss) (GMR, 1.09; 90%CI, 1.03-1.15). The C(max,ss) (GMR, 1.16; 90%CI, 1.01-1.32) and AUC(tau,ss) (GMR, 1.26; 90%CI, 1.17-1.37) of telmisartan were slightly increased. Considering the therapeutic range of the components, the interaction would have limited clinical impact.

[11] *Boppana SH, Syed HA, Antwi-Amoabeng D et al.* **Atorvastatin-Induced Necrotizing Myopathy and its Response to Combination Therapy**. Cureus 2021; 13:e12957.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33659112

ABSTRACT

Atorvastatin is the most commonly used statin medication to decrease cholesterol levels and prevent atherosclerosis. Myopathy is a reported side effect of atorvastatin which can happen even after more

than six months after starting the medication. The side effect on the muscle tissue can range from simple reversible myalgia to respiratory muscle compromise. Here we present a 46-year-old male who presented with myopathy after taking atorvastatin for two years. Biopsy proved immune-mediated necrotizing myopathy which responded to a combination of Rituximab and intravenous immunoglobulin therapy.

[12] *Ozkalayci F, Kocabas U, Altun BU et al.* **Relationship Between Melatonin and Cardiovascular Disease**. Cureus 2021; 13:e12935.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33654615
ABSTRACT
Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide. The coronary atherosclerotic process involves different pathological mechanisms; inflammation is one of the major triggers for the development of atherosclerotic plaque. Although several studies showed the favorable effects of melatonin on the cardiovascular system (CVS), melatonin seems not to take its rightful place in today's clinical practice. This review aims to point out the role of melatonin on cardiovascular disease (CVD) and its' risk factors. All data were obtained via PubMed, Wikipedia, and Google.

[13] *Bahiru E, Hsiao R, Phillipson D, Watson KE*. **Mechanisms and Treatment of Dyslipidemia in Diabetes**. Current cardiology reports 2021; 23:26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33655372
ABSTRACT
PURPOSE OF REVIEW: Type 2 diabetes mellitus is widespread throughout the world and is a powerful risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). This manuscript explored the mechanisms underlying dyslipidemia in type 2 diabetes as well as currently available treatment options and guideline recommendations. RECENT FINDINGS: Type 2 diabetes is associated with a characteristic pattern of dyslipidemia, often termed diabetic dyslipidemia. Patients with type 2 diabetes often present with low HDL levels, elevated levels of small dense LDL particles, and elevated triglyceride levels. LDL lowering is the cornerstone of managing diabetic dyslipidemia, and statins are the mainstay of therapy. The cholesterol absorption inhibitor ezetimibe and PCSK9 inhibitors have also been shown to lower risk in patients with diabetes. Recently, the eicosapentaenoic (EPA) only n-3 fatty acid, icosapent ethyl, has also shown benefit for cardiovascular risk reduction in patients with diabetes. To date, no agents targeting HDL increase have shown cardiovascular benefit in patients on background statin therapy. Diabetic dyslipidemia is significant cardiovascular disease risk factor, and LDL-lowering therapy with statins, PCSK9 inhibitors, and ezetimibe continues to be mainstay therapy to reduce cardiovascular risk. Future studies targeting low HDL and high triglycerides levels associated with type 2 diabetes could provide additional novel therapies to manage diabetic dyslipidemia.

[14] *Ali AH, Younis N, Abdallah R et al.* **Lipid-Lowering Therapies for Atherosclerosis: Statins, Fibrates, Ezetimibe and PCSK9 monoclonal antibodies**. Curr Med Chem 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33655822
ABSTRACT

Cardiovascular disease (CVD) remains the primary cause of global morbidity and mortality. CVD includes various life-threatening conditions such as myocardial infarction, stroke and peripheral arterial diseases. In this context, atherosclerosis continues to play the principal role in the pathogenesis of these conditions. Atherosclerosis emanates from a set of modifiable and non-modifiable risk factors that include age, male gender, family history, obesity, smoking, diabetes mellitus and hypertension. Recent evidence classifies atherosclerosis as a latent disease affecting all-sized arteries with a predilection for arterial branching points of decreased or absent blood supply. Atherosclerosis is not only a lipid metabolism disorder, but is also a chronic inflammatory one. In this review, we provide a synoptic discussion of the underlying pathological mechanisms of atherosclerosis along with the currently applied therapeutic interventions. We then discuss the classical lipid-lowering therapies as well as the newly discovered therapies. For the classical therapies, we point out the importance of statins and ezetimibe in reducing plasma cholesterol levels by virtue of their effects on synthesis, reuptake and intestinal absorption of cholesterol. We also discuss the role of fibrates in modulating lipid metabolism and improving the ratio of high-density to low-density density lipoproteins. We then focus on the more recent molecular and genetic interventions exemplified by proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, evinacumab, and microRNA inhibitors. Special attention is also given to clinical trials involving these therapies.

[15] *Marrache MK, Rockey DC*. **Statins for treatment of chronic liver disease**. Curr Opin Gastroenterol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33654016
ABSTRACT
PURPOSE OF REVIEW: Statins are a class of lipid lower medications used primarily in patients with high-risk cardiovascular disease. Since their development, statins have been considered to be harmful in patients with liver disease, and many of the prescribing information labels consider them to be contraindicated in patients with active liver disease. However, recent studies have shown the contrary, warranting further investigation and discussion. This review aims to describe the latest literature on the mechanism, safety profile and potential benefits of statins use on the natural history of chronic liver disease (CLD) progression and its complications. RECENT FINDINGS: A number of recently published studies have added to the existing body of literature supporting the concept that statins are safe and likely to be beneficial for treating patients with CLD. Patients with CLD including hepatitis B virus infection, hepatitis C virus infection, nonalcoholic fatty liver disease and alcohol on statins have been shown to have a lower rate of decompensating events, lower incidence of hepatocellular cancer, a lower rate of infections, and increased survival. However, the majority of the available literature supporting statin use in patients with liver disease comes from retrospective observational studies with high potential for bias. SUMMARY: Statins appear to be safe in patients with compensated cirrhosis, and evidence suggests that they may reduce fibrosis, even in patients with advanced fibrosis and cirrhosis. Further high-quality research on this topic is needed to fully delineate the effect of statins in patients with liver disease.

[16] *Ling JZJ, Montvida O, Khunti K et al.* **Therapeutic inertia in the management of dyslipidaemia and hypertension in incident type 2 diabetes and the resulting risk factor burden: real-world evidence from primary care**. Diabetes Obes Metab 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33651456

ABSTRACT

OBJECTIVE: The trends in prevalence of hypertension and dyslipidaemia in incident type 2 diabetes (T2DM), time to antihypertensive (AHT) and lipid lowering (LLT) therapy, and the association with SBP/lipid control, are not known. RESEARCH DESIGN AND METHODS: Using THIN UK primary care database, 254,925 people with incident T2DM and existing dyslipidaemia/hypertension were identified. Among those without atherosclerotic cardiovascular disease (ASCVD) history and not on AHT/LLT at diagnosis, adjusted median months to initiating an AHT/LLT, and the probabilities of high SBP/lipids over 2-years in people initiating therapy within/after 1-year were evaluated by high and low ASCVD risk status. RESULTS: At diabetes diagnosis 66/66% had dyslipidaemia/hypertension. During 2005-2016, dyslipidaemia prevalence increased by 10% in people aged <60 years, while remained stable for hypertension in all age groups. Among those with high ASCVD risk-status in the 18-39, 40-49 and 50-59 years-groups, median months (95% CI) to initiate therapy were 20.4 (20.3-20.5), 10.9 (10.8-11.0) and 9.5 (9.4-9.6) months in dyslipidemia sub-cohort; and 28.1 (28.0-28.2), 19.2 (19.1-19.3) and 19.9 (19.8-20.0) in hypertension sub-cohort. Among people with high and low ASCVD risk status, compared to early LLT initiators, those who initiated LLT after 1-year had 65.3-85.3% and 65.0-85.3% significantly higher probability of failing lipid control over 2-years follow-up, while late AHT initiators had 46.5-57.9% and 65.0-40.0-58.7% significantly higher probability of failing SBP control. CONCLUSIONS: Significant delay in initiating cardioprotective therapies was observed, time to first prescription was similar in primary prevention people irrespective of ASCVD risk status across all T2DM diagnosis age groups, resulting in poor risk factor control over 2-years follow-up. This article is protected by copyright. All rights reserved.

[17] *Xu M, Lei G, Chen M et al.* **Development of a novel, fully human, anti-PCSK9 antibody with potent hypolipidemic activity by utilizing phage display-based strategy**. EBioMedicine 2021; 65:103250.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33647772

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates serum LDL cholesterol (LDL-C) levels by facilitating the degradation of the LDL receptor (LDLR) and is an attractive therapeutic target for hypercholesterolemia intervention. Herein, we generated a novel fully human antibody with favourable druggability by utilizing phage display-based strategy. METHODS: A potent single-chain variable fragment (scFv) named AP2M21 was obtained by screening a fully human scFv phage display library with hPCSK9, and performing two in vitro affinity maturation processes including CDR-targeted tailored mutagenesis and cross-cloning. Thereafter, it was transformed to a full-length Fc-silenced anti-PCSK9 antibody FAP2M21 by fusing to a modified human IgG1 Fc fragment with L234A/L235A/N297G mutations and C-terminal lysine deletion, thus eliminating its immune effector functions and mitigating mAb heterogeneity. FINDINGS: Our data showed that the generated full-length anti-PCSK9 antibody FAP2M21 binds to hPCSK9 with a K(D) as low as 1.42 nM, and a dramatically slow dissociation rate (k(off), 4.68 × 10(-6) s(-1)), which could be attributed to its lower binding energy (-47.51 kcal/mol) than its parent counterpart FAP2 (-30.39 kcal/mol). We verified that FAP2M21 potently inhibited PCSK9-induced reduction of LDL-C uptake in HepG2 cells, with an EC(50) of 43.56 nM. Further, in hPCSK9 overexpressed C57BL/6 mice, a single tail i.v. injection of FAP2M21 at 1, 3 and 10 mg/kg, dose-dependently up-regulated

hepatic LDLR levels, and concomitantly reduced serum LDL-C by 3.3% (P = 0.658, unpaired Student's t-test), 30.2% (P = 0.002, Mann-Whitney U-test) and 37.2% (P = 0.002, Mann-Whitney U-test), respectively. INTERPRETATION: FAP2M21 with potent inhibitory effect on PCSK9 may serve as a promising therapeutic agent for treating hypercholesterolemia and associated cardiovascular diseases.

[18] *Santulli G, Jankauskas SS, Gambardella J*. **Inclisiran: a new milestone on the PCSK9 road to tackle cardiovascular risk**. European heart journal. Cardiovascular pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33655296
ABSTRACT

[19] *Messas E, Goudot G, Halliday A et al.* **Management of carotid stenosis for primary and secondary prevention of stroke: state-of-the-art 2020: a critical review**. European heart journal supplements : journal of the European Society of Cardiology 2020; 22:M35-m42.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33664638
ABSTRACT
Carotid atherosclerotic plaque is encountered frequently in patients at high cardiovascular risk, especially in the elderly. When plaque reaches 50% of carotid lumen, it induces haemodynamically significant carotid stenosis, for which management is currently at a turning point. Improved control of blood pressure, smoking ban campaigns, and the widespread use of statins have reduced the risk of cerebral infarction to <1% per year. However, about 15% of strokes are still secondary to a carotid stenosis, which can potentially be detected by effective imaging techniques. For symptomatic carotid stenosis, current ESC guidelines put a threshold of 70% for formal indication for revascularization. A revascularization should be discussed for symptomatic stenosis over 50% and for asymptomatic carotid stenosis over 60%. This evaluation should be performed by ultrasound as a first-line examination. As a complement, computed tomography angiography (CTA) and/or magnetic resonance angiography are recommended for evaluating the extent and severity of extracranial carotid stenosis. In perspective, new high-risk markers are currently being developed using markers of plaque neovascularization, plaque inflammation, or plaque tissue stiffness. Medical management of patient with carotid stenosis is always warranted and applied to any patient with atheromatous lesions. Best medical therapy is based on cardiovascular risk factors correction, including lifestyle intervention and a pharmacological treatment. It is based on the tri-therapy strategy with antiplatelet, statins, and ACE inhibitors. The indications for carotid endarterectomy (CEA) and carotid artery stenting (CAS) are similar: for symptomatic patients (recent stroke or transient ischaemic attack) if stenosis >50%; for asymptomatic patients: tight stenosis (>60%) and a perceived high long-term risk of stroke (determined mainly by imaging criteria). Choice of procedure may be influenced by anatomy (high stenosis, difficult CAS or CEA access, incomplete circle of Willis), prior illness or treatment (radiotherapy, other neck surgery), or patient risk (unable to lie flat, poor AHA assessment). In conclusion, neither systematic nor abandoned, the place of carotid revascularization must necessarily be limited to the plaques at highest risk, leaving a large place for optimized medical treatment as first line management. An evaluation of the value of performing endarterectomy on plaques considered to be at high risk is currently underway in the ACTRIS and CREST 2 studies. These studies, along with the next result of ACST-2 trial, will provide us a more precise strategy in case of carotid stenosis.

[20] *Gopaul VS, Pieterman EJ, Princen HMG et al.* **Effects of mineral oil administration on the pharmacokinetics, metabolism and pharmacodynamics of atorvastatin and pravastatin in mice and dogs**. Eur J Pharm Sci 2021:105776.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33667667
ABSTRACT
We investigated the effects of mineral oil on statin pharmacokinetics and inflammatory markers in animal models. A new synthesis strategy produced regioisomers that facilitated the characterization of the main metabolite (M1) of atorvastatin, a lipophilic statin, in C57BL/6NCrl mice. The chemical structure of M1 in mice was confirmed as ortho-hydroxy β-oxidized atorvastatin. Atorvastatin and M1 pharmacokinetics and inflammatory markers were assessed in C57BL6/J mice given atorvastatin 5 mg/kg/day or 10 mg/kg/day, as a single dose or for 21 days, with or without 10 μL or 30 μL mineral oil. No consistent differences in plasma exposure of atorvastatin or M1 were observed in mice after single or repeat dosing of atorvastatin with or without mineral oil. However, mice administered atorvastatin 10 mg/kg with 30 μL mineral oil for 21 days had significantly increased plasma levels of serum amyloid A (mean 9.6 μg/mL vs 7.9 μg/mL without mineral oil; $p < 0.01$) and significantly increased proportions of C62L(high) B cells (mean 18% vs 12% without mineral oil; $p = 0.04$). There were no statistically significant differences for other inflammatory markers assessed. In dogs, pharmacokinetics of atorvastatin, its two hydroxy metabolites and pravastatin (a hydrophilic statin) were evaluated after single administration of atorvastatin 10 mg plus pravastatin 40 mg with or without 2 g mineral oil. Pharmacokinetics of atorvastatin, hydroxylated atorvastatin metabolites or pravastatin were not significantly different after single dosing with or without mineral oil in dogs. Collectively, the results in mice and dogs indicate that mineral oil does not affect atorvastatin or pravastatin pharmacokinetics, but could cause low-grade inflammation with chronic oral administration, which warrants further investigation.

[21] *Choi H, Kim JY, Lee KH et al.* **Omega-3 fatty acids supplementation on major cardiovascular outcomes: an umbrella review of meta-analyses of observational studies and randomized controlled trials**. European review for medical and pharmacological sciences 2021; 25:2079-2092.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33660821
ABSTRACT
OBJECTIVE: Omega-3 fatty acids are commonly used as a lipid-lowering agent or dietary supplement for the purpose of prevention of cardiovascular diseases. However, even large-scale clinical trials have not shown significant results demonstrating clear clinical benefits in cardiovascular diseases. Thus, this umbrella review aims to summarize and evaluate the evidence of clinical effects of omega-3 fatty acids supplementation on cardiovascular outcomes through comprehensive analyses of previous randomized controlled trials (RCTs) or observational cohort studies. MATERIALS AND METHODS: We conducted relevant publication search in PubMed, Embase, and Cochrane Database of Systematic Reviews. We retrieved and analyzed 3,298 articles published until August 28th, 2019. RESULTS: We identified 29 relevant articles and analyzed 83 meta-analyses of RCTs or cohort studies therefrom. As a result, we identified 12 cardiovascular outcomes that are related to omega-3 fatty acids supplementation. Among them, total mortality from major cardiovascular causes (RR 0.92, 95% CI 0.86 to 0.98) had significant inverse associations, and moreover, statistical significances were maintained even in subgroup analysis of large-scale RCTs including more than 1,000 patients (RR 0.94, 95% CI 0.88 to 0.99). CONCLUSIONS: Our umbrella

review study shows that omega-3 fatty acids supplementation have a clinical benefit in reducing mortality from cardiovascular causes. However, many studies still have shown conflicting results, and therefore, further studies will be needed to verify the clinical benefit of omega-3 supplementation.

[22] *Karpouzas GA, Bui VL, Ronda N et al.* **Biologics and atherosclerotic cardiovascular risk in rheumatoid arthritis: a review of evidence and mechanistic insights**. Expert Rev Clin Immunol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33673792
ABSTRACT
INTRODUCTION: Cardiovascular disease is a leading comorbidity in rheumatoid arthritis. Timely introduction of biologic therapies in a treat-to target approach has optimized disease-related outcomes and attenuated accrual of comorbidities, including cardiovascular risk. AREAS COVERED: A literature search in MEDLINE (via pubmed) was performed between January 2009 and November 2020. This manuscript explores recent developments in atherosclerotic cardiovascular risk in RA compared with non-RA individuals; it synopsizes differences in vascular function and inflammation, prevalence, burden, vulnerability and progression of atherosclerotic plaque and their underlying cellular and molecular mechanisms. Lastly, it reviews the recent literature on cardioprotective benefits of biologics and draws mechanistic links with inhibition of new plaque formation, stabilization of high-risk lesions and improvement in endothelial function, arterial stiffness, lipid metabolism and traditional cardiac risk factors. EXPERT OPINION: Increasing evidence points to a solid cardioprotective influence of earlier, longer, and ongoing use of biologic treatments in RA. Nevertheless, the precise mechanistic effects on plaque progression and remodeling, vascular stiffness, endothelial dysfunction, lipid metabolism, and traditional cardiac risk factors are less rigorously characterized.

[23] *Tsigkas G, Koufou EE, Katsanos K et al.* **Potential Relationship Between Lifestyle Changes and Incidence of Hospital Admissions for Acute Coronary Syndrome During the COVID-19 Lockdown**. Frontiers in cardiovascular medicine 2021; 8:604374.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33644128
ABSTRACT
Aims: To evaluate the impact of lockdown during the COVID-19 pandemic on lifestyle changes of the general population, and on admissions for acute coronary syndrome (ACS). Methods and Results: All ACS admissions during the COVID-19 lockdown (10 March to 4 May, 2020), in 3 municipalities (3 spoke, and 1 hub hospital), in Southwestern Greece (411,576 inhabitants), were prospectively recorded and compared to the equivalent periods during 2018, and 2019. A telephone survey of 1014 participants was conducted to explore the lifestyle habits of citizens aged ≥35-years-old before and during lockdown. The median ACS incidence rate decreased from 19.0 cases per week in 2018 and 21.5 in 2019 down to 13.0 in 2020 (RR: 0.66 during the Covid-19 lockdown; 95%CI: 0.53-0.82; P = 0.0002). This was driven by a significant reduction of admissions for Non-ST elevation myocardial infarction (NSTEMI) (RR: 0.68; 95%CI: 0.52-0.88; P = 0.0037), mainly in patients with a lower burden of cardiovascular risk factors, as we noticed an inverse association between the reduction of the incidence of ACS during the Covid-19 lockdown period and the number of registered patient risk factors. There was no difference in the rates of STEMI and population-based all-cause mortality across the examined time periods. The telephone survey demonstrated reduction of passive smoking, working hours, alcohol, junk food and salt consumption, and an increase in sleeping hours, mainly in

participants with a lower burden of cardiovascular risk factors. Conclusions: A significant decline in ACS admissions during the COVID-19 lockdown was noted, affecting mainly NSTEMI patients with a lower burden of cardiovascular risk factors. This was accompanied by significant lifestyle changes. Thus, it is tempting to speculate that to some extend the latter might be associated with the observed decline in ACS admissions.

[24] *Paland N, Pechkovsky A, Aswad M et al.* **The Immunopathology of COVID-19 and the Cannabis Paradigm**. Frontiers in immunology 2021; 12:631233.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33643316
ABSTRACT
Coronavirus disease-19 caused by the novel RNA betacoronavirus SARS-CoV2 has first emerged in Wuhan, China in December 2019, and since then developed into a worldwide pandemic with >99 million people afflicted and >2.1 million fatal outcomes as of 24th January 2021. SARS-CoV2 targets the lower respiratory tract system leading to pneumonia with fever, cough, and dyspnea. Most patients develop only mild symptoms. However, a certain percentage develop severe symptoms with dyspnea, hypoxia, and lung involvement which can further progress to a critical stage where respiratory support due to respiratory failure is required. Most of the COVID-19 symptoms are related to hyperinflammation as seen in cytokine release syndrome and it is believed that fatalities are due to a COVID-19 related cytokine storm. Treatments with anti-inflammatory or anti-viral drugs are still in clinical trials or could not reduce mortality. This makes it necessary to develop novel anti-inflammatory therapies. Recently, the therapeutic potential of phytocannabinoids, the unique active compounds of the cannabis plant, has been discovered in the area of immunology. Phytocannabinoids are a group of terpenophenolic compounds which biological functions are conveyed by their interactions with the endocannabinoid system in humans. Here, we explore the anti-inflammatory function of cannabinoids in relation to inflammatory events that happen during severe COVID-19 disease, and how cannabinoids might help to prevent the progression from mild to severe disease.

[25] *Cárdenas-Jaén K, Vaillo-Rocamora A, Gracia Á et al.* **Simvastatin in the Prevention of Recurrent Pancreatitis: Design and Rationale of a Multicenter Triple-Blind Randomized Controlled Trial, the SIMBA Trial**. Frontiers in medicine 2020; 7:494.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33644082
ABSTRACT
Background: One in every four patients with a first episode of non-gallstone-related acute pancreatitis (AP) develops recurrent disease. Recurrent episodes of AP or acute flares of chronic pancreatitis (CP) are associated with decreased quality of life and progression of the disease. Besides removing the etiology of pancreatitis (which sometimes is not possible), there are no effective measures to prevent recurrence. Meta-analyses of randomized controlled trials, as well as epidemiological and cohort studies, suggest that statins may be protective against the development of index AP. Methods: The SIMBA study is a triple-blind randomized placebo-controlled, parallel-group multicenter trial. Patients with recurrent AP or with acute flares of CP (at least two episodes in the last 12 months) will be randomized to receive simvastatin 40 mg daily or placebo. During a 3-year study period, 144 patients (72 per arm of treatment) from 26 centers will be enrolled. The patients will receive the study treatment for 1 year. The primary aim is to compare the recurrence of AP or acute flares in CP.

Secondary endpoints include the incidence of new-onset diabetes mellitus, new-onset exocrine pancreatic insufficiency (EPI), new-onset imaging signs of CP, frequency of all-cause hospital admissions, severity of AP, adherence to treatment, and frequency of adverse events. Discussion: The SIMBA trial will ascertain whether simvastatin, a safe, widely used and inexpensive drug, can change the natural course of recurrent pancreatitis. Trial Registration: ClinicalTrials.gov Identifier: NCT04021498.

[26] *Wang S, Jia W, Yang S et al.* **The Role of BMI and Blood Pressure in the Relationship Between Total Cholesterol and Disability in Chinese Centenarians: A Cross-Sectional Study**. Frontiers in medicine 2021; 8:608941.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33665198

ABSTRACT

Background: Lower serum lipid metabolism might be associated with the decline of activity of daily living in the extreme longevity group. However, studies on models and possible paths of this correlation between total cholesterol (TC) and disability in centenarians are scarce. The aim of this study was to verify this correlation and explore the mediating effect of BMI and blood pressure on this relationship in Hainan centenarians. Methods: We conducted a cross-sectional analysis of 1002 centenarians from the China Hainan Centenarians Cohort Study (CHCCS). Data on demographics, anthropometry data, lifestyle, and TC levels were collected through interviews, physical examinations, and laboratory tests. The Barthel index and Lawton index, measuring the disability status, were used to estimate the activity of daily living (ADL) and instrumental activity of daily living (IADL). A multivariable logistic regression model was used to explore the correlation between disability and TC levels. Mediation analyses were used to explore the both direct and indirect effects of TC level on disability. Results: After adjusting for covariates, with 1 mmol/L increment in TC, the adjusted odds ratios (ORs) of ADL severe disability and ADL moderate & severe disability were 0.789(95%CI: 0.650-0.959) and 0.822(95%CI: 0. 0.699-0.966), respectively. There was a significant declining trend in the prevalence of different types of disability with increment in TC. The correlation was more pronounced among Hainan female centenarians. In the analysis of mediating effect among the female population, BMI significantly mediated the effect of TC levels on different types of disability. BMI and SBP, as chain mediators, multiply and chain mediated the effect of TC levels on IADL. Conclusion: Low TC levels might be correlated with a higher frequency of disability in female centenarians, and this correlation might be mediated by BMI and blood pressure.

[27] *Valle-Martos R, Valle M, Martos R et al.* **Liver Enzymes Correlate With Metabolic Syndrome, Inflammation, and Endothelial Dysfunction in Prepubertal Children With Obesity**. Frontiers in pediatrics 2021; 9:629346.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33665176

ABSTRACT

Background: Metabolic syndrome (MetS) can start in children with obesity at very young ages. Non-alcoholic fatty liver disease (NAFLD) is considered to be the hepatic component of metabolic syndrome. If left untreated, the clinical course of NAFLD can be progressive and can become chronic if not detected at an early stage. Objective: We aimed to quantify the differences in liver enzymes between prepubertal children with obesity and children with normal weight to determine any associations between them and parameters related to MetS, adipokines, or markers of endothelial

dysfunction and inflammation. Methods: This cross-sectional study included 54 prepuberal children with obesity (aged 6-9 years) and 54 children with normal weight, matched by age and sex. Liver enzymes, C-reactive protein (CRP), interleukin-6, soluble intercellular adhesion molecule-1 (sICAM-1), adipokines, and parameters related to metabolic syndrome (MetS) were all measured. Results: Alanine aminotransferase (ALT) levels, serum butyryl cholinesterase (BChE), leptin, CRP, sICAM-1, triglycerides, blood pressure, and homeostasis model assessment for insulin resistance were significantly higher in children with obesity, while Apolipoprotein A-1, HDL-cholesterol, and adiponectin were significantly lower. In the children with obesity group, ALT and BChE levels correlated with anthropometric measurements, insulin resistance, and lipid parameters, leptin, interleukin-6, CRP, and sICAM-1 while BChE levels negatively correlated with adiponectin. Conclusions: Compared to children with normal weight, prepubertal children with obesity had elevated values for liver enzymes, leptin, markers of insulin resistance, inflammation, and endothelial dysfunction, and variables associated with MetS. There was also a correlation between these disorders and liver enzyme levels.

[28] *Ying Q, Chan DC, Watts GF*. **New Insights Into the Regulation of Lipoprotein Metabolism by PCSK9: Lessons From Stable Isotope Tracer Studies in Human Subjects**. Front Physiol 2021; 12:603910.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33643062

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a convertase enzyme mostly produced by the liver. It is a key regulator of LDL metabolism because of its ability to enhance degradation of the LDL receptor. PCSK9 also regulates the metabolism of lipoprotein(a) [Lp(a)] and triglyceride-rich lipoproteins (TRLs). Its key role in modulating atherosclerotic cardiovascular disease (ASCVD) is supported by genetic studies and clinical outcome trials. Kinetic studies provide mechanistic insight into the role of PCSK9 in regulating the physiology and pathophysiology of plasma lipids and lipoproteins. Kinetic data have demonstrated that plasma PCSK9 concentration is inversely associated with the clearance of LDL in men. Gain-of-function mutations of PCSK9 markedly increase plasma LDL-cholesterol concentrations due to impaired LDL-apoB catabolism. Conversely, PCSK9 deficiency results in low LDL-cholesterol associated with enhanced LDL-apoB clearance. Inhibition of PCSK9 with monoclonal antibodies (such as evolocumab or alirocumab) lowers plasma LDL-cholesterol and apoB levels chiefly by upregulating the catabolism of LDL particles in healthy individuals. As monotherapy, PCSK9 inhibitor reduced Lp(a) concentrations by decreasing the production rate. However, as combination therapy, it reduced the plasma concentration of Lp(a) by increasing the fractional catabolism of Lp(a) particles. In statin-treated patients with high Lp(a), PCSK9 inhibition lowers plasma Lp(a) concentrations by accelerating the catabolism of Lp(a) particles. The effect of PCSK9 inhibition on TRL metabolism has been studied in healthy individuals and in patients with type 2 diabetes. These findings suggest that PCSK9 appears to play a less important role in TRL than LDL metabolism. Kinetic studies of PCSK9 inhibition therapy on lipoprotein metabolism in diverse high risk patient populations (such as familial hypercholesterolemia) and new therapeutic combination also merit further investigation.

[29] *Backes JM, Hilleman DE*. **New and emerging lipid-lowering therapy**. Future cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33646009

ABSTRACT
Statins remain the drugs of choice in patients at risk of or with atherosclerotic cardiovascular disease (ASCVD). Statins have limitations that drive the development of investigational agents to manage dyslipidemias and/or reduce ASCVD risk. There are a few small-molecule drugs that have the potential to mitigate ASCVD risk either alone or in combination with statins. Most lipid-modifying drugs in clinical development are biologic agents that target specific enzymes or genetic-based protein synthesis. Limitations of the biologic agents include complex mechanisms of action and manufacturing processes with indications in select patients with genetic dyslipidemia or who have failed traditional therapies. The ultimate clinical utility of the new and investigational agents will become established over the next several years.

[30] *Gvianishvili T, Kakauridze N, Gogiashvili L et al.* **CORRELATION OF THYROID AUTOIMMUNITY WITH ATHEROSCLEROSIS EVALUATION IN HASHIMOTO'S THYROIDITIS**. Georgian medical news 2021:142-149.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33658423

ABSTRACT
The relationship between subclinical hypothyroidism (SH) and Atherosclerotic (At) cardiovascular diseases (CVD) has been one of the most popular topics but causal connection between Hashimoto thyroiditis (HT), lipid profile and follicular epithelial molecular biology is controversial. We investigated 3 groups of patients (group I - HT, group II - HT+At, group III - At). All laboratory tests for thyroid function and lipid profile detection were used according to international guideline recommendations, coronary and femoral arteries intima-media thickness (IMT) were tested by high-resolution ultrasonography, thyroid gland histology and immunohistochemistry carried out by p63 and S100 protein expression control. The statistical analysis was performed using Microsoft Excel 7.0, SPSS-20 version, Mann-Whitney U-test and Pearson's correlation. Comparisons between groups and factors were made using Multiple Linear Regression model. With the results obtained, dyslipidemia and the diastolic hypertension accelerate the hypothyroidism in HT+At group to predispose carotid and femoral arteries IMT. TSH and anti-TPO antibody levels are directly linked to the cardiovascular complications. Biomarkers S100 and p63 data show negative feedback effects of hypercholesterolemia on the high morphological risk features in Hashimoto parenchyma, which may partially explain the significant trend and pathobiological link of HT with Papillary thyroid carcinoma.

[31] *Jaspers Faijer-Westerink H, Stavnsbo M, Hutten BA et al.* **Ideal cardiovascular health at age 5-6 years and cardiometabolic outcomes in preadolescence**. Int J Behav Nutr Phys Act 2021; 18:33.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33676545

ABSTRACT
BACKGROUND: The American Heart Association (AHA) developed a definition of ideal cardiovascular health (ICH) based on the presence of both ideal health behaviours (diet, physical activity, weight status and smoking) and ideal health factors (glucose, total cholesterol and blood pressure levels). However, research of ICH in the paediatric population is scarce. We aimed to study ICH at age 5-6 years by extending the original ICH score with the health behaviours: sleep duration, screen time and prenatal smoke exposure, and to evaluate its association with cardiometabolic outcomes at age 11-12. METHODS: A total of 1666 children aged 5-6 years were selected from the

database of the ABCD-study, a prospective cohort study on the health and development of children born in Amsterdam, the Netherlands. Of these, 846 (50.8%) were boys and 1460 (87.6%) had a healthy weight. Data on self-reported health behaviours and health factors were used to calculate the ICH scores (original and extended) by adding the frequency of scoring 'healthy' on each indicator, based on international cut-offs. The children were followed up for 6 years and cardiometabolic outcomes (carotid intima-media thickness (CIMT), blood pressure, glucose and lipids) were measured. Associations between ICH (both original and extended) and cardiometabolic outcomes were examined using multivariable regression models. RESULTS: At age 5-6 years, 11% scored poor (score 1-5), 56% intermediate (score 6-7) and 33% good (score 8-9) on extended ICH. Healthy diet and normal total cholesterol concentrations were the least prevalent. Neither the original nor the extended ICH scores were associated with CIMT at age 11-12. A higher score on the extended ICH was associated with lower total cholesterol (p for trend <0.001), lower systolic (p for trend = 0.012) and diastolic blood pressure (p for trend = 0.011), and lower body mass index (BMI) (p <0.001) at age 11-12. The original ICH score was associated with lower total cholesterol (p<0.001) and BMI (p <0.001) only. CONCLUSION: Our findings suggest that extending the ICH score in young children with additional health behaviours improves prediction of some cardiometabolic outcomes, but not CIMT in preadolescence, compared to the original ICH score. We would recommend other researchers to incorporate objective measures of health behaviours and longer follow-up to find out whether associations persist into adulthood.

[32] *Wang J, Wang Y, Yang X et al.* **Purification, structural characterization, and PCSK9 secretion inhibitory effect of the novel alkali-extracted polysaccharide from Cordyceps militaris**. Int J Biol Macromol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33662421
ABSTRACT
One novel alkali-extracted polysaccharide, CM3-SII, was obtained from the fruiting body of C. militaris via column chromatography. Its structural characteristics were investigated via chemical and spectroscopic methods. The backbone of CM3-SII was composed of →4)-β-D-Manp(1→, →6)-β-D-Manp(1→, and →6)-α-D-Manp(1→ glycosyls, and branching at the O-4 positions of →6)-β-D-Manp(1→ glycosyls with β-D-Galp, (1→2) linked-β-D-Galf, and →2,6)-α-D-Manp(1→ residues. Furthermore, O-6 and O-2 positions of the →2,6)-α-D-Manp(1→ residues were substituted with methyl and β-D-Galp, respectively. This polysaccharide significantly enhanced the intracellular protein expression of low-density lipoprotein receptor and proprotein convertase subtilisin/kexin type 9 (PCSK9) via regulating sterol regulatory element-binding protein 2 in hepatoma Huh7 cells. Of note, CM3-SII significantly decreased PCSK9 secretion at the concentration of 200 μg/mL. Collectively, CM3-SII is different from the previously reported alkali-extracted polysaccharides isolated from the fruiting body of C. militaris, and it may have potential application in hypolipidemia or as a pharmaceutical additive.

[33] *Shoji K, Wakana N, Zen K, Matoba S.* **Non-culprit ruptured vulnerable plaque healing and stabilization by an aggressive lipid-lowering therapy**. The international journal of cardiovascular imaging 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33649899
ABSTRACT

[34] *Nqweniso S, Walter C, du Randt R et al.* **Physical Activity, Cardiorespiratory Fitness and Clustered Cardiovascular Risk in South African Primary Schoolchildren from Disadvantaged Communities: A Cross-Sectional Study**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669905

ABSTRACT

The coexistence of multiple cardiovascular risk factors has been reported in school-aged children from the age of nine years, but most evidence stems from high-income countries. This cross-sectional study aimed at describing the cardiovascular health risk, physical activity (PA) behavior and cardiorespiratory fitness (CRF) levels of South African primary schoolchildren, and at examining the associations between PA/CRF and a composite measure of cardiovascular risk. Cross-sectional data from 832 primary schoolchildren (grade 1-4) were analyzed. Total cholesterol/HDL ratio, triglycerides, systolic/diastolic blood pressure, body fat, and glycated hemoglobin were assessed as cardiovascular risk markers. Data were analyzed via mixed linear regressions and analyses of covariance. Overall, 24.2% of the participants did not meet current PA standards. Higher CRF/PA were associated with lower body fat and lower clustered cardiovascular risk ($p < 0.05$). When categorizing children into CRF/PA quartiles, a lower clustered cardiovascular risk gradient was found in children with higher CRF ($p < 0.05$) or PA ($p < 0.05$). Our data shows that higher CRF/PA is associated with lower clustered cardiovascular risk already from a young age. Given that clustered cardiovascular risk present during childhood can track into adulthood, we advocate for PA participation and a healthy weight from a young age onwards.

[35] *Russo V, Cassini R, Caso V et al.* **Nursing Teleconsultation for the Outpatient Management of Patients with Cardiovascular Disease during COVID-19 Pandemic**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669951

ABSTRACT

Introduction: During the COVID-19 outbreak, non-urgent clinic visits or cardiac interventional procedures were postponed to a later date, and the implementation of telemedicine has guaranteed continuity of care for patients with chronic diseases. The aim of our study was to describe the medical interventions following nursing teleconsultation for the outpatient management of patients with cardiovascular diseases during the COVID-19 pandemic. Materials and Methods: All patients who did not attend the follow-up visit from 4 to 15 April 2020 at our institution and who were re-scheduled due to the COVID-19 lockdown were selected to be enrolled in the study. Each patient was followed by a semi-structured telephonic interview performed by a nurse. The outcomes of our study were to assess the patients' adherence to nursing teleconsultation and the usefulness of nursing teleconsultation to detect clinical conditions in need of medical intervention. Results: In total, 203 patients (81%) underwent nursing teleconsultation in a mean time of 7 ± 3 days from the outpatient visit lost due to the COVID-19 lockdown. Furthermore, 53 patients (26%) showed poor adherence to nursing teleconsultation. Among the 150 patients (mean age 67 ± 10 years; 68% male) who completed the telephonic interview, the nursing teleconsultation revealed the need of medical intervention in 69 patients (46%), who were more likely at very high cardiovascular risk (77% vs. 48%; $p < 0.0003$) and who showed a higher prevalence of dyslipidemia (97% vs. 64%; $p < 0.0001$) and

coronary artery disease (75% vs. 48%, $p < 0.0008$) compared to those not in need of any intervention. The up-titration of the lipid-lowering drugs (n: 32, 74%) was the most frequent medical intervention following the nursing teleconsultation. The mean time between the nursing teleconsultation and the date of the rescheduled in-person follow-up visit was 164 ± 36 days. Conclusions: Nursing teleconsultation is a simple and well-tolerated strategy that ensures the continuity of care and outpatient management for patients with cardiovascular diseases during the COVID-19 pandemic.

[36] *Mantovani A, Dalbeni A*. **Treatments for NAFLD: State of Art**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33652942
ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) is to date the most common chronic liver disease in clinical practice and, consequently, a major health problem worldwide. It affects approximately 30% of adults in the general population and up to 70% of patients with type 2 diabetes (T2DM). Despite the current knowledge of the epidemiology, pathogenesis, and natural history of NAFLD, no specific pharmacological therapies are until now approved for this disease and, consequently, general strategies have been proposed to manage it. They include: (a) lifestyle change in order to promote weight loss by diet and physical activity, (b) control of the main cardiometabolic risk factors, (c) correction of all modifiable risk factors leading the development and progression of advanced forms of NAFLD, and (d) prevention of hepatic and extra-hepatic complications. In the last decade, several potential agents have been widely investigated for the treatment of NAFLD and its advanced forms-shedding some light but casting a few shadows. They include some glucose-lowering drugs (such as pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter-2 (SGLT-2) inhibitors), antioxidants (such as vitamin E), statins or other lipid lowering agents, bile and non-bile acid farnesoid X activated receptor (FXR) agonists, and others. This narrative review discusses in detail the different available approaches with the potential to prevent and treat NAFLD and its advanced forms.

[37] *Moretti R, Giuffré M, Caruso P et al.* **Homocysteine in Neurology: A Possible Contributing Factor to Small Vessel Disease**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669577
ABSTRACT
Homocysteine (Hcy) is a sulfur-containing amino acid generated during methionine metabolism, accumulation of which may be caused by genetic defects or the deficit of vitamin B12 and folate. A serum level greater than 15 micro-mols/L is defined as hyperhomocysteinemia (HHcy). Hcy has many roles, the most important being the active participation in the transmethylation reactions, fundamental for the brain. Many studies focused on the role of homocysteine accumulation in vascular or degenerative neurological diseases, but the results are still undefined. More is known in cardiovascular disease. HHcy is a determinant for the development and progression of inflammation, atherosclerotic plaque formation, endothelium, arteriolar damage, smooth muscle cell proliferation, and altered-oxidative stress response. Conversely, few studies focused on the relationship between HHcy and small vessel disease (SVD), despite the evidence that mice with HHcy showed a significant end-feet disruption of astrocytes with a diffuse SVD. A severe reduction of vascular aquaporin-4-

water channels, lower levels of high-functioning potassium channels, and higher metalloproteinases are also observed. HHcy modulates the N-homocysteinylation process, promoting a pro-coagulative state and damage of the cellular protein integrity. This altered process could be directly involved in the altered endothelium activation, typical of SVD and protein quality, inhibiting the ubiquitin-proteasome system control. HHcy also promotes a constant enhancement of microglia activation, inducing the sustained pro-inflammatory status observed in SVD. This review article addresses the possible role of HHcy in small-vessel disease and understands its pathogenic impact.

[38] *Grune C, Zens C, Czapka A et al.* **Sustainable preparation of anti-inflammatory atorvastatin PLGA nanoparticles**. Int J Pharm 2021:120404.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33647413
ABSTRACT
In the present study, the anti-inflammatory lipophilic drug atorvastatin was encapsulated in poly(D,L-lactide-co-glycolide) (PLGA) using a sustainable method in comparison to the standard emulsion-diffusion-evaporation technique. For the sustainable method the organic solvent ethyl acetate was fully replaced by 400 g/mol poly(ethylene glycol) (PEG 400). Both techniques led to the formation of nanoparticles with comparable sizes of about 170 to 247 nm depending on the polymer type, with monomodal size distribution and negative zeta potential. All nanoparticles demonstrated a high biocompatibility in a shell-less hen's egg model and displayed an anti-inflammatory effect in human monocytes. The use of PEG 400 resulted in plasticizing effects and a lower crystallinity of the PLGA nanoparticles as determined by differential scanning calorimetry and Raman spectroscopy, which correlated with a faster drug release. Interestingly, the particles prepared by the sustainable method showed a crystallinity and drug release kinetics similar to nanoparticles made of PEG-PLGA using the standard method. Conclusively, the sustainable method is a fast and easy to perform technique suitable to prepare atorvastatin PLGA nanoparticles avoiding toxic and environmentally damaging drawbacks associated with classical organic solvents.

[39] *Guo H, Yu Y, Ye Y, Zhou S.* **Accuracy of Self-Reported Hypertension, Diabetes, and Hyperlipidemia among Adults of Liwan, Guangzhou, China**. Iranian journal of public health 2020; 49:1622-1630.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33643935
ABSTRACT
BACKGROUND: We aimed to determine the accuracy of self-reported diabetes, hypertension, and hyperlipidemia in Chinese adults and examine factors that affect the accuracy of self-reports. METHODS: This representative cross-sectional survey was conducted in Liwan District, Guangzhou City, Southeast China. Self-reported data were collected using a structured questionnaire. Biometrical data were recorded, including blood lipid, blood glucose and arterial blood pressure levels. Sensitivity, specificity, and κ values of self-reports were used as measurements of accuracy or agreements. The Robust Poisson-GEE was applied to determine the association of participants' characteristics with the accuracy of self-reports. RESULTS: Self-reported and biometrical data of 1278 residents aged 18 yr and older (693 women and 585 men) were used to calculate three measures of agreement. The agreement between self-reports and biomedical measurements was substantial for both hypertension and diabetes (κ=0.77 and 0.76), but only slight for hyperlipidemia (κ=0.06). Similarly, the sensitivity was higher for hypertension and diabetes (72.3% and 71.2%) than for hyperlipidemia (6.8%), while

the specificity was high overall (≥98%). The factors associated with an accurate self-reported diagnosis in respondents with disease included having undergone blood pressure measurement (for hypertension) or blood glucose measurement (for diabetes) in the past 6 month, having attended health knowledge lectures in the past year and having social health insurances (for hypertension), and having undergone physical discomfort in the past 2 weeks (for hypertension and diabetes). CONCLUSION: The accuracy of self-reported hypertension and diabetes was high, whereas that of self-reported hyperlipidemia was lower among the population.

[40] *Nambi V, Agha A.* **Inclisiran: A Game Changer in a Changing Game?** Journal of the American College of Cardiology 2021; 77:1194-1196.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33663736
ABSTRACT

[41] *Wright RS, Ray KK, Raal FJ et al.* **Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis**. Journal of the American College of Cardiology 2021; 77:1182-1193.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33663735
ABSTRACT
BACKGROUND: Inclisiran is a double-stranded small interfering RNA that suppresses proprotein convertase subtilisin-kexin type 9 (PCSK9) translation in the liver, leading to sustained reductions in low-density lipoprotein cholesterol (LDL-C) and other atherogenic lipoproteins with twice-yearly dosing. OBJECTIVES: The purpose of this study was to conduct a patient-level pooled analysis from 3 phase 3 studies of inclisiran. METHODS: Participants with heterozygous familial hypercholesterolemia (ORION-9 [Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol (LDL-C) in Subjects With Heterozygous Familial Hypercholesterolemia (HeFH)]), atherosclerotic cardiovascular disease (ASCVD) (ORION-10 [Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol]), or ASCVD and ASCVD risk equivalents (ORION-11 [Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol]) taking maximally tolerated statin therapy, with or without other LDL-C-lowering agents, were randomly assigned in a 1:1 ratio to receive either inclisiran or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter for 540 days. The coprimary endpoints were the placebo-corrected percentage change in LDL-C level from baseline to day 510 and the time-adjusted percentage change in LDL-C level from baseline after day 90 to day 540. Levels of other atherogenic lipoproteins and treatment-emergent adverse events were also assessed. RESULTS: A total of 3,660 participants (n = 482, n = 1,561, and n = 1,617 from ORION-9, -10, and -11, respectively) underwent randomization. The placebo-corrected change in LDL-C with inclisiran at day 510 was -50.7% (95% confidence interval: -52.9% to -48.4%; $p < 0.0001$). The corresponding time-adjusted change in LDL-C was -50.5% (95% confidence interval: -52.1% to -48.9%; $p < 0.0001$). Safety was similar in both groups. Treatment-emergent adverse events at the injection site were more frequent with inclisiran than placebo (5.0% vs. 0.7%), but were predominantly mild, and none were severe or persistent. Liver and kidney function tests, creatine kinase values, and platelet counts did not differ between groups. CONCLUSIONS: These pooled safety and efficacy data show that inclisiran, given twice yearly in addition to maximally tolerated statin therapy with or without other LDL-C lowering agents, is

an effective, safe, and well-tolerated treatment to lower LDL-C in adults with heterozygous familial hypercholesterolemia, ASCVD, or ASCVD risk equivalents.

[42] *Zachariah JP, Wang Y, Newburger JW et al.* **Biological Pathways in Adolescent Aortic Stiffness**. Journal of the American Heart Association 2021:e018419.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33641350

ABSTRACT

Background Aortic stiffening begins in youth and antedates future hypertension. In adults, excess weight, systemic inflammation, dyslipidemia, insulin resistance, neurohormonal activation, and altered adipokines are implicated in the pathogenesis of increased aortic stiffness. In adolescents, we assessed the relations of comprehensive measures of aortic stiffness with body mass index (BMI) and related but distinct circulating biomarkers. Methods and Results A convenience sample of 246 adolescents (mean age, 16±2 years; 45% female, 24% Black, and 43% Hispanic) attending primary care or preventive cardiology clinics at 2 tertiary hospitals was grouped as normal weight (N=98) or excess weight (N=148, defined as BMI ≥age- and sex-referenced 85th percentile). After an overnight fast, participants underwent anthropometry, noninvasive arterial tonometry, and assays for serum lipids, CRP (C-reactive protein), glucose, insulin, renin, aldosterone, and leptin. We used multivariable linear regression to relate arterial stiffness markers (including carotid-femoral pulse wave velocity) to BMI z score and a biomarker panel. Carotid-femoral pulse wave velocity was higher in excess weight compared with normal weight group (5.0±0.7 versus 4.6±0.6 m/s; P<0.01). After multivariable adjustment, carotid-femoral pulse wave velocity was associated with BMI z score (0.09 [95% CI, 0.01-0.18]; P=0.04) and with low-density lipoprotein cholesterol (0.26 [95% CI, 0.03-0.50]; P=0.03). Conclusions Higher BMI and low-density lipoprotein cholesterol were associated with greater aortic stiffness in adolescents. Maintaining optimal BMI and lipid levels may mitigate aortic stiffness.

[43] *Nagayama D, Saiki A, Watanabe Y et al.* **Prevention of Cardiovascular Events with Pitavastatin is Associated with Increased Serum Lipoprotein Lipase Mass Level: Subgroup Analysis of the TOHO-LIP**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33642441

ABSTRACT

AIM: To clarify the mechanism by which pitavastatin reduced cardiovascular (CV) events more effectively than atorvastatin in the TOHO Lipid Intervention Trial Using Pitavastatin (TOHO-LIP), the changes in (Δ) non-heparinized serum level of lipoprotein lipase mass (LPL mass) during administration of the respective statins were investigated. METHODS: From TOHO-LIP data, 223 hypercholesterolemic patients with any CV risks followed at Toho University Sakura Medical Center were analyzed. The patients were randomized to pitavastatin (2 mg/day) group (n=107) or atorvastatin (10 mg/day) group (n=116), and followed for 240 weeks. In this subgroup study, the primary and secondary end points were the same as those in TOHO-LIP, and 3-point major adverse cardiovascular events (3P-MACE) was added. The relationship between ΔLPL mass during the first year and the incidences of each end point was analyzed. RESULTS: The lipid-lowering effect was not different between the two statins. Cumulative 240-week incidence of each end point was significantly lower in pitavastatin group (primary: 1.9% vs. 10.3%, secondary: 4.7% vs. 18.1%, 3P-MACE: 0.9% vs. 6.9%). Mean LPL mass (64.9 to 69.0 ng/mL) and eGFR (70.1 to 73.6 ml/min/1.73m(2)) increased

in pitavastatin group, but not in atorvastatin group during the first year. Cox proportional-hazards model revealed that ΔLPL mass (1 ng/mL or 1SD) contributed to almost all end points. CONCLUSIONS: Pitavastatin administration reduced CV events more efficaciously than atorvastatin despite similar LDL cholesterol-lowering effect of the two statins. Increased LPL mass during the first year by pitavastatin treatment may be associated with this efficacy.

[44] *Nishikawa R, Furuhashi M, Hori M et al.* **A Resuscitated Case of Acute Myocardial Infarction with both Familial Hypercholesterolemia Phenotype Caused by Possibly Oligogenic Variants of the PCSK9 and ABCG5 Genes and Type I CD36 Deficiency**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33642439
ABSTRACT
A 56-year-old postmenopausal woman with out-of-hospital cardiac arrest caused by acute myocardial infraction was successfully resuscitated by intensive treatments and recovered without any neurological disability. She was diagnosed as having familial hypercholesterolemia (FH) based on a markedly elevated low-density lipoprotein cholesterol (LDL-C) level and family history of premature coronary artery disease. Genetic testing in her family members showed that a variant of the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene (c.2004C＞A, p.S668R), which had been previously reported as having uncertain significance, was associated with FH, indicating that the variant is a potential candidate for the FH phenotype. Next-generation sequencing analysis for the proband also showed that there was a heterozygous mutation of the ATP-binding cassette sub-family G member 5 (ABCG5) gene (c.1166G＞A, R389H), which has been reported to increase LDL-C level and the risk of cardiovascular disease. She was also diagnosed as having type 1 CD36 deficiency based on a lack of myocardial uptake of (123) I-labeled 15-(p-iodophenyl)-3-R,S-methyl-pentadecanoic acid in scintigraphy and the absence of CD36 antigen in both monocytes and platelets in flow cytometry. She had a homozygous mutation of the CD36 gene (c.1126-5_1127delTTTAGAT), which occurs in a canonical splice site (acceptor) and is predicted to disrupt or distort the normal gene product. To our knowledge, this is the first report of a heterozygous FH phenotype caused by possibly oligogenic variants of the PCSK9 and ABCG5 genes complicated with type I CD36 deficiency caused by a novel homozygous mutation. Both FH phenotype and CD36 deficiency might have caused extensive atherosclerosis, leading to acute myocardial infarction in the present case.

[45] *Nomani H, Mohammadpour AH, Reiner Ž et al.* **Statin Therapy in Post-Operative Atrial Fibrillation: Focus on the Anti-Inflammatory Effects**. Journal of cardiovascular development and disease 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33652637
ABSTRACT
BACKGROUND: Atrial fibrillation (AF) occurring after cardiac surgery, post-operative AF (POAF), is a serious and common complication of this treatment. POAF may be life-threatening and the available preventive strategies are insufficient or are associated with significantly increased risk of adverse effects, especially in long-term use. Therefore, more appropriate treatment strategies are needed. METHODS: In this paper, the efficacy, safety, and other aspects of using statins in the prevention of POAF focusing on their anti-inflammatory effects are reviewed. RESULTS: Recent studies have

suggested that inflammation has a significant role in POAF, from the first AF episode to its serious complications including stroke and peripheral embolism. On the other hand, statins, the most widely used medications in cardiovascular patients, have pleiotropic effects, including anti-inflammatory properties. Therefore, they may potentially be effective in POAF prevention. Statins, especially atorvastatin, appear to be an effective option for primary prevention of POAF, especially in patients who had coronary artery bypass grafting (CABG), a cardiac surgery treatment associated with inflammation in the heart muscle. However, several large studies, particularly with rosuvastatin, did not confirm the beneficial effect of statins on POAF. One large clinical trial reported higher risk of acute kidney injury (AKI) following high-dose rosuvastatin in Chinese population. In this study, rosuvastatin reduced the level of C-reactive protein (CRP) but did not reduce the rate of POAF. CONCLUSION: Further studies are required to find the most effective statin regimen for POAF prevention with the least safety concern and the highest health benefits.

[46] *Colivicchi F, Di Fusco SA, Arca M et al.* **Non-high-density lipoprotein cholesterol versus low-density lipoprotein cholesterol in clinical practice: ANMCO position paper**. Journal of cardiovascular medicine (Hagerstown, Md.) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33651721
ABSTRACT
Bloodstream cholesterol is a central contributor to atherosclerotic cardiovascular diseases. For several decades, low-density lipoprotein cholesterol (LDL-C) has been the main biomarker for the prediction of cardiovascular events and therapeutic target of lipid-lowering treatments. More recently, several findings have supported the greater reliability of non-high-density lipoprotein cholesterol (non-HDL-C) as a predictive factor and possible therapeutic target in refining antiatherogenic treatments, especially among patients with lower LDL-C and higher triglyceride values. This article discusses the limits of current standard methods for assessing LDL-C levels and emphasizes the persistent residual cardiovascular risk in patients treated with lipid-lowering agents on the basis of recommended LDL-C targets. It highlights that patients with controlled LDL-C and non-targeted non-HDL-C have a higher cardiovascular risk. The article focuses on the role of non-HDL-C as a better predictor of atherosclerotic disease as compared with LDL-C and as a therapeutic target. Finally, this article includes an executive summary aimed at refining preventive approaches in atherosclerotic cardiovascular disease.

[47] *Temporelli PL, Arca M, D'Erasmo L, De Caterina R*. **Lipid-Lowering Therapy in Patients with Coronary Heart Disease and Prior Stroke: Mission Impossible?** Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33671688
ABSTRACT
Hyperlipidemia is a powerful risk factor for coronary heart disease (CHD). It has been known for a long time that lipid-lowering drugs significantly reduce morbidity from CHD, thus proving a causal role for cholesterol in coronary events. Conversely, the relationship between low-density lipoprotein cholesterol (LDL-C) levels and stroke has been less clear and debated for many years. Recent data conclusively demonstrate not only the inverse epidemiological relationship of blood LDL-C with stroke, but also the efficacy of different strategies to attain cholesterol-lowering on stroke. They also dissipate lingering doubts about the possibility that lipid-lowering is linked to an increase in

hemorrhagic stroke. However, despite current international lipid guidelines now strongly recommend aggressive lipid-lowering therapy in patients with atherosclerotic cardiovascular disease, including CHD and cerebrovascular disease (CeVD), secondary prevention patients are often undertreated with lipid-lowering therapies in routine clinical practice. This review highlights that patients with CHD and concomitant CeVD do not receive aggressive lipid-lowering therapy despite being at very high risk and with clear evidence of benefit from lowering LDL-C levels below current targets.

[48] *Yue W, Xiaoqiong P, Jinbo H et al.* **Low-dose Colchicine in Type 2 Diabetes with Microalbuminuria: A Double-blind Randomized Clinical Trial**. Journal of diabetes 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33660924

ABSTRACT

BACKGROUND: Neutrophil-related chronic inflammation (NRCI) may contribute to the pathogenesis of diabetic kidney disease (DKD). We evaluated whether blocking NRCI with a low-dose colchicine prevents DKD. METHODS: A double-blind, randomized, placebo-controlled study was conducted. A total of 160 Patients with type 2 diabetes (T2D) and microalbuminuria (urinary albumin creatinine ratio [UACR] 30 to 300 mg/g Cr) who received angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) for at least 3 months were included. Subjects were 1:1 randomized to a placebo or colchicine group (0.5 mg/day). RESULTS: The primary endpoint was the incidence of overt nephropathy (UACR>300 mg/g Cr). During the 36 months, 38 patients (51.4%) in colchicine group and 39 (54.1%) in the control group developed overt nephropathy (HR = 1.066; 95%CI = 0.679 to 1.673; P = 0.78). Compared with placebo, colchicine modestly lowered levels of NRCI parameters (P values <0.05 for hs-CRP, WBCC, NC and NLR), while the changes of UACR and estimated glomerular filtration rate (eGFR) were similar between the two groups. There were no significant differences between two groups in drug-related adverse events, including infection, gastrointestinal symptoms and limb numbness. CONCLUSIONS: In patients with T2D with microalbuminuria, low-dose colchicine effectively and safely lowered NRCI but did not prevent the incidence of overt nephropathy.

[49] *Celiker H, Erekul G, Turhan SA et al.* **Early detection of neuropathy in patients with type 2 diabetes with or without microalbuminuria in the absence of peripheral neuropathy and retinopathy**. J Fr Ophtalmol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33648764

ABSTRACT

PURPOSE: Our goal is early detection of neuropathy in patients with type 2 diabetes with or without microalbuminuria in the absence of diabetic retinopathy and peripheral neuropathy by using in vivo corneal confocal microscopy (IVCCM). METHODS: A total of 60 type-2 diabetic patients, assigned to either a diabetes mellitus (DM) with microalbuminuria group (DM/MA+, n=30) or a DM without microalbuminuria group (DM/MA-, n=30), and 30 age-matched control subjects were enrolled in this study. All cases underwent evaluation of blood glucose level, HbA(1c), lipid fractions, body mass index (BMI), and corneal sensitivity (CS). Corneal nerve fiber length (NFL), nerve fiber density (NFD), nerve branch density (NBD), and tortuosity coefficient (TC) were quantified by IVCCM. None of the patients had peripheral neuropathy or retinopathy. RESULTS: Compared with the healthy subjects, NFL and NFD were reduced in both diabetic groups (P<0.0001), while NBD was significantly reduced in the DM/MA+ group. Between the diabetic groups, NFL, NFD, and NBD were significantly higher in

the DM/MA- group (all P's<0.001). CS was significantly lower in DM/MA+ compared with DM/MA- and controls (both P's<0.0001). NFD and NFL were inversely correlated with age, triglyceride level, and BMI. CONCLUSION: These results indicate that significant damage to small nerves, quantified using IVCCM, can be detected in the absence of retinopathy, peripheral neuropathy or microalbuminuria in type 2 diabetic patients. The severity of corneal nerve involvement may further increase in the presence of nephropathy. This feature may also be valuable for early detection of microvascular complications of DM, allowing for the prevention of progression of life threatening microvascular complications.

[50] *Chemello K, García-Nafría J, Gallo A et al.* **Lipoprotein Metabolism in Familial Hypercholesterolemia**. Journal of lipid research 2021:100062.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33675717
ABSTRACT
Familial hypercholesterolemia (FH) is one of the most common genetic disorders in humans. It is an extremely atherogenic metabolic disorder characterized by lifelong elevations of circulating LDL cholesterol levels often leading to premature cardiovascular events. In this review we discuss the clinical phenotypes of heterozygous and homozygous FH, the genetic variants in four genes (LDLR/APOB/PCSK9/LDLRAP1) underpinning the FH phenotype as well as the most recent in vitro experimental approaches used to investigate molecular defects affecting the LDL receptor pathway. In addition, we review perturbations in the metabolism of lipoproteins other than LDL in FH, with a major focus on lipoprotein (a). Finally, we discuss the mode of action and efficacy of many of the currently approved hypocholesterolemic agents used to treat FH patients, with a special emphasis on the treatment of phenotypically more severe forms of FH.

[51] *Chung YH, Lee BK, Kwon HM et al.* **Coronary calcification is associated with elevated serum lipoprotein (a) levels in asymptomatic men over the age of 45 years: A cross-sectional study of the Korean national health checkup data**. Medicine (Baltimore) 2021; 100:e24962.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33655963
ABSTRACT
Lipoprotein a (Lp (a)) and coronary artery calcification (CAC) are markers of coronary artery and cardiovascular diseases. However, the association between Lp (a) and CAC in asymptomatic individuals remains unclear. In this study, we aimed to determine the influence of Lp (a) on CAC in asymptomatic individuals.We included 2019 asymptomatic Korean adults who underwent testing for a coronary artery calcium score (CACS) and Lp (a) at the Gangnam Severance Hospital Health Checkup Center in Korea from January 2017 to August 2019. Participants were divided into 2 groups: CACS=0 and CACS>0. Factors affecting the CACS were analyzed by sex. Because age is a major risk factor for atherosclerosis, ≥45years in men and ≥55years in women, we further divided participants into 4 subgroups (≥45 and <45 in men, ≥55 and <55 in women). Factors affecting the CACS in the 4 groups were analyzed.There was a positive correlation between the CACS and traditional cardiovascular risk factors. Lp (a) positively correlated with the CACS in men (P<.01) and remained significant after multivariable logistic regression (P<.01). The same result was observed in men aged ≥45years (P<.01).Lp (a) is an independently associated factor of CAC and a marker of coronary atherosclerosis in asymptomatic men aged ≥45years. In asymptomatic men aged ≥45years, Lp (a) should be measured, and intensive Lp (a)-lowering treatment should be considered.

[52] *Su X*. **ANGPLT3 in cardio-metabolic disorders**. Molecular biology reports 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33677817
ABSTRACT
Dyslipidemia is associated with numerous health problems that include the combination of insulin resistance, hypertension and obesity, which is always grouped together asmetabolic syndrome. Given that metabolic syndrome leads to a high mortality and poses serious risks to human health worldwide, it is vital to explore the mechanisms whereby dyslipidemia modulates the risk and the severity of cardio-metabolic disorders. Recently, a specific secretory protein family, named angiopoietin-like protein (ANGPTL), is considered as one of the significant biomarkers which facilitate the development of angiogenesis. Among the eight proteins of ANGPTL family, ANGPTL3 has been demonstrated as an essential modulator of lipid catabolism within circulation by inhibiting the activity of lipoprotein lipase (LPL) and endothelial lipase (EL). Consistent with these notions, mice with ANGPTL3 gene-deficiency presented reduced circulating levels of low density lipoprotein cholesterol (LDL-C) and lower risk of atherosclerosis. On the other hand, participants carrying homozygous loss-of function (LOF) mutation in ANGPTL3 gene also displayed lower circulating LDL-C levels and atherosclerotic risk. In the current review, we summarized the recent understanding of ANGPTL3 in controlling the risk and the development of dyslipidemia and its related cardio-metabolic disorders. Moreover, we also provided the perspectives which potentially suggested that ANGPTL3 could be considered as a promising target in treating metabolic syndrome.

[53] *Gibbons GH, Seidman CE, Topol EJ*. **Conquering Atherosclerotic Cardiovascular Disease - 50 Years of Progress**. The New England journal of medicine 2021; 384:785-788.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33657686
ABSTRACT

[54] *Shah PP, Brady TM, Meyers KEC et al.* **Association of Obesity with Cardiovascular Risk Factors and Kidney Disease Outcomes in Primary Proteinuric Glomerulopathies**. Nephron 2021:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33677435
ABSTRACT
BACKGROUND/AIMS: Obesity is a known risk factor for cardiovascular disease and contributes to the development and progression of kidney disease. However, the specific influence of obesity on outcomes in primary glomerular disease has not been well characterized. METHODS: In this prospective cohort study, data were from 541 participants enrolled in the Nephrotic Syndrome Study Network (NEPTUNE), between 2010 and 2019, at 23 sites across North America. Blood pressure, lipids, and kidney disease outcomes including complete proteinuria remission, kidney failure, and chronic kidney disease progression were evaluated. Data were analyzed using linear and logistic regression with generalized estimating equations and time-varying Cox regression with Kaplan-Meier plots. RESULTS: The prevalence of obesity at baseline was 43.3% (N = 156) in adults and 37.6% (N = 68) in children. In adults, obesity was longitudinally associated with higher systolic BP (β = 6.49, 95% CI: 2.41, 10.56, p = 0.002), dyslipidemia (OR = 1.74, 95% CI: 1.30, 2.32, p < 0.001), triglycerides (β = 41.92, 95% CI: 17.12, 66.71, p = 0.001), and lower HDL (β = -6.92, 95% CI: -9.32, -4.51, p < 0.001). In children, obesity over time was associated with higher systolic BP index (β = 0.04, 95% CI:

0.02, 0.06, p < 0.001) and hypertension (OR = 1.43, 95% CI: 1.04, 1.98, p = 0.03). In both adults and children, obesity was associated with a significantly lower hazard of achieving complete remission of proteinuria (adult HR = 0.80, 95% CI: 0.69, 0.88, p < 0.001; pediatric HR = 0.72, 95% CI: 0.61, 0.84, p < 0.001). CONCLUSION: Obesity was associated with higher cardiovascular risk and less proteinuria remission from nephrotic syndrome in adults and children with proteinuric glomerulopathies. Weight-loss strategies may forestall cardiovascular disease and progressive kidney function decline in this high-risk patient group.

[55] *Abdullah MMH, Vazquez-Vidal I, Baer DJ et al.* **Common Genetic Variations Involved in the Inter-Individual Variability of Circulating Cholesterol Concentrations in Response to Diets: A Narrative Review of Recent Evidence**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33671529

ABSTRACT

The number of nutrigenetic studies dedicated to the identification of single nucleotide polymorphisms (SNPs) modulating blood lipid profiles in response to dietary interventions has increased considerably over the last decade. However, the robustness of the evidence-based science supporting the area remains to be evaluated. The objective of this review was to present recent findings concerning the effects of interactions between SNPs in genes involved in cholesterol metabolism and transport, and dietary intakes or interventions on circulating cholesterol concentrations, which are causally involved in cardiovascular diseases and established biomarkers of cardiovascular health. We identified recent studies (2014-2020) that reported significant SNP-diet interactions in 14 cholesterol-related genes (NPC1L1, ABCA1, ABCG5, ABCG8, APOA1, APOA2, APOA5, APOB, APOE, CETP, CYP7A1, DHCR7, LPL, and LIPC), and which replicated associations observed in previous studies. Some studies have also shown that combinations of SNPs could explain a higher proportion of variability in response to dietary interventions. Although some findings still need replication, including in larger and more diverse study populations, there is good evidence that some SNPs are consistently associated with differing circulating cholesterol concentrations in response to dietary interventions. These results could help clinicians provide patients with more personalized dietary recommendations, in order to lower their risk for cardiovascular disease.

[56] *Antraco VJ, Hirata BKS, de Jesus Simão J et al.* **Omega-3 Polyunsaturated Fatty Acids Prevent Nonalcoholic Steatohepatitis (NASH) and Stimulate Adipogenesis**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33671850

ABSTRACT

The increasing impact of obesity on global human health intensifies the importance of studies focusing on agents interfering with the metabolism and remodeling not only of the white adipose tissue (WAT) but also of the liver. In the present study, we have addressed the impact of n-3 PUFA in adipose cells' proliferation and adipogenesis, as well as in the hepatic lipid profile and morphology. Mice were induced to obesity by the consumption of a high-fat diet (HFD) for 16 weeks. At the 9th week, the treatment with fish oil (FO) was initiated and maintained until the end of the period. The FO treatment reduced the animals' body mass, plasma lipids, glucose, plasma transaminases, liver mass, triacylglycerol, and cholesterol liver content when compared to animals consuming only HFD. FO also decreased the inguinal (ing) WAT mass, reduced adipocyte volume, increased adipose cellularity (hyperplasia), and increased the proliferation of adipose-derived stromal cells (AdSCs)

which corroborates the increment in the proliferation of 3T3-L1 pre-adipocytes or AdSCs treated in vitro with n-3 PUFA. After submitting the in vitro treated (n-3 PUFA) cells, 3T3-L1 and AdSCs, to an adipogenic cocktail, there was an increase in the mRNA expression of adipogenic transcriptional factors and other late adipocyte markers, as well as an increase in lipid accumulation when compared to not treated cells. Finally, the expression of browning-related genes was also higher in the n-3 PUFA treated group. We conclude that n-3 PUFA exerts an attenuating effect on body mass, dyslipidemia, and hepatic steatosis induced by HFD. FO treatment led to decreasing adiposity and adipocyte hypertrophy in ingWAT while increasing hyperplasia. Data suggest that FO treatment might induce recruitment (by increased proliferation and differentiation) of new adipocytes (white and/or beige) to the ingWAT, which is fundamental for the healthy expansion of WAT.

[57] *De Bandt JP, Monin C*. **Obesity, Nutrients and the Immune System in the Era of COVID-19**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33668493
ABSTRACT
The past year has shown that obesity is a risk factor for severe complications of SARS-CoV-2 infection. Excess fat mass during obesity is known to be a risk factor for chronic diseases but also for severe infections and infectious complications. We have focused here on the elements responsible for this particular susceptibility to infections and more specifically to COVID-19. Excess fat is, in itself, responsible for alterations of the immune system by disrupting the production and function of immune cells. Indeed, hypertrophic adipocytes produce more pro-inflammatory adipokines (including cytokines). The increase in their apoptosis induces a release of pro-inflammatory compounds into the circulation and a recruitment of pro-inflammatory macrophages into the adipose tissue. A chronic systemic inflammatory state is then observed. In addition, diet, apart from its role in the development of adipose tissue, can also affect the immune system, with excess simple sugars and saturated fats exerting pro-inflammatory effects. This inflammation, the adipokines released by the adipocytes, and the infiltration of lipids into the lymphoid organs affects the production of immune cells and, directly, the functions of these cells. The alteration of the immune system increases the risk of infection as well as complications, including secondary bacterial infections and septic states, and increases infection-related mortality. During COVID-19, the chronic inflammatory state promotes the cytokine shock, characteristic of severe forms, caused in particular by excessive activation of the NLRP3 inflammasome. Furthermore, in obese subjects, the already present endothelial dysfunction will render endothelial inflammation (endotheliitis) due to viral infiltration all the more severe. Added to this is a state of hypercoagulability and a decrease in respiratory capacity, leading to a risk of severe COVID-19 with cardiovascular complications, acute respiratory distress syndrome, and disseminated intravascular coagulation, which can lead to multiple organ failure and even death.

[58] *Feldman F, Koudoufio M, Desjardins Y et al.* **Efficacy of Polyphenols in the Management of Dyslipidemia: A Focus on Clinical Studies**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669729
ABSTRACT
Polyphenols (PLPs), phytochemicals found in a wide range of plant-based foods, have gained extensive attention in view of their antioxidant, anti-inflammatory, immunomodulatory and several additional beneficial activities. The health-promoting effects noted in animal models of various non-

communicable diseases explain the growing interest in these molecules. In particular, in vitro and animal studies reported an attenuation of lipid disorders in response to PLPs. However, despite promising preclinical investigations, the effectiveness of PLPs in human dyslipidemia (DLP) is less clear and necessitates revision of available literature. Therefore, the present review analyzes the role of PLPs in managing clinical DLP, notably by dissecting their potential in ameliorating lipid/lipoprotein metabolism and alleviating hyperlipidemia, both postprandially and in long-term interventions. To this end, PubMed was used for article search. The search terms included polyphenols, lipids, triglycerides, cholesterol, LDL-cholesterol and /or HDL-cholesterol. The critical examination of the trials published to date illustrates certain benefits on blood lipids along with co-morbidities in participant's health status. However, inconsistent results document significant research gaps, potentially owing to study heterogeneity and lack of rigor in establishing PLP bioavailability during supplementation. This underlines the need for further efforts in order to elucidate and support a potential role of PLPs in fighting DLP.

[59] *Malo S, Rabanaque MJ, Maldonado L et al.* **Identifying Clusters of Adherence to Cardiovascular Risk Reduction Behaviors and Persistence with Medication in New Lipid-Lowering Drug Users. Impact on Healthcare Utilization**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33668726

ABSTRACT

We sought to identify specific profiles of new lipid-lowering drug users based on adherence to a healthy lifestyle and persistence with medication, and to characterize co-morbidities, co-treatments, and healthcare utilization for each of the profiles identified. Observational study in 517 participants in the Aragon Workers' Health Study (AWHS) without previous cardiovascular disease (CVD) and who initiated lipid-lowering therapy. Data were collected from workplace medical examinations and administrative health databases (2010-2018). Using cluster analysis, we identified distinct patient profiles based on persistence with therapy and lifestyle. We then compared characteristics, morbidity, and healthcare utilization across clusters. Participants were aggregated into four clusters based on persistence with therapy, smoking status, adherence to Mediterranean diet, and physical activity. In cluster 1 (n = 113), comprising those with a healthiest lifestyle (14.2% smokers, 84.0% with medium-high adherence to Mediterranean diet, high physical activity), 16.8% were persistent. In cluster 3 (n = 108), comprising patients with the least healthy lifestyle (100% smokers, poor adherence to the Mediterranean diet, low level of physical activity), all were non-persistent. Clusters 2 (n = 150) and 4 (n = 146) both comprised patients with intermediate lifestyle behaviors, but differed in terms of persistence (100 and 0%, respectively). Compared with other clusters, the burden of morbidity, cardiovascular score, and healthcare utilization were lower in cluster 1. The healthy adherer effect was only observed in new lipid-lowering drug users of certain profiles. Furthermore, we found that differences in adherence to lifestyle and medication recommendations for CVD prevention influenced morbidity burden and healthcare utilization.

[60] *Tsiroukidou K, Hatziagorou E, Grammatikopoulou MG et al.* **Cardiorespiratory Fitness Predicted by Fibrinogen and Leptin Concentrations in Children with Obesity and Risk for Diabetes: A Cross-Sectional Study and a ROC Curve Analysis**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33669882

ABSTRACT

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. The ability to exercise is affected by adiposity, and this mechanism involves low-grade chronic inflammation and homeostatic stress produced mainly in adipocytes, which can result in abnormal adipokine secretion. To date, the gold standard for cardiorespiratory fitness assessment is considered to be the maximum oxygen uptake (VO(2max)). The aim of the present study was to assess the prognostic value of hematological parameters of childhood obesity, as potential predictors of cardiorespiratory fitness (VO(2max)), using a sample of children and adolescents with obesity and risk for diabetes. A total of 84 clinically healthy children and adolescents were recruited, of which 21 were considered lean, 22 overweight and 41 obese, with a mean age of 12.0 ± 1.9, 11.4 ± 2.0, and 11.2 ± 2.1 years old, in each weight status category, respectively. Age and sex did not differ between groups. Hematologic testing was performed after 12 h of fasting including glucose, serum lipids, insulin, hc-CRP, adiponectin, leptin and fibrinogen levels. Cardiorespiratory capacity for exercise was assessed to determine VO(2max), using a cycle ergometer. The VO(2max) was negatively correlated with progressive strength to the BMIz (-0.656, $p \leq 0.001$), hs-CRP ($r = -0.341$, $p \leq 0.002$), glucose ($r = -0.404$, $p \leq 0.001$) and insulin levels ($r = -0.348$, $p \leq 0.001$), the homeostasis model assessment of insulin resistance (HOMA-IR) ($r = -0.345$, $p \leq 0.002$), as well as to the leptin ($r = -0.639$, $p \leq 0.001$) and fibrinogen concentrations ($r = -0.520$, $p \leq 0.001$). The multivariate analysis revealed that only leptin and fibrinogen concentrations could predict the VO(2max) adjusted for the BMIz of participants. The receiver operating characteristic (ROC) curve for the diagnostic accuracy of leptin, hs-CRP and fibrinogen concentrations for the prediction of VO(2max) revealed a good diagnostic ability for all parameters, with leptin being the most promising one (area under the curve (AUC): 99%). The results verify that in children with obesity, VO(2max) may be predicted from hematological parameters (leptin and fibrinogen), possibly bypassing more invasive methods.

[61] *Zaloga GP*. **Narrative Review of n-3 Polyunsaturated Fatty Acid Supplementation upon Immune Functions, Resolution Molecules and Lipid Peroxidation**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33670710

ABSTRACT

Fish oil supplementation is commonplace in human nutrition and is being used in both enteral and parenteral formulations during the treatment of patients with a large variety of diseases and immune status. The biological effects of fish oil are believed to result from their content of n-3 polyunsaturated fatty acids (PUFA), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These fatty acids are known to have numerous effects upon immune functions and are described as immunomodulatory. However, immunomodulatory is a nondescript term that encompasses immunostimulation and immunosuppression. The primary goal of this review is to better describe the immune effects of n-3 PUFA as they relate to immunostimulatory vs. immunosuppressive effects. One mechanism proposed for the immune effects of n-3 PUFA relates to the production of specialized pro-resolving mediators (SPMs). A second goal of this review is to evaluate the effects of n-3 PUFA supplementation upon production of SPMs. Although n-3 PUFA are stated to possess anti-oxidative properties, these molecules are highly oxidizable due to multiple double bonds and may increase oxidative stress. Thus, the third goal of this review is to evaluate the effects of n-3 PUFA upon lipid oxidation. We conclude, based upon current scientific evidence, that n-3 PUFA suppress inflammatory responses and most cellular immune responses such as chemotaxis, transmigration, antigen presentation, and lymphocyte functions and should be considered immunosuppressive. n-3

PUFA induced production of resolution molecules is inconsistent with many resolution molecules failing to respond to n-3 PUFA supplementation. n-3 PUFA supplementation is associated with increased lipid peroxidation in most studies. Vitamin E co-administration is unreliable for prevention of the lipid peroxidation. These effects should be considered when administering n-3 PUFA to patients that may be immunosuppressed or under high oxidative stress due to illness or other treatments.

[62] *Zhou E, Li Z, Nakashima H et al.* **Beneficial effects of brown fat activation on top of PCSK9 inhibition with alirocumab on dyslipidemia and atherosclerosis development in APOE*3-Leiden.CETP mice**. Pharmacological research : the official journal of the Italian Pharmacological Society 2021:105524.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33667684

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition, by increasing hepatic low density lipoprotein (LDL) receptor (LDLR) levels, has emerged as a strategy to reduce atherosclerosis by lowering circulating very low density lipoprotein (VLDL)-cholesterol. We hypothesized that the therapeutic effectiveness of PCSK9 inhibition can be increased by accelerating the generation of VLDL remnants, which typically have a high affinity for the LDLR. Therefore, we aimed to investigate whether accelerating lipolytic processing of VLDL by brown fat activation can further lower (V)LDL and reduce atherosclerosis on top of PCSK9 inhibition. APOE⁎3-Leiden.CETP mice were fed a Western-type diet and treated with the anti-PCSK9 antibody alirocumab or saline. After 2 weeks, both groups of mice were randomized to receive either the selective β3-adrenergic receptor (AR) agonist CL316,243 to activate brown fat or saline for 3 additional weeks to evaluate VLDL clearance or 12 additional weeks to analyze atherosclerosis development. β3-AR agonism and alirocumab combined decreased (V)LDL-cholesterol compared to alirocumab alone, which was explained by an accelerated plasma clearance of VLDL-cholesteryl esters that were mainly taken up by the liver. In addition, the combination promoted the transfer of VLDL-phospholipids to HDL to a higher extent than alirocumab alone, accompanied by higher plasma HDL-cholesterol levels and increased cholesterol efflux capacity. Consequently, combination treatment largely reduced atherosclerotic lesion area compared to vehicle. Together, β3-AR agonism enhances the lipoprotein-modulating effects of alirocumab to further improve dyslipidaemia and non-significantly further attenuate atherosclerosis development. Our findings demonstrate that brown fat activation may enhance the therapeutic effects of PCSK9 inhibition in dyslipidemia.

[63] *Parkkila K, Kiviniemi A, Tulppo M et al.* **Resistin is a risk factor for all-cause mortality in elderly Finnish population: A prospective study in the OPERA cohort**. PloS one 2021; 16:e0248015.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33651847

ABSTRACT

OBJECTIVE: Resistin is a small, cysteine-rich proinflammatory molecule that is primarily secreted by peripheral blood mononuclear cells and macrophages in humans. Previous studies have shown resistin to participate in various pathological processes including atherosclerosis and cancer progression but not many studies have assessed the role of resistin as a risk factor for all-cause mortality. The objective of this prospective study was to evaluate whether resistin predicts mortality among elderly Finnish people. METHODS: The study population consisted of 599 elderly (71.7 ± 5.4

years) patients and the follow-up was approximately six years. A thorough clinical examination including anthropometric and other clinical measurements such as blood pressure as well as various laboratory parameters (including resistin) was conducted at baseline. RESULTS: After the follow-up, 65 (11%) of the patients died. Resistin was a significant risk factor for all-cause mortality (HR 3.02, 95% CI: 1.64-5.56, p<0.001) when the highest tertile was compared to the lowest. Resistin remained as a significant risk factor even after adjusting for various covariates such as age, sex, systolic blood pressure, smoking habits, alcohol consumption, medications (antihypertensive, lipid-lowering, glucose-lowering), hsCRP and leisure time physical activity. Receiver operating characteristic (ROC) curve analysis for resistin demonstrated area under the curve (AUC) of 0.656 (95% CI: 0.577-0.734), p<0.001 and an optimal cutoff value of 12.88 ng/ml. CONCLUSIONS: Our results indicate that resistin is a significant risk factor for all-cause mortality among elderly Finnish subjects, independent from traditional cardiovascular risk factors.

[64] *Zeynalova S, Bucksch K, Scholz M et al.* **Monocyte subtype counts are associated with 10-year cardiovascular disease risk as determined by the Framingham Risk Score among subjects of the LIFE-Adult study**. PloS one 2021; 16:e0247480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33647042
ABSTRACT
Coronary heart disease, an inflammatory disease, is the leading cause of death globally. White blood cell counts (including monocytes) are easily available biomarkers of systemic inflammation. Monocyte subtypes can be measured by flow cytometry and classified into classical (CD14high, CD16neg), intermediate (CD14high, CD16+) and non-classical (CD14+, CD16high) with distinct functional properties. The goal of this study was to investigate the association of monocyte total count and its subtypes with cardiovascular risk groups defined by the Framingham Risk Score, which is used to estimate the 10-year risk of developing myocardial infarction or predict mortality following coronary heart disease. We also aimed to investigate whether monocyte counts are associated with relevant cardiovascular risk factors not included in the Framingham Risk Score, such as carotid atherosclerotic plaque and intima-media thickness. Our data came from the LIFE-Adult study, a population-based cohort study of 10,000 randomly selected participants in Leipzig, Germany. Data was gathered using self-administered questionnaires and physical examinations. Carotid plaques and intima-media thickness were measured using carotid artery sonography. Monocyte subtypes in blood were determined by 10-color flow cytometry for a total of 690 individuals. In a multivariate regression analysis adjusting for the risk factors BMI, intima-media thickness, presence of carotid plaques and diabetes mellitus, monocyte subtypes and total count were found to be significantly associated with the dichotomized Framingham Risk Score (≥10% versus <10%): Odds ratios [95% confidence interval] for monocyte subtypes: classical: 11.19 [3.79-34.26]; intermediate: 2.27 [1.11-4.71]; non-classical: 4.18 [1.75-10.20]; total: 14.59 [4.61-47.95]. In absence of prospective data, the FRS was used as a surrogate for CHD. Our results indicate that monocyte counts could provide useful predictive value for cardiovascular disease risk.

[65] *Qiu M, Glass Z, Chen J et al.* **Lipid nanoparticle-mediated codelivery of Cas9 mRNA and single-guide RNA achieves liver-specific in vivo genome editing of Angptl3**. Proceedings of the National Academy of Sciences of the United States of America 2021; 118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33649229

ABSTRACT
Loss-of-function mutations in Angiopoietin-like 3 (Angptl3) are associated with lowered blood lipid levels, making Angptl3 an attractive therapeutic target for the treatment of human lipoprotein metabolism disorders. In this study, we developed a lipid nanoparticle delivery platform carrying Cas9 messenger RNA (mRNA) and guide RNA for CRISPR-Cas9-based genome editing of Angptl3 in vivo. This system mediated specific and efficient Angptl3 gene knockdown in the liver of wild-type C57BL/6 mice, resulting in profound reductions in serum ANGPTL3 protein, low density lipoprotein cholesterol, and triglyceride levels. Our delivery platform is significantly more efficient than the FDA-approved MC-3 LNP, the current gold standard. No evidence of off-target mutagenesis was detected at any of the nine top-predicted sites, and no evidence of toxicity was detected in the liver. Importantly, the therapeutic effect of genome editing was stable for at least 100 d after a single dose administration. This study highlights the potential of LNP-mediated delivery as a specific, effective, and safe platform for Cas9-based therapeutics.

[66] *Dashti H, Roche EC, Bates DW et al.* **SARS2 simplified scores to estimate risk of hospitalization and death among patients with COVID-19**. Scientific reports 2021; 11:4945.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33654180

ABSTRACT
Although models have been developed for predicting severity of COVID-19 from the medical history of patients, simplified models with good accuracy could be more practical. In this study, we examined utility of simpler models for estimating risk of hospitalization of patients with COVID-19 and mortality of these patients based on demographic characteristics (sex, age, race, median household income based on zip code) and smoking status of 12,347 patients who tested positive at Mass General Brigham centers. The corresponding electronic records were queried (02/26-07/14/2020) to construct derivation and validation cohorts. The derivation cohort was used to fit generalized linear models for estimating risk of hospitalization within 30 days of COVID-19 diagnosis and mortality within approximately 3 months for the hospitalized patients. In the validation cohort, the model resulted in c-statistics of 0.77 [95% CI 0.73-0.80] for hospitalization, and 0.84 [95% CI 0.74-0.94] for mortality among hospitalized patients. Higher risk was associated with older age, male sex, Black ethnicity, lower socioeconomic status, and current/past smoking status. The models can be applied to predict the absolute risks of hospitalization and mortality, and could aid in individualizing the decision making when detailed medical history of patients is not readily available.

[67] *Zhang XL, Yuan SY, Wan G et al.* **The effects of acarbose therapy on reductions of myocardial infarction and all-cause death in T2DM during 10-year multifactorial interventions (The Beijing Community Diabetes Study 24)**. Scientific reports 2021; 11:4839.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33649485

ABSTRACT
To investigate the potential benefits of acarbose therapy on cardiovascular events (CVD) in Type 2 diabetes (T2DM) in an urban community over 10-year follow-up. The study population of Beijing Community Diabetes Study (BCDS) were type 2 diabetes (T2DM) living in 21 communities in Beijing. All patients received comprehensive intervention in accordance with the Chinese guidelines for the prevention and treatment of diabetes. Professors in endocrinology from top tier hospitals regularly visited the communities for consultations, which was a feature of this study. A total of 1797 T2DM in

BCDS study had complete screening data, including blood glucose, blood pressure, lipid profiles and acarbose continuous therapy. After 10-year follow-up, the risks of CVD outcomes were assessed according to whether patients had received acarbose therapy or not. All patients were followed-up to assess the long-term effects of the multifactorial interventions. At baseline, compared with the acarbose therapy free in T2DM, there was no significant difference in achieving the joint target control in patients with acarbose therapy. From the beginning of 8th year follow-up, the joint target control rate in patients with acarbose therapy was significantly higher than that of acarbose therapy free. During the 10-year follow-up, a total of 446 endpoint events occurred, including all-cause death, cardiovascular events, cerebrovascular events. The incidences of myocardial infarction (from the 4th year of follow-up) and all-cause death (from the 2nd year of follow-up) in patients who received acarbose therapy were significantly lower than that of acarbose therapy free respectively. In Cox multivariate analyses, there were significant differences in incidences of myocardial infarction and all-cause death between afore two groups during the 10-year follow-up, and the adjusted HRs were 0.50 and 0.52, respectively. After multifactorial interventions, T2DM with acarbose therapy revealed significant reductions of myocardial infarction and all-cause death. The long-term effects of with acarbose therapy on improving joint target control might be one of the main reasons of myocardial infarction and all-cause death reduction.Trial Registration: ChiCTR-TRC-13003978, ChiCTR-OOC-15006090.

[68] *Almeida CR, Ferreira BH, Duarte IF*. **Targeting PCSK9: a promising adjuvant strategy in cancer immunotherapy**. Signal Transduct Target Ther 2021; 6:111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33677469
ABSTRACT