[1] *Gumuser ED, Haidermota S, Finneran P et al.* **Trends in cholesterol testing during the COVID-19 pandemic: COVID-19 and cholesterol testing**. Am J Prev Cardiol 2021; 6:100152.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33778798

ABSTRACT

OBJECTIVE: To characterize trends in cholesterol testing since the start of the COVID-19 pandemic. METHODS: We extracted testing for total cholesterol performed in adults ≥40 years old within the Mass General Brigham healthcare system between March and September 2020, as well those performed between March and September 2019 (reference period). Weekly cholesterol testing rates during the 2020 vs. 2019 study periods were compared using the paired samples t-test. Secondary analyses compared testing volumes and patient characteristics during the first vs. second half of the 2020 study period. RESULTS: The study sample included 296,599 tests for total cholesterol performed in 220,215 individuals. The mean (SD) weekly cholesterol tests performed were 6,361 (682) in 2019 vs. 3,867 (2,373) in 2020 (P = 2.6 × 10(-5)), representing an overall decline of 39.2%. However, weekly testing rates in 2020 were not uniform. Greatest reductions coincided with the "first wave" of the pandemic (March-May 2020), with up to 92% reductions in testing observed. In the first 14 weeks of each study period (March to mid-June), weekly testing rates were 71.8% lower in 2020. Among individuals tested in 2020, those tested between March and mid-June had substantially lower total cholesterol compared with individuals tested after mid-June (174.2 vs. 181.5 mg/dL, P<2.2 × 10(-16)). CONCLUSIONS: In a large integrated healthcare system, cholesterol testing rates were 39% lower between March-September 2020 compared with the same time period in 2019. Mechanisms for safely facilitating cholesterol testing and management for high-risk patients will be important as COVID-19 re-surges across the U.S. until widespread vaccination and population immunity allow resumption of routine preventive care.

[2] *Kłosiewicz-Latoszek L, Cybulska B, Stoś K, Tyszko P*. **Hypolipaemic nutraceutics: red yeast rice and Armolipid, berberine and bergamot**. Ann Agric Environ Med 2021; 28:81-88.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33775071

ABSTRACT

INTRODUCTION: Increased serum cholesterol levels constitute one of the main risk factors for cardiovascular diseases. Statins are a major method for reducing the levels which also lower the risk of cardiovascular events. However, these valuable drugs cannot be used in all patients who need them due to contraindications and intolerance. In such cases, help can be sought from nutraceutics that reduce the serum cholesterol concentration. Since there are numerous products of this type available at drugstores, registered as supplements, there seems to be a need to demonstrate their effectiveness in preventing cardiovascular diseases induced by atherosclerosis. In literature, increasingly more attention is drawn to red yeast rice, Armolipid, berberine and bergamot. BRIEF DESCRIPTION: This article presents knowledge about these nutraceutics based on clinical studies and expert statements relating to their use. The results of clinical studies and metaanalyses have shown that nutraceutics with cholesterol lowering properties, red yeast rice and Armolipid are the most favourable for reducing cardiovascular events. However, the evidence of benefits of berberine and bergamot is not so conclusive. CONCLUSIONS: Red yeast rice products and Armolipid may be used as an alternative treatment in statin intolerant patients, especially in combination with ezetimibe. These nutraceutics can be also considered, as an adjunct to diet therapy in primary prevention of

cardiovascular diseases in patients with mild and moderate hypercholesterolaemia. The opinion of experts on berberine and bergamot is ambiguous.

[3] *Ribó-Coll M, Castro-Barquero S, Lassale C et al.* **Mediterranean Diet and Physical Activity Decrease the Initiation of Cardiovascular Drug Use in High Cardiovascular Risk Individuals: A Cohort Study**. Antioxidants (Basel, Switzerland) 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33808041
ABSTRACT
Our aim was to assess whether long-term adherence to a Mediterranean diet (MedDiet) and leisure-time physical activity (LTPA) were associated with a lower initiation of cardiovascular drug use. We studied the association between cumulative average of MedDiet adherence and LTPA and the risk of cardiovascular drug initiation in older adults at high cardiovascular risk (PREvención con DIeta MEDiterránea trial participants) non-medicated at baseline: glucose-lowering drugs (n = 4437), antihypertensives (n = 2145), statins (n = 3977), fibrates (n = 6391), antiplatelets (n = 5760), vitamin K antagonists (n = 6877), antianginal drugs (n = 6837), and cardiac glycosides (n = 6954). One-point increases in MedDiet adherence were linearly associated with a decreased initiation of glucose-lowering (HR: 0.76 [0.71-0.80]), antihypertensive (HR: 0.79 [0.75-0.82]), statin (HR: 0.82 [0.78-0.85]), fibrate (HR: 0.78 [0.68-0.89]), antiplatelet (HR: 0.79 [0.75-0.83]), vitamin K antagonist (HR: 0.83 [0.74; 0.93]), antianginal (HR: 0.84 [0.74-0.96]), and cardiac glycoside therapy (HR: 0.69 [0.56-0.84]). LTPA was non-linearly related to a delayed initiation of glucose-lowering, antihypertensive, statin, fibrate, antiplatelet, antianginal, and cardiac glycoside therapy (minimum risk: 180-360 metabolic equivalents of task-min/day). Both combined were synergistically associated with a decreased onset of glucose-lowering drugs (p-interaction = 0.04), antihypertensive drugs (p-interaction < 0.001), vitamin K antagonists (p-interaction = 0.04), and cardiac glycosides (p-interaction = 0.01). Summarizing, sustained adherence to a MedDiet and LTPA were associated with lower risk of initiating cardiovascular-related medications.

[4] *Durrington PN, Soran H*. **Cholesterol lowering in secondary prevention: Could do better**. Atherosclerosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33810859
ABSTRACT

[5] *Pisaniello AD, Psaltis PJ, King PM et al.* **Omega-3 fatty acids ameliorate vascular inflammation: A rationale for their atheroprotective effects**. Atherosclerosis 2021; 324:27-37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33812168
ABSTRACT
BACKGROUND AND AIMS: Clinical trials have demonstrated reductions in major adverse cardiovascular events with purified high-dose eicosapentaenoic acid (EPA), independent of effects on lipids. We aimed to investigate whether omega-3 fatty acids reduce vascular inflammation, a critical mediator of atherosclerosis, and hypothesised that EPA is superior to docosahexaenoic acid (DHA). METHODS: In a double-blind randomised controlled trial and cell-culture study, 40 healthy volunteers were supplemented with 4 g daily of either EPA, DHA, fish oil (2:1 EPA:DHA), or placebo for 30 days. Serum was incubated with TNF-stimulated human umbilical vein endothelial cells (HUVECs), and markers of acute vascular inflammation (AVI) were measured. The effects of EPA, DHA

(600 mg/kg/day), olive oil, or no treatment were also measured in preclinical models of [1] AVI using a periarterial collar (C57Bl/6J; n = 40 mice) and [2] atherosclerosis where ApoE(-/-) mice (n = 40) were fed a 16-week atherogenic diet. RESULTS: EPA supplementation reduced expression of C-C motif chemokine ligand 2 (CCL2) by 25% compared to placebo (p = 0.03). In the AVI model, EPA reduced vascular expression of VCAM1 by 43% (p = 0.02) and CCL2 by 41% (p = 0.03). Significant inverse correlations were observed between EPA levels and vascular expression of VCAM1 (r = -0.56, p = 0.001) and CCL2 (r = -0.56, p = 0.001). In ApoE(-/-) mice, EPA reduced aortic expression of Il1b by 44% (p = 0.04) and Tnf by 49% (p = 0.04), with similar inverse correlations between EPA levels and both Il1b (r = -0.63, p = 0.009) and Tnf (r = -0.50, p = 0.04). CONCLUSIONS: Supplementation with EPA, more so than DHA, ameliorates acute and chronic vascular inflammation, providing a rationale for the cardiovascular benefit observed with high dose omega-3 fatty acid administration.

[6] *Zafeiropoulos S, Farmakis I, Kartas A et al.* **Reinforcing adherence to lipid-lowering therapy after an acute coronary syndrome: A pragmatic randomized controlled trial**. Atherosclerosis 2021; 323:37-43.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33780749
ABSTRACT
BACKGROUND AND AIMS: Achieving the low-density lipoprotein cholesterol (LDL-C) goal following an acute coronary syndrome (ACS) is a milestone often missed due to suboptimal adherence to secondary prevention treatments. Whether improved adherence could result in reduced LDL-C levels is unclear. We aimed to evaluate whether an educational-motivational intervention increases long-term lipid-lowering therapy (LLT) adherence and LDL-C goal attainment rate among post-ACS patients. METHODS: IDEAL-LDL was a parallel, two-arm, single-center, pragmatic, investigator-initiated randomized controlled trial. Hospitalized patients for ACS were randomized to a physician-led integrated intervention consisting of an educational session at baseline, followed by regular motivational interviewing phone sessions or usual care. Co-primary outcomes were the LLT adherence (measured by Proportion of Days Covered (PDC); good adherence defined as PDC>80%), and LDL-C goal (<70 mg/dl or 50% reduction from baseline) achievement rate at one year. RESULTS: In total, 360 patients (mean age 62 years, 81% male) were randomized. Overall, good adherence was positively associated with LDL-C goal achievement rate at one year. Median PDC was higher in the intervention group than the control group [0.92 (IQR, 0.82-1.00) vs. 0.86 (0.62-0.98); p = 0.03] while the intervention group had increased odds of good adherence (odds ratio: 1.76 (95% confidence interval 1.02 to 2.62; p = 0.04). However, neither the LDL-C goal achievement rate (49.6% in the intervention vs. 44.9% in the control group; p = 0.49) nor clinical outcomes differed significantly between the two groups. CONCLUSIONS: A multifaceted intervention improved LLT adherence in post-ACS patients without a significant difference in LDL-C goal attainment.

[7] *Zhang K, Zheng J, Chen Y et al.* **Inducible phospholipid transfer protein deficiency ameliorates atherosclerosis**. Atherosclerosis 2021; 324:9-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33798923
ABSTRACT
BACKGROUND AND AIMS: Atherosclerosis progression and regression studies are related to its prevention and treatment. Although we have gained extensive knowledge on germline phospholipid transfer protein (PLTP) deficiency, the effect of inducible PLTP deficiency in atherosclerosis remains

unexplored. METHODS: We generated inducible PLTP (iPLTP)-knockout (KO) mice and measured their plasma lipid levels after feeding a normal chow or a Western-type diet. Adenovirus associated virus-proprotein convertase subtilisin/kexin type 9 (AAV-PCSK9) was used to induce hypercholesterolemia in the mice. Collars were placed around the common carotid arteries, and atherosclerosis progression and regression in the carotid arteries and aortic roots were evaluated. RESULTS: On a normal chow diet, iPLTP-KO mice exhibited decreased cholesterol, phospholipid, apoA-I, and apoB levels compared with control mice. Furthermore, the overall amount of high-density lipoprotein (HDL) particles was reduced in these mice, but this effect was more profound for larger HDL particles. On a Western-type diet, iPLTP-KO mice again exhibited reduced levels of all tested lipids, even though the basal lipid levels were increased. Additionally, these mice displayed significantly reduced atherosclerotic plaque sizes with increased plaque stability. Importantly, inducible PLTP deficiency significantly ameliorated atherosclerosis by reducing the size of established plaques and the number of macrophages in the plaques without causing lipid accumulation in the liver. CONCLUSIONS: Induced PLTP deficiency in adult mice reduces plasma total cholesterol and triglycerides, prevents atherosclerosis progression, and promotes atherosclerosis regression. Thus, PLTP inhibition is a promising therapeutic approach for atherosclerosis.

[8] *Sluiter TJ, van Buul JD, Huveneers S et al.* **Endothelial Barrier Function and Leukocyte Transmigration in Atherosclerosis**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33804952
ABSTRACT
The vascular endothelium is a highly specialized barrier that controls passage of fluids and migration of cells from the lumen into the vessel wall. Endothelial cells assist leukocytes to extravasate and despite the variety in the specific mechanisms utilized by different leukocytes to cross different vascular beds, there is a general principle of capture, rolling, slow rolling, arrest, crawling, and ultimately diapedesis via a paracellular or transcellular route. In atherosclerosis, the barrier function of the endothelium is impaired leading to uncontrolled leukocyte extravasation and vascular leakage. This is also observed in the neovessels that grow into the atherosclerotic plaque leading to intraplaque hemorrhage and plaque destabilization. This review focuses on the vascular endothelial barrier function and the interaction between endothelial cells and leukocytes during transmigration. We will discuss the role of endothelial dysfunction, transendothelial migration of leukocytes and plaque angiogenesis in atherosclerosis.

[9] *Higgins V, Habeeb NW, Venner AA et al.* **A Snapshot of Lipid Reporting Practices in Canadian Clinical Laboratories: An Urgent Need for Harmonization**. The Canadian journal of cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33775880
ABSTRACT
To effectively implement the Canadian Cardiovascular Society (CCS) Guidelines for dyslipidemia management into clinical laboratories, clear recommendations for lipid reporting are essential. In this study, the Canadian Society of Clinical Chemists (CSCC) Working Group on Reference Interval Harmonization (hRI) surveyed Canadian laboratories on adult lipid reporting practices to set a foundation for the development and implementation of harmonized lipid reporting across Canada. Key

aspects of the survey asked laboratories: what reporting parameters were in place to assess lipid results; what interpretative comments were provided; whether non-fasting lipids were permitted and, if so, what strategy was used to document fasting status; and whether there was interest in implementing a harmonized lipid report. A total of 101 laboratories were represented by 24 respondents, as many responses were submitted by laboratory networks. There was at least one response from nine Canadian provinces and representation across five testing platforms. Upper and lower limits for lipid parameters and referenced source of limits varied substantially across laboratories, with only 56% of laboratories (9 respondents) referencing the 2016 CCS Guidelines. Eighty-six percent of laboratories (19 respondents) report non-fasting lipids, although the method of documenting non-fasting status varied. Overall, 36% of laboratories (8 respondents) reported interest in implementing a harmonized lipid report. Assessment of current lipid reporting practices supports the need for harmonized lipid reporting across Canada. Development of a harmonized lipid report for the adult population, consistent with up-to-date Canadian guidelines, will improve continuity of lipid test interpretation across Canada and improve clinical decision making.

[10] *Pearson GJ, Thanassoulis G, Anderson TJ et al.* **2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult**. The Canadian journal of cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33781847
ABSTRACT
The 2021 guidelines primary panel selected clinically relevant questions and produced updated recommendations, on the basis of important new findings emerging since the 2016 guidelines. In subjects with clinical atherosclerosis, abdominal aortic aneurysm, most subjects with diabetes or chronic kidney disease, and those with low-density lipoprotein cholesterol (LDL-C) ≥5 mmol/L, statin therapy continues to be recommended. We have introduced the concept of lipid/lipoprotein treatment thresholds for intensifying lipid-lowering therapy with non-statin agents, and have identified the secondary prevention patients who have been shown to derive the largest benefit from intensification of therapy with these agents. For all other patients, we emphasize risk assessment linked to lipid/lipoprotein evaluation to optimize clinical decision-making. Lipoprotein(a) measurement is now recommended once in a patient's lifetime, as part of initial lipid screening to assess cardiovascular risk. For any patient with triglycerides >1.5 mmol/L, either non-high-density lipoprotein cholesterol or apolipoprotein-B are the preferred lipid parameter for screening, rather than LDL-C. We provide updated recommendations regarding the role of coronary artery calcium scoring as a clinical decision tool to aid the decision to initiate statin therapy. There are new recommendations on the preventative care of women with hypertensive disorders of pregnancy. Health behaviour modification, including regular exercise and a heart-healthy diet, remain the cornerstone of cardiovascular disease prevention. These guidelines are intended to provide a platform for meaningful conversation and shared-decision making between patient and care provider, so that individual decisions can be made for risk screening, assessment, and treatment.

[11] *Cho Y, Cho EJ, Yoo JJ et al.* **Association between Lipid Profiles and the Incidence of Hepatocellular Carcinoma: A Nationwide Population-Based Study**. Cancers 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33808412
ABSTRACT

BACKGROUND AND AIMS: Altered lipid metabolism has been implicated in the development of hepatocellular carcinoma (HCC). This study investigated the relationships between lipid profiles and HCC development. METHODS: Data were obtained from the Korean National Health Insurance Service from 2009 to 2017. Cox regression analysis was used to examine the hazard ratios of HCC in 8,528,790 individuals who had undergone health check-ups in 2009. RESULTS: During a median of 7.3 years follow-up, 26,891 incidents of HCCs were identified. The incidence of HCC (per 100,000 person-years) gradually decreased according to the increase in total-cholesterol and LDL-cholesterol; the incidence of HCC was 69.2, 44.0, 33.9, and 25.8 in quartile-1 (Q1), Q2, Q3, and Q4 population of total-cholesterol, and 63.6, 44.5, 37.2, and 28.3 in Q1, Q2, Q3, and Q4 population of LDL-cholesterol, respectively. Compared to Q1 of total-cholesterol, subjects in higher total-cholesterol levels were associated with a lower incidence of HCC (multiple covariates-adjusted hazard ratio (aHR): Q2 0.61; Q3 0.46; Q4 0.36). These associations were consistently observed in stratified subgroup analysis by the presence of liver cirrhosis or viral hepatitis. CONCLUSIONS: Low serum lipid levels were significantly associated with the increased risk of developing HCC. A low lipid profile might be an independent risk factor and preclinical marker for HCC.

[12] *Molnár G, Gyarmathy VA, Zádori N et al.* **Severe Hypertriglyceridemia-Induced Acute Pancreatitis**. Case Rep Gastroenterol 2021; 15:218-224.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33790708

ABSTRACT

The prevalence of familial hypercholesterolemia (FH) is about 1 in 200-500 in the general population, but approximately less than 1% of those affected are actually diagnosed. One of the most promising approaches to treat FH is utilizing human monoclonal antibodies. This is a case study describing a 47-year-old male patient who presented to the Emergency Department with acute abdominal pain caused by severe hypertriglyceridemia (HTG)-induced acute pancreatitis (AP). We report the steps necessary for establishing the right diagnosis and the management of HTG-induced AP, which are inevitable for the reduction of severity and mortality. This case study shows that hypercholesterolemia is an underdiagnosed and potentially lethal disease. Once diagnosed, all measures should be considered to control blood cholesterol and lipid levels. The decision to administer PCSK9 inhibitors should not be solely based on economical calculation, but rather individual factors should also be considered to weigh the risk/benefit ratio.

[13] *Rhainds D, Packard CJ, Brodeur MR et al.* **Role of Adenylate Cyclase 9 in the Pharmacogenomic Response to Dalcetrapib: Clinical Paradigm and Molecular Mechanisms in Precision Cardiovascular Medicine**. Circulation. Genomic and precision medicine 2021:Circgen121003219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33794646

ABSTRACT

Following the neutral results of the dal-OUTCOMES trial, a genome-wide study identified the rs1967309 variant in the adenylate cyclase type 9 (ADCY9) gene on chromosome 16 as being associated with the risk of future cardiovascular events only in subjects taking dalcetrapib, a CETP (cholesterol ester transfer protein) modulator. Homozygotes for the minor A allele (AA) were protected from recurrent cardiovascular events when treated with dalcetrapib, while homozygotes for the major G allele (GG) had increased risk. Here, we present the current state of knowledge

regarding the impact of rs1967309 in ADCY9 on clinical observations and biomarkers in dalcetrapib trials and the effects of mouse ADCY9 gene inactivation on cardiovascular physiology. Finally, we present our current model of the interaction between dalcetrapib and ADCY9 gene variants in the arterial wall macrophage, based on the intracellular role of CETP in the transfer of complex lipids from endoplasmic reticulum membranes to lipid droplets. Briefly, the concept is that dalcetrapib would inhibit CETP-mediated transfer of cholesteryl esters, resulting in a progressive inhibition of cholesteryl ester synthesis and free cholesterol accumulation in the endoplasmic reticulum. Reduced ADCY9 activity, by paradoxically leading to higher cyclic AMP levels and in turn increased cellular cholesterol efflux, could impart cardiovascular protection in rs1967309 AA patients. The ongoing dal-GenE trial recruited 6145 patients with the protective AA genotype and will provide a definitive answer to whether dalcetrapib will be protective in this population.

[14] *Boutouyrie P, Chowienczyk P, Humphrey JD, Mitchell GF*. **Arterial Stiffness and Cardiovascular Risk in Hypertension**. Circulation research 2021; 128:864-886.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33793325

ABSTRACT

Arterial stiffness, a leading marker of risk in hypertension, can be measured at material or structural levels, with the latter combining effects of the geometry and composition of the wall, including intramural organization. Numerous studies have shown that structural stiffness predicts outcomes in models that adjust for conventional risk factors. Elastic arteries, nearer to the heart, are most sensitive to effects of blood pressure and age, major determinants of stiffness. Stiffness is usually considered as an index of vascular aging, wherein individuals excessively affected by risk factor exposure represent early vascular aging, whereas those resistant to risk factors represent supernormal vascular aging. Stiffness affects the function of the brain and kidneys by increasing pulsatile loads within their microvascular beds, and the heart by increasing left ventricular systolic load; excessive pressure pulsatility also decreases diastolic pressure, necessary for coronary perfusion. Stiffness promotes inward remodeling of small arteries, which increases resistance, blood pressure, and in turn, central artery stiffness, thus creating an insidious feedback loop. Chronic antihypertensive treatments can reduce stiffness beyond passive reductions due to decreased blood pressure. Preventive drugs, such as lipid-lowering drugs and antidiabetic drugs, have additional effects on stiffness, independent of pressure. Newer anti-inflammatory drugs also have blood pressure independent effects. Reduction of stiffness is expected to confer benefit beyond the lowering of pressure, although this hypothesis is not yet proven. We summarize different steps for making arterial stiffness measurement a keystone in hypertension management and cardiovascular prevention as a whole.

[15] *Farhan S, Kamran H, Vogel B et al.* **Considerations for Patients With Peripheral Artery Disease During the COVID-19 Pandemic**. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2021; 27:1076029620986877.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33783244

ABSTRACT

New York City was one of the epicenters of the COVID-19 pandemic. The management of peripheral artery disease (PAD) during this time has been a major challenge for health care systems and

medical personnel. This document is based on the experiences of experts from various medical fields involved in the treatment of patients with PAD practicing in hospitals across New York City during the outbreak. The recommendations are based on certain aspects including the COVID-19 infection status as well as the clinical PAD presentation of the patient. Our case-based algorithm aims at guiding the treatment of patients with PAD during the pandemic in a safe and efficient way.

[16] *Jordy AB, Albayaty M, Breitschaft A et al.* **Effect of Oral Semaglutide on the Pharmacokinetics of Levonorgestrel and Ethinylestradiol in Healthy Postmenopausal Women and Furosemide and Rosuvastatin in Healthy Subjects**. Clinical pharmacokinetics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33782832

ABSTRACT

BACKGROUND: The first oral glucagon-like peptide-1 receptor agonist (GLP-1RA) comprises semaglutide co-formulated with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Oral semaglutide may alter the pharmacokinetics of co-administered drugs via effects of semaglutide or SNAC. Two separate one-sequence crossover trials investigated the effects of oral semaglutide and SNAC on the pharmacokinetics of ethinylestradiol, levonorgestrel, furosemide and rosuvastatin. METHODS: Healthy, postmenopausal women (n = 25) received once-daily combined ethinylestradiol and levonorgestrel (Trial 1) and healthy male and female subjects (n = 41) received single doses of furosemide and rosuvastatin (Trial 2), either alone, with SNAC alone or with oral semaglutide. Lack of drug-drug interaction was concluded if 90% confidence intervals (CIs) for the ratio of area under the plasma concentration-time curve (AUC) or maximum concentration (C(max)), with/without oral semaglutide, were within a pre-specified interval (0.80-1.25). RESULTS: The AUC values of ethinylestradiol and levonorgestrel were not affected by oral semaglutide co-administration (estimated ratios [90% CI] 1.06 [1.01-1.10] and 1.06 [0.97-1.17], respectively); C(max) was not affected. The no-effect criterion was not met for furosemide or rosuvastatin for the AUC (1.28 [1.16-1.42] and 1.41 [1.24-1.60], respectively) or C(max). SNAC alone did not affect the AUC or C(max) of ethinylestradiol, levonorgestrel or rosuvastatin; the C(max) of furosemide was slightly decreased. Adverse events were similar to those previously observed for GLP-1RAs (both trials). CONCLUSION: Co-administration with oral semaglutide did not affect the pharmacokinetics of ethinylestradiol or levonorgestrel. There was a small increase in exposure of furosemide and rosuvastatin; however, these increases are not expected to be of clinical relevance. CLINICAL TRIAL REGISTRATION NUMBERS: NCT02845219 and NCT03010475.

[17] *Türkuçar S, Yıldız K, Küme T et al.* **Does Familial Mediterranean Fever Provoke Atherosclerosis in Children? Evaluation of Arterial Stiffness and Serum Endocan Levels**. Clinical rheumatology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33813620

ABSTRACT

OBJECTIVES: This study aimed to evaluate the risk for atherosclerosis by using echocardiographic arterial stiffness (AS) parameters and serum endocan levels, as a biomarker of endothelial dysfunction (ED) in children with FMF. METHODS: Seventy-nine children with FMF (12-18 years) and 41 healthy children were included, and clinical features (age at the first attack, age at the time of diagnosis, diagnosis delay time, colchicine dose, biological agent usage, MEFV mutations, and symptoms of attacks) of patients were noted. Arterial stiffness parameters were calculated by using

echocardiographic aortic measurements with blood pressure monitoring. Hemogram parameters, acute phase reactants, blood glucose and lipid levels of 12 hours of fasting, and serum endocan levels were evaluated for all participants. RESULTS: There were no statistically significance regarding demographic features, acute phase reactants, and hemogram parameters. Blood glucose and lipid levels were similar, except for HDL (lower in FMF group, p=0.029). Serum endocan levels did not differ in two groups (p=0.906). Only stiffness of descending aorta was lower in FMF group (p=0.028), and the other AS parameters were similar between two groups (p>0.05 for each parameters). CONCLUSION: Good disease control could be preventive for atherosclerosis in children with FMF. On the other hand, screening for cardiovascular diseases is essential, particularly for uncontrolled cases. Distribution of MEFV gene mutations KEY POINTS: • Exaggerated inflammation is the prominent feature of FMF attacks; moreover, it is shown that subclinical inflammation might also continue in attack-free periods. • Chronic inflammation contributes to atherosclerotic process in almost all stages by activating endothelial cells, producing reactive oxygen species, and accelerating foam cell and atherosclerotic plaque formations. • However, the results of this study showed that there was no difference in terms of atherosclerotic markers such as serum endocan levels and arterial stiffness parameters between pediatric FMF patients and healthy peers. • Good disease control in pediatric FMF patients may prevent early atherosclerotic changes during childhood, which then may lead a probable decreased risk of subsequent CVD in adulthood.

[18] *Zhou YL, Chen LQ, Du XG*. **Efficacy of short-term moderate or high-dose statin therapy for the prevention of contrast-induced nephropathy in high-risk patients with chronic kidney disease: systematic review and meta-analysis**. Clinics (Sao Paulo, Brazil) 2021; 76:e1876.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33787670

ABSTRACT

Although previous studies have indicated that statin therapy can effectively prevent the development of CIN, this observation remains controversial, especially in high-risk patients. A meta-analysis was performed to evaluate the efficacy of statin pretreatment for preventing the development of CIN in patients with chronic kidney disease (CKD) and to determine its effectiveness in various subgroups. We searched the online databases PubMed, EMBASE, and the Cochrane Library. RCTs that involved the comparison of the short-term moderate or high-dose statin pretreatment with placebo for CIN prevention in CKD patients undergoing angiography were included. The primary outcome was CIN prevalence. Seven RCTs comprising 4256 participants were investigated in this analysis. The risk of developing CIN in patients pretreated with statins was significantly lower than that in patients pretreated with placebo (RR=0.57, 95%CI=0.43-0.76, p=0.000). The SCr values of the statin group, when analyzed 48h after angiography were lower than those of the placebo group ((SMD=-0.15, 95% CI=-0.27 to -0.04, p=0.011). In the subgroup analysis, statin pretreatment could decrease the risk of CIN in CKD patients with DM (RR=0.54, 95% CI=0.39-0.76, p=0.000), but not in CKD patients without DM (RR=0.84, 95% CI=0.44-1.60, p=0.606). The efficacy of atorvastatin for preventing CIN was consistent with that observed with the use of rosuvastatin. The risk ratios (RR) were 0.51 (95% CI=0.32-0.81, p=0.004) and 0.60 (95% CI=0.41-0.88, p=0.009), respectively. Our study demonstrated that statin pretreatment could prevent the development of CIN in CKD patients. However, subgroup analysis demonstrated that statin pretreatment, despite being effective in preventing CIN in patients with CKD and DM, was not helpful for CKD patients without DM. Rosuvastatin and atorvastatin exhibited similar preventive effects with respect to CIN.

[19] *Kim H, Rebholz CM*. **Metabolomic Biomarkers of Healthy Dietary Patterns and Cardiovascular Outcomes**. Current atherosclerosis reports 2021; 23:26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33782776
ABSTRACT
PURPOSE OF REVIEW: Healthy dietary patterns are recommended for prevention of CVD. Recently, metabolomics has been used to identify biomarkers of healthy dietary patterns and elucidate mechanisms underlying diet-disease associations. This review provides an overview of approaches to define healthy dietary patterns, discusses important issues related to using metabolomics to describe healthy dietary patterns, and summarizes studies identifying blood metabolites associated with hypothesis-driven healthy dietary patterns and cardiovascular risk factors and incident CVD. RECENT FINDINGS: We identified 17 studies which reported on blood metabolomic signatures of 5 healthy dietary patterns (Healthy Eating Index, Alternative Healthy Eating Index, the Dietary Approaches to Stop Hypertension diet, Mediterranean diet, vegetarian diet). Four of these studies evaluated associations between diet-related metabolites and cardiovascular outcomes. Many metabolites replicated across different healthy dietary patterns, which suggest that they may represent biomarkers of generally healthy diets. Unsaturated lipids positively associated with healthy dietary patterns were inversely associated with incident CVD, suggesting that they may be a pathway through which diet is associated with a lower risk of CVD. Although many metabolites replicated across cross-sectional studies, few metabolites identified as candidate biomarkers of healthy diets in feeding studies replicated in observational studies. Additionally, limited evidence exists on the ability of diet-related metabolites to predict cardiovascular outcomes. Replication of candidate biomarkers of dietary patterns in different study designs and more studies evaluating the associations between diet-related metabolites and cardiovascular outcomes are needed.

[20] *Esan O, Wierzbicki AS*. **Triglycerides and cardiovascular disease**. Current opinion in cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33797418
ABSTRACT
PURPOSE OF REVIEW: Triglycerides (TGs) are measured as part of routine lipid profiles but their relationship to cardiovascular disease (CVD) risk has been controversial and overshadowed by high-density lipoprotein cholesterol (HDL-C). RECENT FINDINGS: Epidemiological studies show a clear relationship of TG-containing lipoproteins including remnant particles with CVD risk with the effect being most clearly demonstrated through the excess risk captured by non-HDL-C compared with low-density lipoprotein-cholesterol (LDL-C). Mendelian randomisation studies show a consistent relationship of gene variants linked to TG metabolism with rates of CVD. Furthermore, meta-analyses of intervention trials with statins and other nonstatin drugs also suggest that reducing TGs is associated with benefits on rates of CVD events. Historical subgroup data from fibrate trials suggest benefits in patients with high TG:HDL ratios but seem to add little to optimized statin therapy. Recent trials with omega-3 fatty acids (specifically eicosapentaenoic acid) have suggested that high-dose formulations in contrast to low dose formulations have benefits on CVD outcomes. SUMMARY: Further studies with newer agents are required to determine the place of TG-lowering drugs in therapeutic pathways. Trials with agents such as pemafibrate and vupanorsen may finally answer these questions.

[21] *Fras Z*. **Current Choice for LDL-C Lowering in High-Risk CVD Patients Intolerant to Statins**. Current vascular pharmacology 2021; 19:398-402.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33783343
ABSTRACT

[22] *Hakim O, Bello O, Ladwa M et al.* **Adiponectin is associated with insulin sensitivity in white European men but not black African men**. Diabetic medicine : a journal of the British Diabetic Association 2021:e14571.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33783876
ABSTRACT
AIMS: We aimed to assess ethnic differences in inflammatory markers and their relationships with insulin sensitivity and regional adiposity between white European and black African men. METHODS: 53 white European and 53 black African men underwent assessment of inflammatory markers alongside Dixon-magnetic resonance imaging to quantify subcutaneous and visceral adipose tissue, and intrahepatic lipid. A hyperinsulinaemic-euglycaemic clamp was used to measure whole-body and adipose tissue insulin sensitivity. To assess ethnic differences in relationships, the statistical significance of an interaction term between adipokines and ethnic group was tested in multivariable regression models. RESULTS: The black African men exhibited significantly lower adiponectin and tumour necrosis factor-α (TNF-α) and greater interleukin-10 (IL-10) compared to white European men (all $P<0.05$). There were no statistically significant ethnic differences in leptin, resistin, IL-6, interferon-γ, IL-13, IL-1β, IL-8 and vascular endothelial growth factor. Several relationships differed significantly by ethnicity such that they were stronger in white European than black African men including IL-6 with visceral adipose tissue; adiponectin with subcutaneous adipose tissue; leptin with intrahepatic lipid; adiponectin, IL-6 and TNF-α with whole-body insulin sensitivity; and TNF-α with adipose tissue insulin sensitivity (all $P(\text{interaction}) <0.05$). Leptin significantly predicted whole-body insulin sensitivity in white European ($R(2) =0.51$) and black African ($R(2) =0.29$) men, however, adiponectin was a statistically significant predictor in only white European men ($R(2) =0.22$). CONCLUSIONS: While adiponectin is lower in black African men, its insulin sensitising effects may be greater in white men suggesting that the role of adipokines in the development of type 2 diabetes may differ by ethnicity.

[23] *Banerjee S, De A*. **Pathophysiology and inhibition of cholesteryl ester transfer protein for prevention of cardiovascular diseases: an update**. Drug discovery today 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33781947
ABSTRACT
The enzyme cholesteryl ester transfer protein (CETP), involved in cholesterol metabolism and transportation, is one of the main causes of cardiovascular (CV) disease (CVD). When the CETP concentration is decreased by CETP inhibitors (e.g., anacetrapib, torcetrapib, obicetrapib, etc.), high-density lipoprotein (HDL) particles are formed and low-density lipoprotein (LDL) is decreased along with cholesterol transportation alteration, which reduces the development of atherosclerosis. Here, we discuss the role of CETP inhibitors in reducing well-known 'bad' cholesterols and the current status of trials of different CETP inhibitors, their adverse effects, and limitations, as well as the pathophysiology of CETP.

[24] *Torres-Peña JD, Pérez-Belmonte LM, Fuentes-Jiménez F et al.* **Prior Treatment with Statins is Associated with Improved Outcomes of Patients with COVID-19: Data from the SEMI-COVID-19 Registry**. Drugs 2021:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33782908

ABSTRACT
BACKGROUND: The impact of statins on COVID-19 outcomes is important given the high prevalence of their use among individuals at risk for severe COVID-19. Our aim is to assess whether patients receiving chronic statin treatment who are hospitalized with COVID-19 have reduced in-hospital mortality if statin therapy is maintained during hospitalization. METHODS: This work is a cross-sectional, observational, retrospective multicenter study that analyzed 2921 patients who required hospital admission at 150 Spanish centers included in the nationwide SEMI-COVID-19 Network. We compared the clinical characteristics and COVID-19 disease outcomes between patients receiving chronic statin therapy who maintained this therapy during hospitalization versus those who did not. Propensity score matching was used to match each statin user whose therapy was maintained during hospitalization to a statin user whose therapy was withdrawn during hospitalization. RESULTS: After propensity score matching, continuation of statin therapy was associated with lower all-cause mortality (OR 0.67, 0.54-0.83, $p < 0.001$); lower incidence of acute kidney injury (AKI) (OR 0.76,0.6-0.97, $p = 0.025$), acute respiratory distress syndrome (ARDS) (OR 0.78, 0.69- 0.89, $p < 0.001$), and sepsis (4.82% vs 9.85%, $p = 0.008$); and less need for invasive mechanical ventilation (IMV) (5.35% vs 8.57, $p < 0.001$) compared to patients whose statin therapy was withdrawn during hospitalization. CONCLUSIONS: Patients previously treated with statins who are hospitalized for COVID-19 and maintain statin therapy during hospitalization have a lower mortality rate than those in whom therapy is withdrawn. In addition, statin therapy was associated with a decreased probability that patients with COVID-19 will develop AKI, ARDS, or sepsis and decreases the need for IMV.

[25] *Li X, Ploner A, Wang Y et al.* **Clinical biomarkers and associations with healthspan and lifespan: Evidence from observational and genetic data**. EBioMedicine 2021; 66:103318.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33813140

ABSTRACT
BACKGROUND: Biomarker-disease relationships are extensively investigated. However, associations between common clinical biomarkers and healthspan, the disease-free lifespan, are largely unknown. We aimed to explore the predictive values of ten biomarkers on healthspan and lifespan, and to identify putative causal mechanisms. METHODS: Using data from 12,098 Swedish individuals aged 47-94 years, we examined both serum concentrations and genetically predicted levels of ten glycemic, lipid-, inflammatory, and hematological biomarkers. During a follow-up period of up to 16 years, 3681 incident cases of any chronic disease (i.e., end of healthspan) and 2674 deaths (i.e., end of lifespan) were documented. Cox regression models were applied to estimate the associations of a one standard deviation increase in biomarkers with healthspan and lifespan. FINDINGS: Seven out of ten serum biomarkers were significantly associated with risks of any chronic disease and death; elevated glycemic biomarkers and high-density lipoprotein-related biomarkers showed the strongest detrimental (hazard ratio [HR] 1·29 [95% CI 1·24-1·34]) and protective effects (HR 0·92 [95% CI 0·89-0·96]), respectively. Genetic predisposition to elevated fasting blood glucose (FBG) was associated with increased risks of any chronic disease (HR 1·05 [95% CI 1·02-1·09]); genetically determined higher C-reactive protein correlated with lower death risks (HR 0·91 [95% CI

0·87-0·95]). Notably, the genetically proxied FBG-healthspan association was largely explained by serum FBG concentration. INTERPRETATION: Circulating concentrations of glycemic, lipid-, and inflammatory biomarkers are predictive of healthspan and lifespan. Glucose control is a putative causal mechanism and a potential intervention target for healthspan maintenance. FUNDING: This study was supported by the Swedish Research Council (2015-03,255, 2018-02,077), FORTE (2013-2292), the Loo & Hans Osterman Foundation, the Foundation for Geriatric Diseases, the Magnus Bergwall Foundation, the Strategic Research Program in Epidemiology at Karolinska Institutet (SH, JJ), the China Scholarship Council, and the Swedish National Graduate School for Competitive Science on Ageing and Health. The Swedish Twin Registry is managed by Karolinska Institutet and receives funding as an infrastructure through the Swedish Research Council, 2017-00,641.

[26] Feingold KR. Cholesterol Lowering Drugs. In: Endotext. Edited by: Feingold KR, Anawalt B, Boyce A *et al.* South Dartmouth (MA): MDText.com, Inc.

[27] *Elmekawy HA, Belal F, Abdelaziz AE et al.* **Pharmacokinetic interaction between atorvastatin and fixed-dose combination of sofosbuvir/ledipasvir in healthy male Egyptian volunteers**. Eur J Clin Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33791829
ABSTRACT
PURPOSE: Comorbid conditions of heart and liver disorders added to HCV-induced hepatic steatosis make co-administration of statins, and direct-acting antivirals is common in clinical practice. This study aimed to evaluate the pharmacokinetic interaction of atorvastatin and fixed-dose combination of sofosbuvir/ledipasvir "FDCSL" with rationalization to the underlying mechanism. METHODS: A randomized, three-phase crossover study that involves 12 healthy volunteers was performed. Participants received a single-dose of atorvastatin 80 mg alone, atorvastatin 80-mg plus tablets containing 400/90 mg FDCSL, or tablets containing 400/90 mg FDCSL alone. Plasma samples were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for atorvastatin, sofosbuvir, ledipasvir, and sofosbuvir metabolite "GS-331007," and their pharmacokinetics parameters were determined. RESULTS: Compared to atorvastatin alone, the administration of FDCSL caused a significant increase in both areas under the concentration-time curve from time zero to infinity (AUC(0-∞)) and maximum plasma concentration (C(max)) of atorvastatin by 65.5% and 156.0%, respectively. Also, atorvastatin caused a significant increase in the AUC(0-∞) and C(max) of sofosbuvir by 32.0% and 11.0%, respectively. Similarly, AUC(0-∞) and C(max) of sofosbuvir metabolite significantly increased by 84.0% and 74.0%, respectively. However, ledipasvir AUC(0-∞) showed no significant change after atorvastatin intake. The elimination rate in all drugs revealed no significant changes. CONCLUSION: After concurrent administration of FDCSL with atorvastatin, the AUC(0-∞) of both atorvastatin and sofosbuvir were increased. Caution should be taken with close monitoring for possible side effects after co-administration of atorvastatin and FDCSL in clinical practice.

[28] *Hopstock LA, Morseth B, Cook S et al.* **Treatment target achievement after myocardial infarction and ischaemic stroke: cardiovascular risk factors, medication use, and lifestyle: the Tromsø Study 2015-16**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33778888

ABSTRACT

AIMS: To investigate European guideline treatment target achievement in cardiovascular risk factors, medication use, and lifestyle, after myocardial infarction (MI) or ischaemic stroke, in women and men living in Norway. METHODS AND RESULTS: In the population-based Tromsø Study 2015-16 (attendance 65%), 904 participants had previous validated MI and/or stroke. Cross-sectionally, we investigated target achievement for blood pressure (<140/90 mmHg, <130/80 mmHg if diabetes), LDL cholesterol (<1.8 mmol/L), HbA1c (<7.0% if diabetes), overweight (body mass index (BMI) <25 kg/m2, waist circumference women <80 cm, men <94 cm), smoking (non-smoking), physical activity (self-reported >sedentary, accelerometer-measured moderate-to-vigorous ≥150 min/week), diet (intake of fruits ≥200 g/day, vegetables ≥200 g/day, fish ≥200 g/week, saturated fat <10E%, fibre ≥30 g/day, alcohol women ≤10 g/day, men ≤20 g/day), and medication use (antihypertensives, lipid-lowering drugs, antithrombotics, and antidiabetics), using regression models. Proportion of target achievement was for blood pressure 55.2%, LDL cholesterol 9.0%, HbA1c 42.5%, BMI 21.1%, waist circumference 15.7%, non-smoking 86.7%, self-reported physical activity 79%, objectively measured physical activity 11.8%, intake of fruit 64.4%, vegetables 40.7%, fish 96.7%, saturated fat 24.3%, fibre 29.9%, and alcohol 78.5%, use of antidiabetics 83.6%, lipid-lowering drugs 81.0%, antihypertensives 75.9%, and antithrombotics 74.6%. Only 0.7% achieved all cardiovascular risk factor targets combined. Largely, there was little difference between the sexes, and in characteristics, medication use, and lifestyle among target achievers compared to non-achievers. CONCLUSION : Secondary prevention of cardiovascular disease was suboptimal. A negligible proportion achieved the treatment target for all risk factors. Improvement in follow-up care and treatment after MI and stroke is needed.

[29] *Liu MM, Peng J, Guo YL et al.* **Impact of diabetes on coronary severity and cardiovascular outcomes in patients with heterozygous familial hypercholesterolaemia**. European journal of preventive cardiology 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33778872

ABSTRACT

AIMS: Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular disease. However, the association between T2DM and coronary artery disease (CAD) in patients with heterozygous familial hypercholesterolaemia (HeFH) has not been thoroughly evaluated. Our study aimed to assess the effect of T2DM on CAD severity and hard cardiovascular endpoints in a HeFH cohort. METHODS AND RESULTS: A total of 432 patients with HeFH with a molecular and/or clinical Dutch Lipid Clinic Network score ≥6 (definite and probable) were enrolled. Patients were divided into a T2DM group (n = 99) and a non-T2DM group (n = 333). The severity of coronary stenosis was assessed by the number of diseased vessels and Gensini, SYNTAX, and Jeopardy scores. Hard endpoints included a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiac death. Cox regression and Kaplan-Meier analyses were used to evaluate the effect of T2DM on hard cardiovascular endpoints. The prevalence of CAD was higher in patients with T2DM compared with those without (96.0% vs. 77.5%, respectively; P < 0.001). Patients with T2DM demonstrated a greater number of diseased vessels (P = 0.029) and more severe coronary lesions with high Gensini, SYNTAX, and Jeopardy score tertiles (P = 0.031, P = 0.001, and P = 0.024, respectively). During a median of 3.75 years up to a maximum of 9 years of follow-up, hard endpoints occurred in 13 of 99 patients with T2DM and 16 of 333 without T2DM at baseline. Compared with patients without T2DM, patients with T2DM were at a significantly greater risk of hard endpoints [multivariate adjusted hazard

ratio (HR) 2.32, 95% confidence interval (CI) 1.02-4.84; P = 0.025]. Additionally, patients with T2DM and good glucose control (HbA1c < 7.0%) were at a lower risk of hard endpoints compared with those with poor glucose control (HbA1c ≥ 7.0%, HR 0.08, 95% CI 0.01-0.56; P = 0.011). CONCLUSION: We conclude that T2DM is an independent predictor of CAD severity when assessed by number of diseased vessels, Gensini, SYNTAX, Jeopardy scores, and hard cardiovascular endpoints, suggesting that T2DM could be further used for risk stratification of patients with HeFH.

[30] *Zhang SZ, Zhu XD, Feng LH et al.* **PCSK9 promotes tumor growth by inhibiting tumor cell apoptosis in hepatocellular carcinoma**. Exp Hematol Oncol 2021; 10:25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33789749
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9), one of the key enzymes in the process of lipid transport, is involved in the disease progression of various types of tumors. This article is to study the role of PCSK9 in the progression of hepatocellular carcinoma (HCC). METHODS: Immunohistochemistry was used to assess the expression of PCSK9 in tumor specimens from 105 HCC patients who underwent curative resection. Western blotting and quantitative real-time PCR were used to test the protein and mRNA expression levels in HCC cell lines. Cell Counting Kit-8 (CCK-8) and clone formation assays were performed to evaluate the proliferation ability of different kinds of cells in vitro. Flow cytometry was used to analyze cell cycle distribution and apoptosis rate. A xenograft model was established to study the effect of PCSK9 on HCC growth in vivo. TUNEL and immunofluorescence assays were used to detect cell apoptosis. RESULTS: High expression of PCSK9 in tumor tissues was related to microvascular invasion (p = 0.036) and large tumor size (p = 0.001) in HCC patients. Overall survival and disease-free survival after surgery were poor in patients with high expression of PCSK9 (p = 0.035 and p = 0.007, respectively). In vivo and in vitro experiments showed that PCSK9 promoted the growth of HCC by inhibiting cell apoptosis. A mechanistic study revealed that PCSK9 increases FASN expression, thereby inhibiting apoptosis of HCC cells via the Bax/Bcl-2/Caspase9/Caspase3 pathway. CONCLUSIONS: PCSK9 expression level in HCC is an indicator of poor prognosis for patients with HCC. FASN-mediated anti-apoptosis plays an important role in PCSK9-induced HCC progression.

[31] *Kow CS, Doi SAR, Hasan SS*. **The coincidence of increased risk of atrial fibrillation in randomized control trials of omega-3 fatty acids: a meta-analysis**. Expert Rev Clin Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33798016
ABSTRACT

[32] *Tucci M, Martini D, Del Bo C et al.* **An Italian-Mediterranean Dietary Pattern Developed Based on the EAT-Lancet Reference Diet (EAT-IT): A Nutritional Evaluation**. Foods (Basel, Switzerland) 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33800396
ABSTRACT
There is an urgent need to promote healthy and sustainable diets that are tailored to the preferences and cultures of different populations. The present study aimed to (i) define a Mediterranean dietary pattern in line with the EAT-Lancet Commission reference diet (ELCRD), based on 2500 kcal/day and

adapted to the Italian food habits (EAT-IT); (ii) develop a mid/long-term dietary plan based on EAT-IT and a dietary plan based on the Italian Dietary Guidelines (IDG); (iii) compare the two dietary plans in terms of portions, frequencies of consumption, and nutritional adequacy based on the nutrient and energy recommendations for the Italian adult population. The main differences between the two plans were related to the higher amount of fruit and vegetables in the IDG compared to the EAT-IT, while the EAT-IT plan was higher in nuts and legumes, which represent the main protein sources in the ELCRD. Differences in the protein sources, especially milk and derivatives, and for cereal-based foods, were also found. Dietary plans were comparable for most nutrients, except for higher energy from lipids and vegetal protein, a higher amount of fiber, and lower levels of calcium that were evidenced for the EAT-IT dietary plan compared to the IDG-based one. In conclusion, the analysis of the EAT-IT demonstrated certain nutritional issues. It remains to be determined whether this may represent a health concern in further studies aimed at investigating the feasibility of sustainable dietary patterns.

[33] *Simeone PG, Vadini F, Tripaldi R et al.* **Sex-Specific Association of Endogenous PCSK9 With Memory Function in Elderly Subjects at High Cardiovascular Risk**. Frontiers in aging neuroscience 2021; 13:632655.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33776743
ABSTRACT
Background: Growing evidence indicates that cognitive decline and cardiovascular diseases (CVDs) share common vascular risk factors. Protease proprotein convertase subtilisin/kexin type 9 (PCSK9) is associated with CV disease risk and has been also involved in neuronal differentiation. Aim: Evaluate whether in patients at high CV risk cognitive function is related to PCSK9 levels. Methods. One hundred sixty-six patients (67 female) were enrolled. A detailed neuropsychological (NP) assessment was performed. PCSK9 levels were measured with ELISA. Results: Men had significantly higher short-term memory, executive function, and praxic and mental representation skills, as reflected by Forward Digit Span (FDS) ($p = 0.005$), Trail Making Test-A (TMT-A) ($p = 0.047$), Clock Drawing Test (CDT) (0.016). Endogenous PCSK9 levels were higher in female ($p = 0.005$). On linear regression analysis PCSK9 predicts short term memory only in females (Beta = 0.408, $p = 0.001$), with an interaction between PCSK9 and gender ($p = 0.004$ for interaction PCSK9 by sex). The association of PCSK9 with FDS in female was partially mediated by waist circumference (mediation effect 8.5%). Conclusions: In patients at high CV risk short term memory was directly related to PCSK9 levels only in women, revealing the relevance of sex in this relationship. The association of PCSK9 with memory function may be mediated, at least in part, by waist circumference.

[34] *Zhang J, Ling N, Lei Y et al.* **Multifaceted Interaction Between Hepatitis B Virus Infection and Lipid Metabolism in Hepatocytes: A Potential Target of Antiviral Therapy for Chronic Hepatitis B**. Frontiers in microbiology 2021; 12:636897.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33776969
ABSTRACT
Hepatitis B virus (HBV) is considered a "metabolic virus" and affects many hepatic metabolic pathways. However, how HBV affects lipid metabolism in hepatocytes remains uncertain yet. Accumulating clinical studies suggested that compared to non-HBV-infected controls, chronic HBV infection was associated with lower levels of serum total cholesterol and triglycerides and a lower

prevalence of hepatic steatosis. In patients with chronic HBV infection, high ALT level, high body mass index, male gender, or old age was found to be positively correlated with hepatic steatosis. Furthermore, mechanisms of how HBV infection affected hepatic lipid metabolism had also been explored in a number of studies based on cell lines and mouse models. These results demonstrated that HBV replication or expression induced extensive and diverse changes in hepatic lipid metabolism, by not only activating expression of some critical lipogenesis and cholesterolgenesis-related proteins but also upregulating fatty acid oxidation and bile acid synthesis. Moreover, increasing studies found some potential targets to inhibit HBV replication or expression by decreasing or enhancing certain lipid metabolism-related proteins or metabolites. Therefore, in this article, we comprehensively reviewed these publications and revealed the connections between clinical observations and experimental findings to better understand the interaction between hepatic lipid metabolism and HBV infection. However, the available data are far from conclusive, and there is still a long way to go before clarifying the complex interaction between HBV infection and hepatic lipid metabolism.

[35] *Colivicchi F, Di Fusco SA, Gabrielli D*. **[Bempedoic acid: a new therapeutic opportunity for the treatment of hypercholesterolemia]**. Giornale italiano di cardiologia (2006) 2021; 22:301-310.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33783450

ABSTRACT

In the last decades, scientific evidence regarding the key role of cholesterol in atherosclerosis pathogenesis has led to the development of lipid-lowering treatments that can be used in addition to statins or in place of them in case of intolerance. Bempedoic acid represents an effective and safe new therapeutic option in hypercholesterolemia management. Clinical studies have demonstrated that bempedoic acid can significantly reduce low-density lipoprotein cholesterol in several clinical settings. Furthermore, bempedoic acid has also been associated with the improvement of other biomarkers, including reduced apolipoprotein B and high-sensitivity C-reactive protein, effects that can increase the clinical benefits of this treatment.

[36] *Packard C, Chapman MJ, Sibartie M et al.* **Intensive low-density lipoprotein cholesterol lowering in cardiovascular disease prevention: opportunities and challenges**. Heart 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33795379

ABSTRACT

Elevated levels of low-density lipoprotein cholesterol (LDL-C) are associated with increased risk of coronary heart disease and stroke. Guidelines for the management of dyslipidaemia from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) were updated in late 2019 in light of recent intervention trials involving the use of innovative lipid-lowering agents in combination with statins. The new guidelines advocate achieving very low LDL-C levels in individuals at highest risk, within the paradigm of 'lower is better'. With the advent of combination therapy using ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitors in addition to statins, the routine attainment of extremely low LDL-C levels in the clinic has become a reality. Moreover, clinical trials in this setting have shown that, over the 5-7 years of treatment experience to date, profound LDL-C lowering leads to further reduction in cardiovascular events compared with more moderate lipid lowering, with no associated safety concerns. These reassuring findings are bolstered by genetic studies showing lifelong very low LDL-C levels (<1.4 mmol/L; <55 mg/dL) are

associated with lower cardiovascular risk than in the general population, with no known detrimental health effects. Nevertheless, long-term safety studies are required to consolidate the present evidence base. This review summarises key data supporting the ESC/EAS recommendation to reduce markedly LDL-C levels, with aggressive goals for LDL-C in patients at highest risk, and provides expert opinion on its significance for clinical practice.

[37] *Zatońska K, Psikus P, Basiak-Rasała A et al.* **Obesity and Chosen Non-Communicable Diseases in PURE Poland Cohort Study**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33800151
ABSTRACT
INTRODUCTION: Obesity has been associated with a higher risk of morbidity, disability, and death. The objective of this study was to assess the prevalence of obesity and chosen non-communicable diseases (NCDs) in the PURE Poland cohort study. MATERIAL AND METHODS: The study covers a group of 2035 people (1281 women and 754 men), who live in urban and rural areas of Lower Silesian voivodeship. The baseline study was conducted between 2007-2010. The data on demographic status and history of diseases were collected using questionnaires. The anthropometric parameters, blood pressure, blood lipids, and glucose level were measured. RESULTS: Normal body weight was observed in 28.1% of participants, whereas overweight and obesity were observed in 40.1% and 31.1% of participants, respectively. Moreover, there was a significant difference in the body weight between genders. Prevalence of obesity was similar in men and women (31.0% and 31.1%, respectively). Obesity was more prevalent in rural vs. urban residents (38.5% and 26.0%, respectively). In a logistic regression analysis, the odds for obesity was two-fold higher in participants aged >64 years and rural inhabitants (OR 1.91; 95% CI 1.36-2.70; OR 1.79; 95% CI 1.48-2.16, respectively). Participants with obesity had 2.5-fold higher odds for diabetes and hypertension and two-fold higher odds for CHD in comparison with non-obese individuals (OR 2.74; 95% CI 2.01-3.73, OR 2.54; 95% CI 2.03-3.17, OR 1.88; 95% CI 1.26-2.80, respectively). CONCLUSIONS: Taken together, the prevalence of obesity was associated with particular socio-demographic factors (age, place of residence, and level of education) as well as diabetes, hypertension, and coronary heart disease.

[38] *Basiak M, Kosowski M, Cyrnek M et al.* **Pleiotropic Effects of PCSK-9 Inhibitors**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33808697
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors are a group of drugs whose main mechanism of action is binding to the PCSK-9 molecule, which reduces the degradation of the low-density lipoprotein receptor (LDL-R) and, hence, increases the uptake of low-density lipoprotein cholesterol (LDLc) from the bloodstream as well as reducing its concentration. The effectiveness of three monoclonal antibodies, namely, alirocumab (human IgG1/κ monoclonal antibody, genetically engineered in Chinese hamster ovary cells), evolocumab (the first fully human monoclonal antibody), and bococizumab (humanized mouse antibody), in inhibiting the action of PCSK-9 and reducing LDLc levels has been confirmed. The first two, after clinical trials, were approved by the Food and Drug Administration (FDA) and are used primarily in the treatment of autosomal familial

hypercholesterolemia and in cases of statin intolerance. They are currently used both as monotherapy and in combination with statins and ezetimibe to intensify therapy and achieve therapeutic goals following the American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines. However, the lipid-lowering effect is not the only effect of action described by researchers that PCSK-9 inhibitors have. This paper is a review of the literature describing the pleiotropic effects of PCSK-9 inhibitors, which belong to a group of drugs that are being increasingly used, especially when standard lipid-lowering therapy fails. The article focuses on activities other than lipid-lowering, such as the anti-atherosclerotic effect and stabilization of atherosclerotic plaque, the anti-aggregation effect, the anticoagulant effect, the antineoplastic effect, and the ability to influence the course of bacterial infections. In this publication, we try to systematically review the current scientific data, both from our own scientific work and knowledge from international publications.

[39] *Dulka K, Szabo M, Lajkó N et al.* **Epigenetic Consequences of in Utero Exposure to Rosuvastatin: Alteration of Histone Methylation Patterns in Newborn Rat Brains**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33810299
ABSTRACT
Rosuvastatin (RST) is primarily used to treat high cholesterol levels. As it has potentially harmful but not well-documented effects on embryos, RST is contraindicated during pregnancy. To demonstrate whether RST could induce molecular epigenetic events in the brains of newborn rats, pregnant mothers were treated daily with oral RST from the 11th day of pregnancy for 10 days (or until delivery). On postnatal day 1, the brains of the control and RST-treated rats were removed for Western blot or immunohistochemical analyses. Several antibodies that recognize different methylation sites for H2A, H2B, H3, and H4 histones were quantified. Analyses of cell-type-specific markers in the newborn brains demonstrated that prenatal RST administration did not affect the composition and cell type ratios as compared to the controls. Prenatal RST administration did, however, induce a general, nonsignificant increase in H2AK118me1, H2BK5me1, H3, H3K9me3, H3K27me3, H3K36me2, H4, H4K20me2, and H4K20me3 levels, compared to the controls. Moreover, significant changes were detected in the number of H3K4me1 and H3K4me3 sites (134.3% ± 19.2% and 127.8% ± 8.5% of the controls, respectively), which are generally recognized as transcriptional activators. Fluorescent/confocal immunohistochemistry for cell-type-specific markers and histone methylation marks on tissue sections indicated that most of the increase at these sites belonged to neuronal cell nuclei. Thus, prenatal RST treatment induces epigenetic changes that could affect neuronal differentiation and development.

[40] *Kowara M, Cudnoch-Jedrzejewska A*. **Pathophysiology of Atherosclerotic Plaque Development-Contemporary Experience and New Directions in Research**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33805303
ABSTRACT
Atherosclerotic plaque is the pathophysiological basis of important and life-threatening diseases such as myocardial infarction. Although key aspects of the process of atherosclerotic plaque development and progression such as local inflammation, LDL oxidation, macrophage activation, and necrotic core

formation have already been discovered, many molecular mechanisms affecting this process are still to be revealed. This minireview aims to describe the current directions in research on atherogenesis and to summarize selected studies published in recent years-in particular, studies on novel cellular pathways, epigenetic regulations, the influence of hemodynamic parameters, as well as tissue and microorganism (microbiome) influence on atherosclerotic plaque development. Finally, some new and interesting ideas are proposed (immune cellular heterogeneity, non-coding RNAs, and immunometabolism) which will hopefully bring new discoveries in this area of investigation.

[41] *Komatsu T, Miura T, Joko K et al.* **Real-world Profile of a Selective Peroxisome Proliferator-activated Receptor α Modulator (SPPARMα) in Japanese Patients with Renal Impairment and Dyslipidemia**. Intern Med 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33776008
ABSTRACT
Objective Although lowering the low-density lipoprotein cholesterol (LDL-C) levels using statins can reduce cardiovascular risk, 70% of the cardiovascular risk remains despite treatment with statins. Several studies have shown that elevated triglyceride (TG)-rich lipoprotein is the primary therapeutic target for reducing the residual risk. However, conventional treatment with fibrates is frequently associated with adverse drug reactions, especially in patients with chronic kidney disease (CKD), and even with a reduction in TG. Pemafibrate is a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα) with fewer side effects and greater effectiveness that can overcome these challenges. We aimed to investigate the safety and efficacy of pemafibrate in patients with CKD and herein present a real-world profile of pemafibrate. Methods Between January 2019 and January 2020, 126 consecutive patients with hyperglyceridemia from two institutions (54 patients with CKD; 43%) who received pemafibrate were enrolled in this retrospective observational study. Blood samples were collected before (baseline) and at 24 weeks after commencing pemafibrate therapy. The primary endpoint was a decrease in the serum lipid levels. The secondary endpoints were the incidence of rhabdomyolysis, hepatargy, and an exacerbation of CKD. Results All patients, including 51% of patients who were concurrently taking statins, reported significantly reduced total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), LDL-C, and TG, and increased HDL-C ($p<0.05$). The subgroup of patients with CKD showed similar results without increased HDL-C. No adverse events were observed in any patients. Conclusion Pemafibrate has a good safety profile and efficacy for treating patients with serum lipid abnormalities, including those with CKD.

[42] *Garshick MS, Ward NL, Krueger JG, Berger JS*. **Cardiovascular Risk in Patients With Psoriasis: JACC Review Topic of the Week**. Journal of the American College of Cardiology 2021; 77:1670-1680.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33795041
ABSTRACT
Psoriasis is a chronic inflammatory skin disease that affects 2% to 3% of the U.S. population. The immune response in psoriasis includes enhanced activation of T cells and myeloid cells, platelet activation, and up-regulation of interferons, tumor necrosis factor-α, and interleukins (ILs) IL-23, IL-17, and IL-6, which are linked to vascular inflammation and atherosclerosis development. Patients with psoriasis are up to 50% more likely to develop cardiovascular disease (CV) disease, and this CV

risk increases with skin severity. Major society guidelines now advocate incorporating a psoriasis diagnosis into CV risk prediction and prevention strategies. Although registry data suggest treatment targeting psoriasis skin disease reduces vascular inflammation and coronary plaque burden, and may reduce CV risk, randomized placebo-controlled trials are inconclusive to date. Further studies are required to define traditional CV risk factor goals, the optimal role of lipid-lowering and antiplatelet therapy, and targeted psoriasis therapies on CV risk.

[43] *Lubert AM, Alsaied T, Palermo JJ et al.* **Fontan-Associated Dyslipidemia**. Journal of the American Heart Association 2021; 10:e019578.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33787283
ABSTRACT
Background Hypocholesterolemia is a marker of liver disease, and patients with a Fontan circulation may have hypocholesterolemia secondary to Fontan-associated liver disease or inflammation. We investigated circulating lipids in adults with a Fontan circulation and assessed the associations with clinical characteristics and adverse events. Methods and Results We enrolled 164 outpatients with a Fontan circulation, aged ≥18 years, in the Boston Adult Congenital Heart Disease Biobank and compared them with 81 healthy controls. The outcome was a combined outcome of nonelective cardiovascular hospitalization or death. Participants with a Fontan (median age, 30.3 [interquartile range, 22.8-34.3 years], 42% women) had lower total cholesterol (149.0±30.1 mg/dL versus 190.8±41.4 mg/dL, P<0.0001), low-density lipoprotein cholesterol (82.5±25.4 mg/dL versus 102.0±34.7 mg/dL, P<0.0001), and high-density lipoprotein cholesterol (42.8±12.2 mg/dL versus 64.1±16.9 mg/dL, P<0.0001) than controls. In those with a Fontan, high-density lipoprotein cholesterol was inversely correlated with body mass index (r=-0.30, P<0.0001), high-sensitivity C-reactive protein (r=-0.27, P=0.0006), and alanine aminotransferase (r=-0.18, P=0.02) but not with other liver disease markers. Lower high-density lipoprotein cholesterol was independently associated with greater hazard for the combined outcome adjusting for age, sex, body mass index, and functional class (hazard ratio [HR] per decrease of 10 mg/dL, 1.37; 95% CI, 1.04-1.81 [P=0.03]). This relationship was attenuated when log high-sensitivity C-reactive protein was added to the model (HR, 1.26; 95% CI, 0.95-1.67 [P=0.10]). Total cholesterol, low-density lipoprotein cholesterol, and triglycerides were not associated with the combined outcome. Conclusions The Fontan circulation is associated with decreased cholesterol levels, and lower high-density lipoprotein cholesterol is associated with adverse outcomes. This association may be driven by inflammation. Further studies are needed to understand the relationship between the severity of Fontan-associated liver disease and lipid metabolism.

[44] *Kobayashi J*. **Pitavastatin versus Atorvastatin: Potential Differences in their Effects on Serum Lipoprotein Lipase and Cardiovascular Disease**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33790128
ABSTRACT

[45] *Suto K, Fukuda D, Shinohara M et al.* **Pemafibrate, A Novel Selective Peroxisome Proliferator-Activated Receptor α Modulator, Reduces Plasma Eicosanoid Levels and**

Ameliorates Endothelial Dysfunction in Diabetic Mice. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33775978

ABSTRACT

AIMS: Various pathological processes related to diabetes cause endothelial dysfunction. Eicosanoids derived from arachidonic acid (AA) have roles in vascular regulation. Fibrates have recently been shown to attenuate vascular complications in diabetics. Here we examined the effects of pemafibrate, a selective peroxisome proliferator-activated receptor α modulator, on plasma eicosanoid levels and endothelial function in diabetic mice. METHODS: Diabetes was induced in 7-week-old male wild-type mice by a single injection of streptozotocin (150 mg/kg). Pemafibrate (0.3 mg/kg/day) was administered orally for 3 weeks. Untreated mice received vehicle. Circulating levels of eicosanoids and free fatty acids were measured using both gas and liquid chromatography-mass spectrometry. Endothelium-dependent and endothelium-independent vascular responses to acetylcholine and sodium nitroprusside, respectively, were analyzed. RESULTS: Pemafibrate reduced both triglyceride and non-high-density lipoprotein -cholesterol levels ($P<0.01$), without affecting body weight. It also decreased circulating levels of AA ($P<0.001$), thromboxane B(2) ($P<0.001$), prostaglandin E(2), leukotriene B(4) ($P<0.05$), and 5-hydroxyeicosatetraenoic acid ($P<0.001$), all of which were elevated by the induction of diabetes. In contrast, the plasma levels of 15-deoxy-Δ(12,14)-prostaglandin J(2), which declined following diabetes induction, remained unaffected by pemafibrate treatment. In diabetic mice, pemafibrate decreased palmitic acid (PA) and stearic acid concentrations ($P<0.05$). Diabetes induction impaired endothelial function, whereas pemafibrate ameliorated it ($P<0.001$). The results of ex vivo experiments indicated that eicosanoids or PA impaired endothelial function. CONCLUSION: Pemafibrate diminished the levels of vasoconstrictive eicosanoids and free fatty acids accompanied by a reduction of triglyceride. These effects may be associated with the improvement of endothelial function by pemafibrate in diabetic mice.

[46] *Chen J, Zhang C, Yan T et al.* **Atorvastatin ameliorates early brain injury after subarachnoid hemorrhage via inhibition of pyroptosis and neuroinflammation**. Journal of cellular physiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33792028

ABSTRACT

Subarachnoid hemorrhage (SAH) is a subtype of stroke with high mortality and morbidity due to the lack of effective therapy. Atorvastatin has been reported to alleviate early brain injury (EBI) following subarachnoid hemorrhage (SAH) via reducing reactive oxygen species, antiapoptosis, regulated autophagy, and neuroinflammation. Which was the related to the pyroptosis? Pyroptosis can be defined as a highly specific inflammatory programmed cell death, distinct from classical apoptosis and necrosis. However, the precise role of pyroptosis in atorvastatin-mediated neuroprotection following SAH has not been confirmed. The present study aimed to investigate the neuroprotection and potential molecular mechanisms of atorvastatin in the SAH-induced EBI via regulating neural pyroptosis using the filament perforation model of SAH in male C57BL/6 mice, and the hemin-induced neuron damage model in HT-22. Atorvastatin or vehicle was administrated 2 h after SAH and hemin-induced neuron damage. The mortality, neurological score, brain water content, and neuronal death

were evaluated. The results show that the atorvastatin treatment markedly increased survival rate, neurological score, greater survival of neurons, downregulated the protein expression of NLRP1, cleaved caspase-1, interleukin-1β (IL-1β), and IL-18, which indicated that atorvastatin-inhibited pyroptosis and neuroinflammation, ameliorated neuron death in vivo/vitro subjected to SAH. Taken together, this study demonstrates that atorvastatin improved the neurological outcome in rats and reduced the neuron death by against neural pyroptosis and neuroinflammation.

[47] *Krychtiuk KA, Lenz M, Hohensinner P et al.* **Circulating levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) are associated with monocyte subsets in patients with stable coronary artery disease**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33789832

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type-9 (PCSK9) is an enzyme promoting the degradation of low-density lipoprotein receptors (LDL-R) in hepatocytes. Inhibition of PCSK9 has emerged as a novel target for lipid-lowering therapy. Monocytes are crucially involved in the pathogenesis of atherosclerosis and can be divided into three subsets. OBJECTIVE: The aim of this study was to examine whether circulating levels of PCSK9 are associated with monocyte subsets. METHODS: We included 69 patients with stable coronary artery disease. PCSK9 levels were measured and monocyte subsets were assessed by flow cytometry and divided into classical monocytes (CD14++CD16-; CM), intermediate monocytes (CD14++CD16+; IM) and non-classical monocytes (CD14+CD16++; NCM). RESULTS: Mean age was 64 years and 80% of patients were male. Patients on statin treatment (n = 55) showed higher PCSK9-levels (245.4 (206.0-305.5) ng/mL) as opposed to those without statin treatment (186.1 (162.3-275.4) ng/mL; p = 0.05). In patients on statin treatment, CM correlated with circulating PCSK9 levels (R = 0.29; p = 0.04), while NCM showed an inverse correlation with PCSK9 levels (R = -0.33; p = 0.02). Patients with PCSK9 levels above the median showed a significantly higher proportion of CM as compared to patients with PCSK9 below the median (83.5 IQR 79.2-86.7 vs. 80.4, IQR 76.5-85.2%; p = 0.05). Conversely, PCSK9 levels >median were associated with a significantly lower proportion of NCM as compared to those with PCSK9 <median (10.2, IQR 7.3-14.6 vs. 14.3, IQR 10.9-18.7%; p = 0.02). In contrast, IM showed no association with PCSK9 levels. CONCLUSIONS: We hereby provide a novel link between PCSK9 regulation, innate immunity and atherosclerotic disease in statin-treated patients.

[48] *Mäkelä KA, Jokelainen J, Stenbäck V et al.* **PCSK9 Levels and Metabolic Profiles in Elderly Subjects with Different Glucose Tolerance under Statin Therapy**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33801208

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) degrades low-density lipoprotein cholesterol (LDL-C) receptors, and thus regulates the LDL-C levels in the circulation. Type 2 diabetics often have elevated LDL-C levels. However, the functions of PCSK9 in patients with alterations of glu-cose metabolism and statin therapy are still unclear. METHOD: we investigated a large cohort of 608 subjects, born in 1945 in Oulu, Finland (Oulu Cohort 1945). We studied the effects of PSCK9 lev-els with different glucose tolerances (normal glucose tolerance (NGT), prediabetes (PreDM) or type 2 diabetes (T2D)) with and without statin medication, and analyzed clinical data, NMR metabolomics

and PCSK9 plasma levels. RESULTS: PCSK9 plasma levels did not significantly differ between the three groups. Statin therapy significantly increased the PCSK9 levels in NGT, PreDM and T2D groups compared with subjects with no statins. In the NGT group, negative associations between PCSK9 and LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), very low-density lipoprotein cholesterol (VLDL-C), total cholesterol and LDL and IDL triglycerides were observed under statin medication. In contrast, in the PreDM and T2D groups, these associa-tions were lost. CONCLUSIONS: our data suggest that in subjects with abnormal glucose metabolism and statin therapy, the significant PCSK9-mediated effects on the lipid metabolites are lost com-pared to NGT subjects, but statins reduced the LDL-C and VLDL-C levels.

[49] *Vlad CE, Foia LG, Popescu R et al.* **Molecular Genetic Approach and Evaluation of Cardiovascular Events in Patients with Clinical Familial Hypercholesterolemia Phenotype from Romania**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33807407
ABSTRACT
This study identifies the genetic background of familial hypercholesterolemia (FH) patients in Romania and evaluates the association between mutations and cardiovascular events. We performed a prospective observational study of 61 patients with a clinical diagnosis of FH selected based on Dutch Lipid Clinic Network (DLCN) and Simon Broome score between 2017 and 2020. Two techniques were used to identify mutations: multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing. The mutation rate was 37.7%, i.e., 23 patients with mutations were identified, of which 7 subjects had pathogenic mutations and 16 had polymorphisms. Moreover, 10 variants of the low-density lipoprotein receptor (LDLR) gene were identified in 22 patients, i.e., one variant of the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene in six patients, and one variant of the apolipoprotein B (APOB) gene in three patients. Of the LDLR gene variants, four were LDLR pathogenic mutations (c.81C > G, c.502G > A, c.1618G > A mutations in exon 2, exon 4, exon 11, and exon 13-15 duplication). The PCSK9 and APOB gene variants were benign mutations. The pathogenic LDLR mutations were significant predictors of the new cardiovascular events, and the time interval for new cardiovascular events occurrence was significantly decreased, compared to FH patients without mutations. In total, 12 variants were identified, with four pathogenic variants identified in the LDLR gene, whereas 62.3% of the study population displayed no pathological mutations.

[50] *Groner J, Göpferich A, Breunig M.* **Atherosclerosis: Conventional intake of cardiovascular drugs versus delivery using nanotechnology - A new chance for causative therapy?** J Control Release 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33794270
ABSTRACT
Atherosclerosis is the leading cause of death in developed countries. The pathogenetic mechanism relies on a macrophage-based immune reaction to low density lipoprotein (LDL) deposition in blood vessels with dysfunctional endothelia. Thus, atherosclerosis is defined as a chronic inflammatory disease. A plethora of cardiovascular drugs have been developed and are on the market, but the major shortcoming of standard medications is that they do not address the root cause of the disease. Statins and thiazolidinediones that have recently been recognized to exert specific anti-atherosclerotic effects represent a potential breakthrough on the horizon. But their whole potential

cannot be realized due to insufficient availability at the pathological site and severe off-target effects. The focus of this review will be to elaborate how both groups of drugs could immensely profit from nanoparticulate carriers. This delivery principle would allow for their accumulation in target macrophages and endothelial cells of the atherosclerotic plaque, increasing bioavailability where it is needed most. Based on the analyzed literature we conclude design criteria for the delivery of statins and thiazolidinediones with nanoparticles for anti-atherosclerotic therapy. Nanoparticles need to be below a diameter of 100 nm to accumulate in the atherosclerotic plaque and should be fabricated using biodegradable materials. Further, the thiazolidinediones or statins must be encapsulated into the particle core, because especially for thiazolidindiones the uptake into cells is prerequisite for their mechanism of action. For optimal uptake into targeted macrophages and endothelial cells, the ideal particle should present ligands on its surface which bind specifically to scavenger receptors. The impact of statins on the lectin-type oxidized LDL receptor 1 (LOX1) seems particularly promising because of its outstanding role in the inflammatory process. Using this pioneering concept, it will be possible to promote the impact of statins and thiazolidinediones on macrophages and endothelial cells and significantly enhance their anti-atherosclerotic therapeutic potential.

[51] *Li X, Sun B, Wang L et al.* **Association of Type 2 Diabetes Mellitus and Glycemic Control With Intracranial Plaque Characteristics in Patients With Acute Ischemic Stroke**. Journal of magnetic resonance imaging : JMRI 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33786939

ABSTRACT
BACKGROUND: Type 2 diabetes mellitus (T2DM) has shown to be associated with carotid plaque vulnerability. However, the impact of T2DM on intracranial artery atherosclerosis is not well-understood. PURPOSE: To evaluate the association of diabetes and glycemic control with intracranial atherosclerotic plaque characteristics identified by three-dimensional contrast enhanced MR vessel wall imaging in patients after acute ischemic stroke. STUDY TYPE: Prospective. POPULATION: Two hundred and eighty-eight symptomatic patients with acute ischemic stroke due to intracranial atherosclerotic plaque. FIELD STRENGTH/SEQUENCE: T(1) WI volume isotropic turbo spin-echo acquisition sequence at 3.0 T. ASSESSMENT: Clinical profiles, blood biomarkers, the number of intracranial plaques, plaque enhanced score, and the features (location, luminal stenotic rate, intraplaque hemorrhage, length, burden, enhancement grade, and ratio) of culprit plaque (defined as the most stenotic lesion ipsilateral to the ischemic event) and nonculprit plaque were analyzed by three radiologists. STATISTICAL TESTS: Analysis of variance (ANOVA), Shapiro-Wilk normality test, Levene's test, ANOVA with Bonferroni post-hoc test, Kruskal Wallis H test with subsequent pairwise comparisons, chi-square with Bonferroni post-hoc test, generalized linear regression, Pearson correlation test, Kendall's W and intra-class correlation coefficient. RESULTS: Two hundred and twenty-five participants (age 60 ± 10 years, 58.7% male) with 958 intracranial plaques were included. More intracranial plaques were found in the T2DM group than the non-T2DM group (4.80 ± 2.22 vs. 3.60 ± 1.78, $P < 0.05$). Patients with poorly-controlled T2DM exhibited higher culprit plaque enhancement ratio than patients with well-controlled T2DM and non-T2DM (2.32 ± 0.61 vs. 1.60 ± 0.62 and 1.39 ± 0.39; respectively, $P < 0.05$). After adjusting for other clinical variables, T2DM was independently associated with increased intracranial plaque number ($\beta = 0.269$, $P < 0.05$), and HbA1c level was independently associated with culprit plaque enhancement ratio ($\beta = 0.641$, $P < 0.05$) in multivariate analysis. DATA CONCLUSION: T2DM is associated with an increased intracranial

plaque number. Higher HbA1c is associated with stronger plaque enhancement. 3D contrast enhanced MR vessel wall imaging may help better understand the association of T2DM and glycemic control with intracranial plaque. LEVEL OF EVIDENCE: 1 TECHNICAL EFFICACY STAGE: 3.

[52] *Zubiaur P, Benedicto MD, Villapalos-García G et al.* **SLCO1B1 Phenotype and CYP3A5 Polymorphism Significantly Affect Atorvastatin Bioavailability**. Journal of personalized medicine 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33805706
ABSTRACT
Atorvastatin, prescribed for the treatment of hypercholesterolemia, demonstrated overwhelming benefits in reducing cardiovascular morbidity and mortality. However, many patients discontinue therapy due to adverse reactions, especially myopathy. The Dutch Pharmacogenetics Working Group (DPWG) recommends an alternative agent to atorvastatin and simvastatin or a dose adjustment depending on other risk factors for statin-induced myopathy in SLCO1B1 rs4149056 CC or TC carriers. In contrast, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published their guideline on simvastatin, but not on atorvastatin. In this work, we aimed to demonstrate the effect of SLCO1B1 phenotype and other variants (e.g., in CYP3A4/5, UGT enzymes or SLC transporters) on atorvastatin pharmacokinetics. For this purpose, a candidate-gene pharmacogenetic study was proposed. The study population comprised 156 healthy volunteers enrolled in atorvastatin bioequivalence clinical trials. The genotyping strategy comprised a total of 60 variants in 15 genes. Women showed higher exposure to atorvastatin compared to men ($p = 0.001$), however this difference disappeared after dose/weight (DW) correction. The most relevant pharmacogenetic differences were the following: AUC/DW and C(max) /DW based on (a) SLCO1B1 phenotype ($p < 0.001$ for both) and (b) CYP3A5*3 ($p = 0.004$ and 0.018, respectively). As secondary findings: SLC22A1 *2/*2 genotype was related to higher C(max)/DW (ANOVA $p = 0.030$) and SLC22A1 *1/*5 genotype was associated with higher Vd/F (ANOVA $p = 0.032$) compared to SLC22A1 *1/*1, respectively. Finally, UGT2B7 rs7439366 *1/*1 genotype was associated with higher t(max) as compared with the *1/*3 genotype (ANOVA $p = 0.024$). Based on our results, we suggest that SLCO1B1 is the best predictor for atorvastatin pharmacokinetic variability and that prescription should be adjusted based on it. We suggest that the CPIC should include atorvastatin in their statin-SLCO1B1 guidelines. Interesting and novel results were observed based on CYP3A5 genotype, which should be confirmed with further studies.

[53] *Kešnerová P, Školoudík D, Herzig R et al.* **Peripheral Vascular Resistance in Cerebral Arteries in Patients With Carotid Atherosclerosis - Substudy Results of the Atherosclerotic Plaque Characteristics Associated with a Progression Rate of the Plaque and a Risk of Stroke in Patients With the Carotid Bifurcation Plaque Study (ANTIQUE)**. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33792942
ABSTRACT
OBJECTIVES: Transcranial color-coded duplex sonography (TCCS) enables to measure blood flow characteristics in cerebral vessels, including vascular resistance and pulsatility. The study aims to identify factors influencing pulsatility (PI) and resistance (RI) indices measured using TCCS in patients with carotid atherosclerosis. METHODS: Self-sufficient patients with atherosclerotic plaque

causing 20-70% carotid stenosis were consecutively enrolled to the study. All patients underwent duplex sonography of cervical arteries and TCCS with measurement of PI and RI in the middle cerebral artery, neurological, and physical examinations. Following data were recorded: age, gender, height, weight, body mass index, systolic and diastolic blood pressure, occurrence of current and previous diseases, surgery, medication, smoking, and daily dose of alcohol. Univariant and multivariant logistic regression analysis were used for identification of the factors influencing RI and PI. RESULTS: Totally 1863 subjects were enrolled to the study: 139 healthy controls (54 males, age 55.52 ± 7.05 years) in derivation cohort and 1724 patients (777 males, age 68.73 ± 9.39 years) in validation cohort. The cut off value for RI was 0.63 and for PI 1.21. Independent factors for increased RI/PI were age (odds ratio [OR] = 1.108/1.105 per 1 year), occurrence of diabetes mellitus (OR = 1.767/2.170), arterial hypertension (OR = 1.700 for RI only), width of the carotid plaque (OR = 1.260 per 10% stenosis for RI only), and male gender (OR = 1.530 for PI only; P < .01 in all cases). CONCLUSIONS: The independent predictors of increased cerebral arterial resistance and/or pulsatility in patients with carotid atherosclerosis were age, arterial hypertension, diabetes mellitus, carotid plaque width, and male gender.

[54] *Slade E, Irvin MR, Xie K et al.* **Age and sex are associated with the plasma lipidome: findings from the GOLDN study**. Lipids in health and disease 2021; 20:30.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33812378
ABSTRACT
BACKGROUND: Developing an understanding of the biochemistry of aging in both sexes is critical for managing disease throughout the lifespan. Lipidomic associations with age and sex have been reported, but prior studies are limited by measurements in serum rather than plasma or by participants taking lipid-lowering medications. METHODS: Our study included lipidomic data from 980 participants aged 18-87 years old from the Genetics of Lipid-Lowering Drugs and Diet Network (GOLDN). Participants were off lipid-lowering medications for at least 4 weeks, and signal intensities of 413 known lipid species were measured in plasma. We examined linear age and sex associations with signal intensity of (a) 413 lipid species; (b) 6 lipid classes (glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, fatty acids, and acylcarnitines); and (c) 15 lipid subclasses; as well as with the particle sizes of three lipoproteins. RESULTS: Significant age associations were identified in 4 classes, 11 subclasses, 147 species, and particle size of one lipoprotein while significant sex differences were identified in 5 classes, 12 subclasses, 248 species, and particle sizes of two lipoproteins. For many lipid species (n = 97), age-related associations were significantly different between males and females. Age*sex interaction effects were most prevalent among phosphatidylcholines, sphingomyelins, and triglycerides. CONCLUSION: We identified several lipid species, subclasses, and classes that differ by age and sex; these lipid phenotypes may serve as useful biomarkers for lipid changes and associated cardiovascular risk with aging in the future. Future studies of age-related changes throughout the adult lifespan of both sexes are warranted. TRIAL REGISTRATION: ClinicalTrials.gov NCT00083369 ; May 21, 2004.

[55] *Xu X, Dong Y, Ma N et al.* **MiR-337-3p lowers serum LDL-C level through targeting PCSK9 in hyperlipidemic mice**. Metabolism 2021:154768.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33775647
ABSTRACT

BACKGROUND: Reducing serum low-density lipoprotein cholesterol (LDL-C) in hyperlipemia is recognized as an effective strategy to minimize the risk of atherosclerotic cardiovascular disease (ASCVD). MiR-337-3p has already been discovered to play regulatory roles in tumor proliferation and metastasis, adipocyte browning and ischemic brain injury, etc. However, the association between miR-337-3p and LDL-C is unknown. METHODS: Gene Expression Omnibus (GEO) dataset and two hyperlipidemic murine models were used to analyze the potential relationship between miR-337-3p and LDL-C. AAV-mediated liver-directed miRNA overexpression in high fat diet (HFD)-fed mouse model was used to examine the effect of miR-337-3p on LDL-C and WB/RT-PCR/ELISA/luciferase assays were used to investigate the underlying mechanism. RESULTS: The expressions of miR-337-3p were obviously lower in multiple hyperlipidemic mouse models and had a negative correlation with serum LDL-C levels. After confirming the effect of miR-337-3p on the improvement of serum LDL-C in vivo, we discovered PCSK9 might be a possible target of miR-337-3p, which was further proved by in vitro experiments. MiR-337-3p could directly interact with both the PCSK9 3'UTR and promoter to inhibit PCSK9 translation and transcription. Furthermore, the result from DiI-LDL uptake assay under the knockdown of PCSK9 demonstrated that miR-337-3p promoting the absorption of LDL-C in HepG2 cells was dependent on PCSK9, and the result from LDLR-/- mouse model indicated that miR-337-3p regulating LDL-C was dependent on PCSK9/LDLR pathway. CONCLUSION: We discovered a new function of miR-337-3p in regulating PCSK9 expression and LDL-C absorption, suggesting miR-337-3p might be a new therapeutic target for the development of antihyperlipidemic drug.

[56] *Armandi A, Rosso C, Caviglia GP, Bugianesi E*. **Insulin Resistance across the Spectrum of Nonalcoholic Fatty Liver Disease**. Metabolites 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33800465

ABSTRACT

Insulin resistance (IR) is defined as a lower-than-expected response to insulin action from target tissues, leading to the development of type 2 diabetes through the impairment of both glucose and lipid metabolism. IR is a common condition in subjects with nonalcoholic fatty liver disease (NAFLD) and is considered one of the main factors involved in the pathogenesis of nonalcoholic steatohepatitis (NASH) and in the progression of liver disease. The liver, the adipose tissue and the skeletal muscle are major contributors for the development and worsening of IR. In this review, we discuss the sites and mechanisms of insulin action and the IR-related impairment along the spectrum of NAFLD, from simple steatosis to progressive NASH and cirrhosis.

[57] *Xu D, Wang S, Feng M et al.* **Serum Metabolomics Reveals Underlying Mechanisms of Cholesterol-Lowering Effects of Oat Consumption: A Randomized Controlled Trial in a Mildly Hypercholesterolemic Population**. Molecular nutrition & food research 2021:e2001059.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33793078

ABSTRACT

SCOPE: The purpose of this study was to examine the effects of oat supplementation on serum lipid in a population of adults with mild hypercholesterolemia and reveal the underlying mechanisms with serum untargeted metabolomics. METHODS AND RESULTS: In this placebo-controlled trial, 62 participants from Nanjing, China, with mild elevations in cholesterol were randomly assigned to receive 80g oats (containing 3g beta-glucan) or rice daily for 45 days. Fasting blood samples were

collected at the beginning, middle, and end of the trial. Compared with the rice group, oat consumption significantly decreased serum TC (-8.41%, P = 0.005), LDL-c (-13.93%, P = 0.001), and non-HDL-c (-10.93%, P = 0.017) levels. There were no significant between-group differences in serum triglyceride (TG), Apo B, glycated albumin, or fasting blood glucose levels. An orthogonal partial least squares discriminant analysis suggested a clear separation in metabolic profiles between the groups after the intervention. Twenty-one metabolites in the oat group were significantly different from those in the rice group, among which fourteen metabolites showed a decreased trend. In comparison, seven metabolites showed an increased trend. Correlations analysis from both groups indicated that most metabolites [e.g., sphinganine and phosphatidylcholine (PC)(20:5(5Z,8Z,11Z,14Z,17Z)/20:1(11Z))] had positive correlations with serum cholesterol levels. Kyoto Encyclopedia of Gene and Genomes pathway analysis suggested that oat consumption regulated glycerophospholipid, alanine, aspartate and glutamate, sphingolipid, and retinol metabolism. CONCLUSION: Oat consumption had beneficial effects on serum lipids profiles. The underlying mechanisms involve glycerophospholipid, alanine, aspartate and glutamate, sphingolipid, and retinol metabolism in adults.

[58] *Agrawal YO, Mahajan UB, Agnihotri VV et al.* **Ezetimibe-Loaded Nanostructured Lipid Carrier Based Formulation Ameliorates Hyperlipidaemia in an Experimental Model of High Fat Diet**. Molecules (Basel, Switzerland) 2021; 26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33803259
ABSTRACT
Ezetimibe (EZE) possesses low aqueous solubility and poor bioavailability and in addition, its extensive hepatic metabolism supports the notion of developing a novel carrier system for EZE. Ezetimibe was encapsulated into nanostructured lipid carriers (EZE-NLCs) via a high pressure homogenization technique (HPH). A three factor, two level (2(3)) full factorial design was employed to study the effect of amount of poloxamer 188 (X1), pressure of HPH (X2) and number of HPH cycle (X3) on dependent variables. Particle size, polydispersity index (PDI), % entrapment efficiency (%EE), zeta potential, drug content and in-vitro drug release were evaluated. The optimized formulation displays pragmatic inferences associated with particle size of 134.5 nm; polydispersity index (PDI) of 0.244 ± 0.03; zeta potential of -28.1 ± 0.3 mV; % EE of 91.32 ± 1.8% and % CDR at 24-h of 97.11%. No interaction was observed after X-ray diffraction (XRD) and differential scanning calorimetry (DSC) studies. EZE-NLCs (6 mg/kg/day p.o.) were evaluated in the high fat diet fed rats induced hyperlipidemia in comparison with EZE (10 mg/kg/day p.o.). Triglyceride, HDL-c, LDL-c and cholesterol were significantly normalized and histopathological evaluation showed normal structure and architecture of the hepatocytes. The results demonstrated the superiority of EZE-NLCs in regard to bioavailability enhancement, dose reduction and dose-dependent side effects.

[59] *Fukami H, Higa Y, Hisano T et al.* **A Review of Red Yeast Rice, a Traditional Fermented Food in Japan and East Asia: Its Characteristic Ingredients and Application in the Maintenance and Improvement of Health in Lipid Metabolism and the Circulatory System**. Molecules (Basel, Switzerland) 2021; 26.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33803982
ABSTRACT

Red yeast rice has been used to produce alcoholic beverages and various fermented foods in China and Korea since ancient times; it has also been used to produce tofuyo (Okinawan-style fermented tofu) in Japan since the 18th century. Recently, monacolin K (lovastatin) which has cholesterol-lowering effects, was found in some strains of Monascus fungi. Since statins have been used world-wide as a cholesterol-lowering agent, processed foods containing natural statins are drawing attention as materials for primary prevention of life-style related diseases. In recent years, large-scale commercial production of red yeast rice using traditional solid-state fermentation has become possible, and various useful materials, including a variety of monascus pigments (polyketides) that spread as natural pigments, in addition to statins, are produced in the fermentation process. Red yeast rice has a lot of potential as a medicinal food. In this paper, we describe the history of red yeast rice as food, especially in Japan and East Asia, its production methods, use, and the ingredients with pharmacological activity. We then review evidence of the beneficial effects of red yeast rice in improving lipid metabolism and the circulatory system and its safety as a functional food.

[60] *West AL, Miles EA, Lillycrop KA et al.* **Genetically modified plants are an alternative to oily fish for providing n-3 polyunsaturated fatty acids in the human diet: A summary of the findings of a Biotechnology and Biological Sciences Research Council funded project**. Nutr Bull 2021; 46:60-68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33776584
ABSTRACT
The n-3 polyunsaturated fatty acids (PUFA) present primarily in oily fish, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are important components of cell membranes and that are needed for normal development and cell function. Humans have very limited capacity for EPA and DHA synthesis from α-linolenic acid and so they must be obtained pre-formed from the diet. However, perceived unpalatability of oily fish and fish oil concerns about contamination with environmental pollutants, dietary choices that exclude fish and animal products, and price limit the effectiveness of recommendations for EPA and DHA intakes. Moreover, marine sources of EPA and DHA are diminishing in the face of increasing demands. Therefore, an alternative source of EPA and DHA is needed that is broadly acceptable, can be upscaled and is sustainable. This review discusses these challenges and, using findings from recent nutritional trials, explains how they may be overcome by seed oils from transgenic plants engineered to produce EPA and DHA. Trials in healthy men and women assessed the acute uptake and appearance in blood over 8 hours of EPA and DHA from transgenic Camelina sativa compared to fish oil, and the incorporation of these PUFA into blood lipids after dietary supplementation. The findings showed that postprandial EPA and DHA incorporation into blood lipids and accumulation in plasma lipids after dietary supplementation was as good as that achieved with fish oil. The oil derived from this transgenic plant was well tolerated. This review also discusses the implications for human nutrition, marine ecology and agriculture.

[61] *Picard K, Senior PA, Adame Perez S et al.* **Low Mediterranean Diet scores are associated with reduced kidney function and health related quality of life but not other markers of cardiovascular risk in adults with diabetes and chronic kidney disease**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33812736
ABSTRACT

BACKGROUND AND AIMS: How Mediterranean-style diets impact cardiovascular and health outcomes in patients with diabetes and chronic kidney disease (CKD) is not well known. Our aim was to investigate the association between diet quality, using Mediterranean Diet Scores (MDS) and health outcomes. METHODS AND RESULTS: This is a post-hoc analysis of an RCT and longitudinal study investigating patients with diabetes and CKD. MDS was calculated annually. Scores were analyzed for correlation with lipids, HbA(1c), serum potassium, health-related quality of life (HRQOL) and depression. 178 diet records from 50 patients who attended two or more visits were included. Mean MDS was moderate (4.1 ± 1.6) and stable over time. Stage 1-2 vs 3-5 CKD had lower raw MDS (3.8 ± 1.5 vs 4.6 ± 1.5, $p < 0.001$). Having hyperkalemia was associated with a lower raw MDS scores (3.6 ± 1.6 vs 4.2 ± 1.5, $p = 0.03$) but not energy adjusted MDS. MDS was not associated with HbA(1c) or lipids. High vs low MDS was associated with improved HRQOL (mental health 84.4 ± 14.3 vs 80.3 ± 17.1, $p < 0.05$; general health 62.6 ± 21.0 vs 56.3 ± 19.8, $p < 0.001$) and fewer depressive symptoms (9.1 ± 7.4 vs 11.7 ± 10.6, $p = 0.01$). CONCLUSIONS: Low MDS was associated with reduced kidney function and health related quality of life, but not other markers of cardiovascular risk. Further studies are needed to understand the nature and direction of the association between diet quality and disease outcomes in this population.

[62] *Ciric MZ, Ostojic M, Baralic I et al.* **Supplementation with Octacosanol Affects the Level of PCSK9 and Restore Its Physiologic Relation with LDL-C in Patients on Chronic Statin Therapy**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33802219
ABSTRACT
Dietary supplementation with sugar cane derivates may modulate low-density lipoprotein cholesterol (LDL-C) and proprotein convertase subtilisin/kexin type 9 (PCSK9) levels. The purpose of this study was to determine if dietary supplement (DS), containing Octacosanol (20 mg) and vitamin K2 (45 μg), could restore the disrupted physiologic relation between LDL-C and serum PCSK9. Double-blind, randomized, placebo-controlled, single-center study including 87 patients on chronic atorvastatin therapy was conducted. Eighty-seven patients were randomized to receive DS (n = 42) or placebo (n = 45), and followed for 13 weeks. Serum PCSK9 levels, lipid parameters and their relationship were the main efficacy endpoints. The absolute levels of PCSK9 and LDL-C were not significantly different from baseline to 13 weeks. However, physiologic correlation between % change of PCSK9 and % change of LDL-C levels was normalized only in the group of patients treated with DS ($r = 0.409$, $p = 0.012$). This study shows that DS can restore statin disrupted physiologic positive correlation between PCSK9 and LDL-C. Elevated PCSK9 level is an independent risk factor so controlling its rise by statins may be important in prevention of cardiovascular events.

[63] *Xu X, Shi Z, Liu G et al.* **The Joint Effects of Diet and Dietary Supplements in Relation to Obesity and Cardiovascular Disease over a 10-Year Follow-Up: A Longitudinal Study of 69,990 Participants in Australia**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33804132
ABSTRACT
It is unknown whether a healthy diet or unhealthy diet combined with specific supplements may jointly contribute to incidence of obesity and cardiovascular disease (CVD). We included 69,990 participants from the 45 and Up Study who completed both baseline (2006-2009) and follow-up (2012-2015)

surveys. We found that compared to participants with a long-term healthy diet and no supplement consumption, those with a long-term healthy diet combined with multivitamins and minerals (MVM) or fish oil consumption were associated with a lower incidence of CVD ($p < 0.001$); whilst those with an unhealthy diet and no MVM or fish oil consumption were associated with a higher risk of obesity ($p < 0.05$). Compared to participants with a long-term healthy diet and no calcium consumption, the combination of a long-term healthy diet and calcium consumption was linked to a lower risk of CVD (IRR = 0.87, 95% CI: 0.78; 0.96). In conclusion, a long-term healthy diet combined with MVM or fish oil was associated with a lower incidence of CVD. Participants who maintained a healthy diet and used calcium supplements were associated with a lower incidence of obesity. However, these associations were not found among those with an unhealthy diet, despite taking similar supplements.

[64] *Torrado-Salmerón C, Guarnizo-Herrero V, Henriques J et al.* **Multiparticulate Systems of Ezetimibe Micellar System and Atorvastatin Solid Dispersion Efficacy of Low-Dose Ezetimibe/Atorvastatin on High-Fat Diet-Induced Hyperlipidemia and Hepatic Steatosis in Diabetic Rats**. Pharmaceutics 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33804727

ABSTRACT

The aim of this study was to develop multiparticulate systems with a combination of ezetimibe micellar systems and atorvastatin solid dispersions using croscarmellose as a hydrophilic vehicle and Kolliphor RH40 as a surfactant. The presence of a surfactant with low hydrophilic polymer ratios produces the rapid dissolution of ezetimibe through a drug-polymer interaction that reduces its crystallinity. The solid dispersion of atorvastatin with low proportions of croscarmellose showed drug-polymer interactions sufficient to produce the fast dissolution of atorvastatin. Efficacy studies were performed in diabetic Goto-Kakizaki rats with induced hyperlipidemia. The administration of multiparticulate systems of ezetimibe and atorvastatin at low (2 and 6.7 mg/kg) and high (3 and 10 mg/kg) doses showed similar improvements in levels of cholesterol, triglycerides, lipoproteins, alanine transaminase, and aspartate transaminase compared to the high-fat diet group. Multiparticulate systems at low doses (2 and 6.7 mg/kg of ezetimibe and atorvastatin) had a similar improvement in hepatic steatosis compared to the administration of ezetimibe and atorvastatin raw materials at high doses (3 and 10 mg/kg). These results confirm the effectiveness of solid dispersions with low doses of ezetimibe and atorvastatin to reduce high lipid levels and hepatic steatosis in diabetic rats fed a high-fat diet.

[65] *Pan J, Cai Y, Wang L et al.* **A prediction tool for plaque progression based on patient-specific multi-physical modeling**. PLoS computational biology 2021; 17:e1008344.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33780445

ABSTRACT

Atherosclerotic plaque rupture is responsible for a majority of acute vascular syndromes and this study aims to develop a prediction tool for plaque progression and rupture. Based on the follow-up coronary intravascular ultrasound imaging data, we performed patient-specific multi-physical modeling study on four patients to obtain the evolutional processes of the microenvironment during plaque progression. Four main pathophysiological processes, i.e., lipid deposition, inflammatory response, migration and proliferation of smooth muscle cells (SMCs), and neovascularization were coupled based on the interactions demonstrated by experimental and clinical observations. A scoring

table integrating the dynamic microenvironmental indicators with the classical risk index was proposed to differentiate their progression to stable and unstable plaques. The heterogeneity of plaque microenvironment for each patient was demonstrated by the growth curves of the main microenvironmental factors. The possible plaque developments were predicted by incorporating the systematic index with microenvironmental indicators. Five microenvironmental factors (LDL, ox-LDL, MCP-1, SMC, and foam cell) showed significant differences between stable and unstable group ($p < 0.01$). The inflammatory microenvironments (monocyte and macrophage) had negative correlations with the necrotic core (NC) expansion in the stable group, while very strong positive correlations in unstable group. The inflammatory microenvironment is strongly correlated to the NC expansion in unstable plaques, suggesting that the inflammatory factors may play an important role in the formation of a vulnerable plaque. This prediction tool will improve our understanding of the mechanism of plaque progression and provide a new strategy for early detection and prediction of high-risk plaques.

[66] *De Giorgi R, De Crescenzo F, Rizzo Pesci N et al.* **Statins for major depressive disorder: A systematic review and meta-analysis of randomized controlled trials**. PloS one 2021; 16:e0249409.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33784356
ABSTRACT
BACKGROUND: The burden of depressive disorder is large and new treatment approaches are required. Repurposing widely available drugs such as statins may be a time- and cost-effective solution. Statins have anti-inflammatory and anti-oxidant properties which have been shown to be relevant to the pathophysiology of depression. This study assesses the efficacy, acceptability, tolerability, and safety of statins in major depressive disorder. METHODS: Our study is an update and extension of a previous meta-analysis published in 2016 by Salagre et al. We performed a systematic review (PubMed/MEDLINE, Cochrane CENTRAL, ISI Web of Science, CINAHL, and ClinicalTrials.gov until the 1st September 2020) and meta-analysis of randomized controlled trials using any statin against placebo or any other statin in the treatment of major depressive disorder. Our primary efficacy outcome measure was the mean value on any standardized scale for depressive symptoms at 8 weeks of treatment. We also calculated outcomes for efficacy, response, and remission at 2, 4, and 12 weeks, as well as acceptability (dropouts for any cause), tolerability (dropouts due to any adverse event), and safety (any adverse event) outcomes at the studies' endpoints. Furthermore, we conducted an exploratory network meta-analysis for the primary efficacy outcome to identify potential differences between statins. RESULTS: We retrieved five randomized controlled trials meeting our inclusion criteria: four used a statin in addition to an antidepressant and compared it to placebo plus antidepressant, and one compared two statins alone. and one comparing one statin with another. Statins compared to placebo in addition to antidepressants were efficacious at 8 weeks (N = 255, SMD = -0.48, 95% CI = -0.74 to -0. 22) and 12 weeks (N = 134, SMD = -0.47, 95% CI = -0.89 to -0.05, moderate certainty) with no difference for acceptability, tolerability, and safety (low certainty). An exploratory network meta-analysis suggested that the most lipophilic statins, especially simvastatin, could be more efficacious than less lipophilic or hydrophilic molecules. CONCLUSIONS: This systematic review suggests the efficacy, acceptability, tolerability, and safety of statins in addition to antidepressants in patients with major depressive disorder. Further clinical trials

in different settings are required to test this result. TRIAL RGISTRATION: PROSPERO registration: CRD42020170938.

[67] *Barrett E, Paige E, Welsh J et al.* **Differences between men and women in the use of preventive medications following a major cardiovascular event: Australian prospective cohort study**. Preventive medicine reports 2021; 22:101342.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33777665
ABSTRACT
Most cardiovascular disease (CVD) events can be prevented with appropriate risk management. Existing evidence suggests women are less likely than men to receive guideline-recommended medications, however data on sex-differences in preventive medication use following a CVD event are lacking. Relative risks (RRs) comparing use of blood pressure- and lipid-lowering medications in men and women at 3-, 6-, 9- and 12-months following hospitalisation for myocardial infarction (MI) or stroke from 2012 to 2017 were quantified using linked data from 8,278 participants enrolled in the Australian 45 and Up Study. Overall, 51% of women and 58% of men were using both blood-pressure- and lipid-lowering medications three months after a MI or stroke event, decreasing to 48% and 53%, respectively, at 12 months after an event. Adjusting for potential confounders, women were 9% less likely than men (RR = 0.91 [95% CI: 0.87, 0.95]) to be using both medications and 19% more likely (RR = 1.19 [95% CI: 1.07, 1.32]) to use neither medication three months after a MI or stroke event. At the 12-month mark, women were 8% less likely (RR = 0.92 [95% CI: 0.88, 0.97]) to be using both medications and 14% more likely (RR = 1.14 [95% CI: 1.03, 1.26]) to use neither medication. Women were consistently less likely to use both preventive medications and more likely to use neither medication at each follow-up time point. Overall, there were major shortfalls in basic preventive medication use post-CVD event and sex disparities are likely to further jeopardise efforts to reduce CVD events in the community.

[68] *Puig-Jové C, Castelblanco E, Falguera M et al.* **Advanced lipoprotein profile in individuals with normal and impaired glucose metabolism**. Revista espanola de cardiologia (English ed.) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33785266
ABSTRACT
INTRODUCTION AND OBJECTIVES: Several types of lipoproteins beyond low-density lipoproteins (LDL) are causally related to cardiovascular disease. We aimed to analyze an advanced lipoprotein profile in individuals with normal and impaired glucose metabolism from different cohorts of a Mediterranean region. METHODS: Cross-sectional study in 929 participants (463 normoglycemia, 250 prediabetes, and 216 type 2 diabetes mellitus) with normal renal function, free from cardiovascular disease, and without lipid-lowering treatment. Conventional and advanced (nuclear magnetic resonance [NMR] spectroscopy) lipoprotein profiles were analyzed. RESULTS: Compared with men, normoglycemic women showed lower serum triglyceride and LDL cholesterol concentrations, lower total LDL particles (P) as well as their subclasses and their cholesterol and triglyceride content, higher high-density lipoproteins (HDL)-P and all HDL-related variables (P≤ .05 for all comparisons). Compared with normoglycemic participants, diabetic participants showed higher large and small very LDL-P concentrations (P <.05) and lower total HDL-P and medium HDL-P concentrations (P <.05). Waist circumference and Fatty Liver Index were positively associated with a

proatherogenic profile. CONCLUSIONS: Women had a better advanced lipoprotein profile than did men. Adiposity indexes related to insulin-resistance were positively associated with a proatherogenic lipid profile. NMR revealed altered lipoprotein particles other than LDL in participants with diabetes, frequently associated with an increased cardiovascular risk. Our findings support the usefulness of extended lipoprotein analysis by NMR spectroscopy to uncover new therapeutic targets to prevent cardiovascular events in at-risk participants.

[69] *Hsu HY, Tsai MC, Yeh TL et al.* **Association of baseline as well as change in lipid levels with the risk of cardiovascular diseases and all-cause deaths**. Scientific reports 2021; 11:7381.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33795701

ABSTRACT

High baseline atherogenic lipid level has been an established risk factor for the risk of cardiovascular events. Evidence concerning the role of lipid changes in cardiovascular and death risks are inconclusive. A cohort study was conducted based on the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (n = 4072, mean 44.8 years, 53.5% women) assessing lipid levels of the participants repeatedly measured in 2002 and 2007. Combined baseline and changes in lipid levels were classified into four groups-stable or decreasing lipid changes and increasing lipid changes with low- and high-risk baseline lipid levels. Developing cardiovascular events (n = 225) and all-cause deaths (n = 345) were ascertained during a median follow-up of 13.3 years. Participants with increasing and higher total cholesterol level were more likely to develop cardiovascular risks. Similar patterns for cardiovascular events were observed across other lipid profile changes. However, participants with increasing total cholesterol, LDL-C, and non-high-density lipoprotein cholesterol (non-HDL-C) levels were more likely to be at a lower risk for all-cause deaths. Baseline and changes in total cholesterol, triglycerides, and LDL-C levels were positively associated with the risk of cardiovascular diseases, whereas baseline and changes in total cholesterol and LDL-C and non-HDL-C levels were inversely associated with all-cause deaths.

[70] *Masana L, Correig E, Ibarretxe D et al.* **Low HDL and high triglycerides predict COVID-19 severity**. Scientific reports 2021; 11:7217.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33785815

ABSTRACT

Lipids are indispensable in the SARS-CoV-2 infection process. The clinical significance of plasma lipid profile during COVID-19 has not been rigorously evaluated. We aim to ascertain the association of the plasma lipid profile with SARS-CoV-2 infection clinical evolution. Observational cross-sectional study including 1411 hospitalized patients with COVID-19 and an available standard lipid profile prior (n: 1305) or during hospitalization (n: 297). The usefulness of serum total, LDL, non-HDL and HDL cholesterol to predict the COVID-19 prognosis (severe vs mild) was analysed. Patients with severe COVID-19 evolution had lower HDL cholesterol and higher triglyceride levels before the infection. The lipid profile measured during hospitalization also showed that a severe outcome was associated with lower HDL cholesterol levels and higher triglycerides. HDL cholesterol and triglyceride concentrations were correlated with ferritin and D-dimer levels but not with CRP levels. The presence of atherogenic dyslipidaemia during the infection was strongly and independently associated with a worse COVID-19 infection prognosis. The low HDL cholesterol and high triglyceride concentrations measured before or during hospitalization are strong predictors of a severe course of the disease. The lipid profile should

be considered as a sensitive marker of inflammation and should be measured in patients with COVID-19.

[71] *Tsutsumi R, Yamasaki Y, Takeo J et al.* **Long-chain monounsaturated fatty acids improve endothelial function with altering microbial flora**. Translational research : the journal of laboratory and clinical medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33775867
ABSTRACT
Fish oil-derived long-chain monounsaturated fatty acids (LCMUFAs) with a carbon chain length longer than 18 units ameliorate cardiovascular risk in mice. In this study, we investigated whether LCMUFAs could improve endothelial functions in mice and humans. In a double-blind, randomized, placebo-controlled, parallel-group, multi-center study, healthy subjects were randomly assigned to either an LCMUFA oil (saury oil) or a control oil (olive and tuna oils) group. Sixty subjects were enrolled and administrated each oil for 4 weeks. For the animal study, ApoE(-/-) mice were fed a Western diet supplemented with 3% of either gadoleic acid (C20:1) or cetoleic acid (C22:1) for 12 weeks. Participants from the LCMUFA group showed improvements in endothelial function and a lower trimethylamine-N-oxide level, which is a predictor of coronary artery disease. C20:1 and C22:1 oils significantly improved atherosclerotic lesions and plasma levels of several inflammatory cytokines, including IL-6 and TNF-α. These beneficial effects were consistent with an improvement in the gut microbiota environment, as evident from the decreased ratio of Firmicutes/Bacteroidetes, increase in the abundance of Akkermansia, and upregulation of short-chain fatty acid (SCFA)-induced glucagon-like peptide-1 (GLP-1) expression and serum GLP-1 level. These data suggest that LCMUFAs alter the microbiota environment that stimulate the production of SCFAs, resulting in the induction of GLP-1 secretion. Fish oil-derived long-chain monounsaturated fatty acids might thus help to protect against cardiovascular disease.

[72] *Koulouri A, Darioli R, Dine Qanadli S et al.* **The atherosclerosis burden score**. VASA. Zeitschrift fur Gefasskrankheiten 2021:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33789435
ABSTRACT
Purpose: We carried out this study to evaluate the predictive value of atherosclerosis burden score (ABS) to predict coronary artery disease (CAD) among asymptomatic patients without known cardiovascular disease (CVD), as compared to other imaging or functional techniques, namely coronary artery calcium (CAC) score, carotid intima-media thickness (C-IMT), and ankle brachial index (ABI). Patients and methods: This prospective study included 198 asymptomatic consecutive patients referred for evaluation of their cardiovascular (CV) risk and for therapeutic advice. Traditional CV risk factors, ABS, CAC score, C-IMT, ABI and an ECG-synchronized coronary CT-angiography (CCTA) were performed for each patient. We compared the predictive values of these atherosclerosis markers to detect CAD defined as coronary stenosis ≥30% objectivated by CCTA. Results: Among the whole sample, the area under the receiver-operating characteristic curve (ROC-AUC) was significantly higher for CAC score (0.81, p=0.015) than for ABS, the reference (0.70) but these values were lower for C-IMT (0.60, p=0.16) and particularly for ABI (0.56, p=0.0015). However, among patients at intermediate risk of coronary heart disease (CHD), according to Framingham risk score (FRS), the differences between the ROC-AUC values for ABS (0.70) and CAC score (0.76, p=0.36)

were less pronounced. Again, as compared to ABS, the ROC-AUC values were lower for C-IMT (0.60, p=0.21) and ABI (0.57, p=0.06). Conclusions: ABS, an ultrasonographic score based on the assessment of carotid and femoral plaque burden, predicts more accurately CAD than other non-radiation tools analyzed here, and has a similar performance to CAC in patients at intermediate CHD risk. Thus, ABS could be an appropriate non-invasive and safe method to improve the detection of high-risk patients who will benefit from a more intensive therapy for the primary prevention of CVD.