[1] *Kawada Y, Kubo T, Baba Y et al.* **Effects of Switching from Treatment with Amlodipine and Atorvastatin Using Two Pills to an Equal Dose of Single-Pill Therapy in Japanese Outpatients**. Acta medica Okayama 2020; 74:103-108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32341583

ABSTRACT

This study examined whether switching from amlodipine and atorvastatin treatment using two pills to an equal dose of single-pill therapy is useful in Japanese outpatients. We retrospectively reviewed data obtained from 94 outpatients for whom treatment with two pills, namely amlodipine and atorvastatin, was switched to an equal dose of single-pill therapy in 11 hospitals. The criterion for enrollment in this study was that patients had switched their medication without changing other anti-hypertensive or anti-cholesterol drugs. Neither systolic nor diastolic blood pressure changed significantly after switching to an equal dose of single-pill therapy, whereas low-density lipoprotein (LDL) cholesterol levels significantly decreased after the medication was switched from 94+/-24 mg/dl to 89+/-17 mg/dl (p=0.015). A switch from medication with two separate pills of amlodipine and atorvastatin to an equal dose of single-pill therapy resulted in an overall decrease in LDL cholesterol. The results indicated that the switch to single-pill therapy might be a useful treatment.

[2] *Ahern TP, Damkier P, Feddersen S et al.* **Predictive pharmacogenetic biomarkers for breast cancer recurrence prevention by simvastatin**. Acta Oncol 2020:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32351149

ABSTRACT

Background: Statins treat hyperlipidemia and prevent cardiovascular morbidity and mortality. Evidence suggests that they also have anti-neoplastic activity. Several studies show a reduced rate of breast cancer recurrence among lipophilic statin users (e.g., simvastatin), motivating calls for clinical trials of statins in breast cancer patients. We measured the impact of genetic variation in statin-metabolizing enzymes and drug transporters on the recurrence rate in simvastatin-treated breast cancer patients.Methods: We conducted a nested case-control study among Danish women diagnosed with non-metastatic, invasive breast cancer between 2004-2010 who had filled >/=1 prescription for simvastatin after diagnosis. Cases were all breast cancer recurrences from the source population; one control was matched to each case on cancer stage, estrogen receptor and hormone therapy status, calendar period of diagnosis, and duration of simvastatin exposure. We genotyped variants in simvastatin-metabolizing enzymes (CYP3A4/rs35599367 and CYP3A5/rs776746) and drug transporters (ABCB1/rs2032582 and SLCO1B1/rs4149056), and estimated their association with recurrence with logistic regression models.Results: We observed protective (though imprecisely-measured) associations between variants in genes encoding drug transporters (ABCB1 and SLCO1B1) and simvastatin-metabolizing enzymes (CYP3A4 and CYP3A5) and breast cancer recurrence in simvastatin-treated women. For example, carrying two variant alleles in ABCB1 was associated with a 31% lower rate of recurrence (multivariable OR = 0.69, 95% CI: 0.31, 1.5).Conclusion: Our study provides weak evidence to support the use of genetic variation in ABCB1, SLCO1B1, CYP3A4, and CYP3A5 as biomarkers of breast tumor response to simvastatin. Validation of these findings within adjuvant clinical trials is encouraged.

[3] *Boden WE, Miller MG, McBride R et al.* **Testosterone concentrations and risk of cardiovascular events in androgen-deficient men with atherosclerotic cardiovascular disease**. American heart journal 2020; 224:65-76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32335402
ABSTRACT
BACKGROUND: Whether androgen deficiency among men increases the risk of cardiovascular (CV) events or is merely a disease marker remains a subject of intense scientific interest. OBJECTIVES: Among male subjects in the AIM-HIGH Trial with metabolic syndrome and low baseline levels of high-density lipoprotein (HDL)-cholesterol who were randomized to niacin or placebo plus simvastatin, we examined the relationship between low baseline testosterone (T) concentrations and subsequent CV outcomes during a mean 3-year follow-up. METHODS: In this post hoc analysis of men with available baseline plasma T concentrations, we examined the relationship between clinical/demographic characteristics and T concentrations both as a continuous and dichotomous variable (<300 ng/dL ["low T"] vs. >/=300 ng/dL ["normal T"]) on rates of pre-specified CV outcomes, using Cox proportional hazards models. RESULTS: Among 2118 male participants in whom T concentrations were measured, 643 (30%) had low T and 1475 had normal T concentrations at baseline. The low T group had higher rates of diabetes mellitus, hypertension, elevated body mass index, metabolic syndrome, higher blood glucose, hemoglobin A1c, and triglyceride levels, but lower levels of both low-density lipoprotein and HDL-cholesterol, and a lower rate of prior myocardial infarction (MI). Men with low T had a higher risk of the primary composite outcome of coronary heart disease (CHD) death, MI, stroke, hospitalization for acute coronary syndrome, or coronary or cerebral revascularization (20.1%) compared with the normal T group (15.2%); final adjusted HR 1.23, P=.07, and a higher risk of the CHD death, MI, and stroke composite endpoint (11.8% vs. 8.2%; final adjusted HR 1.37, P=.04), respectively. CONCLUSIONS: In this post hoc analysis, there was an association between low baseline testosterone concentrations and increased risk of subsequent CV events in androgen-deficient men with established CV disease and metabolic syndrome, particularly for the composite secondary endpoint of CHD death, MI, and stroke. CONDENSED ABSTRACT: In this AIM-HIGH Trial post hoc analysis of 2118 men with metabolic syndrome and low HDL-cholesterol with available baseline plasma testosterone (T) samples, 643 males (30%) had low T (mean: 229 ng/dL) and 1475 (70%) had normal T (mean: 444 ng/dL) concentrations. The "low T" group had a 24% higher risk of the primary 5-component endpoint (20.1%) compared with the normal T group (15.2%); final adjusted HR 1.23, P=.07). There was also a 31% higher risk of the secondary composite endpoint: coronary heart disease death, myocardial infarction, and stroke (11.8% vs. 8.2%, final adjusted HR 1.37, P=.04) in the low vs. normal T group, respectively.

[4] *Lee HAH, An H, Lee E*. **Dietary patterns related to cardiovascular disease based on reduced rank regression analysis of healthy middle-aged Koreans: data from the community-based Korean Genome and Epidemiology Study (KoGES) cohort**. The American journal of clinical nutrition 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32338724
ABSTRACT
BACKGROUND: Dietary patterns (DPs) provide a comprehensive picture of the foods consumed by an individual. OBJECTIVES: Using 12-y follow-up data from the Korean Genome

Epidemiology Study (KoGES), we determined the associations of DPs with incident cardiovascular disease (CVD) using reduced rank regression (RRR). METHODS: This study analyzed the data of 7354 CVD-free subjects aged 40-69 y drawn from the community-based KoGES cohort. Based on the daily intake of 26 food groups at baseline, we identified DPs based on retinol, vitamin B-2 (riboflavin), and vitamin B-3 (niacin) intakes using RRR. The effects of the DPs on incident CVD were assessed using HRs with 95% CIs. Furthermore, using a marginal structural model, the association between DPs and incident CVD was evaluated after adjusting for time-varying confounders. RESULTS: The incidence of CVD during the follow-up period was 3.7 per 1000 person-years (n = 274). The identified DP accounted for 28.99% of the variation in the response variables (i.e., the intake amounts of all 3 nutrients) and was characterized by high intakes of eggs, fish, milk, and dairy products. The effect of DP quintile on incident CVD differed by sex (Pinteraction = 0.03); the highest DP quintile was associated with a protective effect against the development of CVD in women (HR: 0.44; 95% CI: 0.22, 0.89), but not in men (HR: 1.57; 95% CI: 0.82, 3.00), compared with the lowest quintile. Even after adjusting for time-dependent variables, the effect of DP on incident CVD was significant in women (HR: 0.43; 95% CI: 0.22, 0.84), but not in men (HR: 1.49; 95% CI: 0.71, 3.10). CONCLUSIONS: In this study, we identified DPs related to CVD, and a DP characterized by high intakes of eggs, fish, milk, and dairy products protected against incident CVD in women.

[5] *Oh TK, Song IA, Choi S*. **Prior statin therapy and mortality among critically ill patients: a systemic review and meta-analysis of cohort studies**. Annals of translational medicine 2020; 8:396.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32355840
ABSTRACT
The effect of prior statin exposure in critically ill patients remains controversial and has not been established in previous cohort studies. We performed a systematic review of previous cohort studies to evaluate the association of prior statin therapy with mortality in critically ill patients and conducted a meta-analysis. The MEDLINE, EMBASE, and Cochrane CENTRAL databases, from their inception to January 7, 2020, were used for this study. Statin users were defined as patients prescribed statin regularly before intensive care unit admission or diagnosis of a specific disease, such as sepsis. The Cochran chi-square test and I statistics were used to determine heterogeneity between studies. In total, 199,985 critically ill patients from nine studies (44,582 statin users and 155,403 non-statin users) were included in the meta-analysis. According to the random effect model, the 30-day mortality of statin users was 31% lower than that of non-statin users (hazard ratio: 0.69, 95% confidence interval: 0.56 to 0.85). This association was similar in atorvastatin users and simvastatin users. However, hospital mortality in statin users was not significantly associated with that in non-statin users [odds ratios (ORs): 0.71, 95% CI: 0.42 to 1.21]. This study showed that there was a beneficial association of prior statin therapy with 30-day mortality in critically ill patients. However, there was no significant association with hospital mortality. Additional prospective cohort studies with a large sample size should be performed to confirm these findings.

[6] *Ahern AL, Woolston J, Wells E et al.* **Clinical and cost-effectiveness of a diabetes education and behavioural weight management programme versus a diabetes education programme in adults with a recent diagnosis of type 2 diabetes: study**

protocol for the Glucose Lowering through Weight management (GLoW) randomised controlled trial. BMJ open 2020; 10:e035020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350016
ABSTRACT
INTRODUCTION: People with type 2 diabetes (T2D) can improve glycaemic control or even achieve remission through weight loss and reduce their use of medication and risk of cardiovascular disease. The Glucose Lowering through Weight management (GLoW) trial will evaluate whether a tailored diabetes education and behavioural weight management programme (DEW) is more effective and cost-effective than a diabetes education (DE) programme in helping people with overweight or obesity and a recent diagnosis of T2D to lower their blood glucose, lose weight and improve other markers of cardiovascular risk. METHODS AND ANALYSIS: This study is a pragmatic, randomised, single-blind, parallel group, two-arm, superiority trial. We will recruit 576 adults with body mass index>25 kg/m(2) and diagnosis of T2D in the past 3 years and randomise them to a tailored DEW or a DE programme. Participants will attend measurement appointments at a local general practitioner practice or research centre at baseline, 6 and 12 months. The primary outcome is 12-month change in glycated haemoglobin. The effect of the intervention on the primary outcome will be estimated and tested using a linear regression model (analysis of covariance) including randomisation group and adjusted for baseline value of the outcome and the randomisation stratifiers. Participants will be included in the group to which they were randomised, under the intention-to-treat principle. Secondary outcomes include 6-month and 12-month changes in body weight, body fat percentage, systolic and diastolic blood pressure and lipid profile; probability of achieving good glycaemic control; probability of achieving remission from diabetes; probability of losing 5% and 10% body weight and modelled cardiovascular risk (UKPDS). An intention-to-treat within-trial cost-effectiveness analysis will be conducted from NHS and societal perspectives using participant-level data. Qualitative interviews will be conducted with participants to understand why and how the programme achieved its results and how participants manage their weight after the programme ends. ETHICS AND DISSEMINATION: Ethical approval was received from East of Scotland Research Ethics Service on 15 May 2018 (18/ES/0048). This protocol (V.3) was approved on 19 June 2019. Findings will be published in peer-reviewed scientific journals and communicated to other stakeholders as appropriate. TRIAL REGISTRATION NUMBER: ISRCTN18399564.

[7] *Kuang ZM*. **Effect of Combined Antihypertensive and Lipid-Lowering Therapies on Cognitive Function: A New Treatment Strategy?** Cardiology research and practice 2020; 2020:1484357.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32351732
ABSTRACT
Risk factors for cardiovascular disease such as hypertension and hyperlipidemia are associated with cognitive decline. However, there is still no clear evidence that the use of antihypertensive or lipid-lowering therapy can prevent or delay cognitive decline or development of dementia. To provide a reference for clinical treatment, we analyzed the potential mechanisms of cognitive dysfunction induced by hypertension and hyperlipidemia, the clinical research and controversy of antihypertensive and lipid-lowering therapies on cognitive function, and the clinical value of combined antihypertensive and lipid-lowering therapy. It is currently believed that hypertension and elevated blood cholesterol levels in

middle-aged people may be related to cognitive impairment or dementia in the elderly. Some studies suggest that intensive antihypertensive or lipid-lowering therapies are better than standard antihypertensive or lipid-lowering therapy, yet further tests are needed to confirm their effects on cognitive function. Actively controlling potential risk factors from middle age may be important for Alzheimer's disease (AD) prevention.

[8] *Cho JH, Kim EC, Son Y et al.* **CD9 induces cellular senescence and aggravates atherosclerotic plaque formation**. Cell Death Differ 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32346137
ABSTRACT
CD9, a 24 kDa tetraspanin membrane protein, is known to regulate cell adhesion and migration, cancer progression and metastasis, immune and allergic responses, and viral infection. CD9 is upregulated in senescent endothelial cells, neointima hyperplasia, and atherosclerotic plaques. However, its role in cellular senescence and atherosclerosis remains undefined. We investigated the potential mechanism for CD9-mediated cellular senescence and its role in atherosclerotic plaque formation. CD9 knockdown in senescent human umbilical vein endothelial cells significantly rescued senescence phenotypes, while CD9 upregulation in young cells accelerated senescence. CD9 regulated cellular senescence through a phosphatidylinositide 3 kinase-AKT-mTOR-p53 signal pathway. CD9 expression increased in arterial tissues from humans and rats with age, and in atherosclerotic plaques in humans and mice. Anti-mouse CD9 antibody noticeably prevented the formation of atherosclerotic lesions in ApoE(-/-) mice and Ldlr(-/-) mice. Furthermore, CD9 ablation in ApoE(-/-) mice decreased atherosclerotic lesions in aorta and aortic sinus. These results suggest that CD9 plays critical roles in endothelial cell senescence and consequently the pathogenesis of atherosclerosis, implying that CD9 is a novel target for prevention and treatment of vascular aging and atherosclerosis.

[9] *Asai R, Kaneko T, Seki M, Tsuruoka S*. **Effective improvement of minimal change nephrotic syndrome with uncontrollable high low-density lipoprotein cholesterol level using evolocumab accompanied by the development of acute pancreatitis**. CEN case reports 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32358739
ABSTRACT
Nephrotic syndrome is sometimes refractory; however, it is rarely accompanied by acute pancreatitis. A 47-year-old Japanese woman complaining of limb edema was diagnosed with nephrotic syndrome. Blood and urine examinations suggested minimal change nephrotic syndrome (MCNS), and pulse intravenous methylprednisolone was administered, followed by oral prednisolone. Although proteinuria improved, the patient's condition remained unchanged, and diuresis was insufficient. As in patients with other nephrotic syndromes, this patient showed significant dyslipidemia. Atorvastatin was started for remarkable dyslipidemia since her admission, but her low-density lipoprotein cholesterol (LDL-C) level did not improve significantly. During the clinical course, she developed acute pancreatitis, and large-volume fluid replacement was performed. Although diuretic levels were increased in response to the increased fluid volume, diuresis was not enough, and lung edema developed. Extracorporeal ultrafiltration was started to ameliorate the lung edema. With the onset of pancreatitis, oral intake, including atorvastatin, was discontinued, and prednisolone was administered

intravenously. To treat the high-LDL cholesterolemia, 140 mg of evolocumab was injected subcutaneously. Nausea slightly decreased on the following day, and the administration of 150 mg cyclosporine was initiated. LDL-C levels, proteinuria, and renal function promptly ameliorated. The results of a renal biopsy suggested MCNS. On the 44th day of hospitalization, she had complete remission. Evolocumab is potentially effective for severe nephrotic syndrome with uncontrollable dyslipidemia.

[10] *Jang AY, Han SH, Sohn IS et al.* **Lipoprotein(a) and Cardiovascular Diseases-Revisited**. Circulation journal : official journal of the Japanese Circulation Society 2020; 84:867-874.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32336721
ABSTRACT
Two decades ago, it was recognized that lipoprotein(a) (Lp(a)) concentrations were elevated in patients with cardiovascular disease (CVD). However, the importance of Lp(a) was not strongly established due to a lack of both Lp(a)-lowering therapy and evidence that reducing Lp(a) levels improves CVD risk. Recent advances in clinical and genetic research have revealed the crucial role of Lp(a) in the pathogenesis of CVD. Mendelian randomization studies have shown that Lp(a) concentrations are causal for different CVDs, including coronary artery disease, calcified aortic valve disease, stroke, and heart failure, despite optimal low-density lipoprotein cholesterol (LDL-C) management. Lp(a) consists of apolipoprotein (apo) B100 covalently bound to apoA. Thus, Lp(a) has atherothrombotic traits of both apoB (from LDL) and apoA (thrombo-inflammatory aspects). Although conventional pharmacological therapies, such as statin, niacin, and cholesteryl ester transfer protein, have failed to significantly reduce Lp(a) levels, emerging new therapeutic strategies using proprotein convertase subtilisin-kexin type 9 inhibitors or antisesnse oligonucleotide technology have shown promising results in effectively lowering Lp(a). In this review we discuss the revisited important role of L(a) and strategies to overcome residual risk in the statin era.

[11] *Sharma M, Schlegel MP, Afonso MS et al.* **Regulatory T Cells License Macrophage Pro-Resolving Functions During Atherosclerosis Regression**. Circulation research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32336197
ABSTRACT
Rationale: Regression of atherosclerosis is an important clinical goal, however the pathways that mediate the resolution of atherosclerotic inflammation and reversal of plaques are poorly understood. Regulatory T cells (Tregs) have been shown to be atheroprotective, yet the numbers of these immunosuppressive cells decrease with disease progression, and whether they contribute to atherosclerosis regression is not known. Objective: We investigated the roles of Tregs in the resolution of atherosclerotic inflammation, tissue remodeling and plaque contraction during atherosclerosis regression. Methods and Results: Using multiple independent mouse models of atherosclerosis regression, we demonstrate that an increase in plaque Tregs is a common signature of regressing plaques. Single cell RNA-sequencing of plaque immune cells from revealed that Tregs from regressing plaques shared some similarity with splenic Tregs, but were distinct from skin and colon Tregs supporting recent findings of tissue-dependent Treg heterogeneity. Unlike Tregs from progressing plaques that expressed markers of natural Tregs derived from the thymus, Tregs in regressing plaques lacked Nrp1 and Helios expression, suggesting that they are induced in the periphery during lipid lowering

therapy. To test whether Tregs are required for resolution of atherosclerotic inflammation and plaque regression, Tregs were depleted using CD25 monoclonal antibody in atherosclerotic mice during apolipoprotein B anti-sense oligonucleotide-mediated lipid lowering. Morphometric analyses revealed that Treg depletion blocked plaque remodeling and contraction, and impaired hallmarks of inflammation resolution including dampening of the Th1 response, alternative activation of macrophages, efferocytosis, and upregulation of specialized pro-resolving lipid mediators. Conclusions: Our data establish essential roles for Tregs in resolving atherosclerotic cardiovascular disease and provide mechanistic insight into the pathways governing plaque remodeling and regression of disease.

[12] *Liu Y, Smith CE, Parnell LD et al.* **Salivary AMY1 Copy Number Variation Modifies Age-Related Type 2 Diabetes Risk**. Clinical chemistry 2020; 66:718-726.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32337541
ABSTRACT
BACKGROUND: Copy number variation (CNV) in the salivary amylase gene (AMY1) modulates salivary alpha-amylase levels and is associated with postprandial glycemic traits. Whether AMY1-CNV plays a role in age-mediated change in insulin resistance (IR) is uncertain. METHODS: We measured AMY1-CNV using duplex quantitative real-time polymerase chain reaction in two studies, the Boston Puerto Rican Health Study (BPRHS, n = 749) and the Genetics of Lipid-Lowering Drug and Diet Network study (GOLDN, n = 980), and plasma metabolomic profiles in the BPRHS. We examined the interaction between AMY1-CNV and age by assessing the relationship between age with glycemic traits and type 2 diabetes (T2D) according to high or low copy numbers of the AMY1 gene. Furthermore, we investigated associations between metabolites and interacting effects of AMY1-CNV and age on T2D risk. RESULTS: We found positive associations of IR with age among subjects with low AMY1-copy-numbers in both studies. T2D was marginally correlated with age in participants with low AMY1-copy-numbers but not with high AMY1-copy-numbers in the BPRHS. Metabolic pathway enrichment analysis identified the pentose metabolic pathway based on metabolites that were associated with both IR and the interactions between AMY1-CNV and age. Moreover, in older participants, high AMY1-copy-numbers tended to be associated with lower levels of ribonic acid, erythronic acid, and arabinonic acid, all of which were positively associated with IR. CONCLUSIONS: We found evidence supporting a role of AMY1-CNV in modifying the relationship between age and IR. Individuals with low AMY1-copy-numbers tend to have increased IR with advancing age.

[13] *Gutierrez E, Faraji M, Pacheco L*. **Weak Knees: A Case of Atorvastatin-induced Dermatomyositis**. Cureus 2020; 12:e7387.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32337114
ABSTRACT
HMG-CoA reductase inhibitors (statins) are one of the most widely used medications in the primary care setting, and like any medications they have many side effects. The common ones include myalgias and rare ones include dermatomyositis. Here we present the case of atorvastatin-induced dermatomyositis with an unfortunate progression. This mandates a low threshold for first contact doctors to screen their patients for new-onset muscle weakness and rash after starting a statin recently, like our patient who had started atorvastatin several months before. This case adds to the previously reported cases and provides further evidence

for statins being triggers of immune-mediated disease. The appropriate management of this condition requires a collaborative effort involving clinical judgment, laboratory testing, and imaging.

[14] *Bahrami A, Sathyapalan T, Sahebkar A*. **The role of interleukin-18 in the development and progression of atherosclerosis**. Curr Med Chem 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32338205
ABSTRACT
Atherosclerosis (AS) as a chronic inflammatory disorder of the cardiovascular system, is one of the leading cause of ischemic heart disease, stroke and peripheral vascular disease. There is growing evidence on the role of innate and adaptive immunity in the pathogenesis of atherosclerosis. Interleukin-18 is one of the novel proinflammatory cytokines involved in the atherogenesis, atherosclerotic plaque instability and plaque rupture. In this review, we overview the findings of the preclinical and clinical studies about the role and mechanism of action of IL-18 in the pathogenesis of AS, which could offer novel prognostic and therapeutic approaches.

[15] *Tewari D, Sah AN, Bawari S et al.* **Role of Nitric oxide in neurodegeneration: function, regulation and inhibition**. Curr Neuropharmacol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32348225
ABSTRACT
Reactive nitrogen species (RNS) and reactive oxygen species (ROS) collectively known as reactive oxygen and nitrogen species (RONS) are the products of normal cellular metabolism and interact with several vital biomolecules including nucleic acid, proteins, and membrane lipids and alter their function in an irreversible manner which can lead finally to cell death. There is an imperative role for oxidative stress in the pathogenesis of cognitive impairments and the development and progression of neural injury. Elevated production of higher amounts of nitric oxide (NO) takes place in numerous pathological conditions such as neurodegenerative diseases, inflammation, and ischemia which occur concurrently with elevated nitrosative/oxidative stress. The enzyme nitric oxide synthase (NOS) is responsible for the generation of NO in different cells by conversion of L-arginine (Arg) to L-citrulline. Therefore, the NO signaling pathway represents a viable therapeutic target. Naturally occurring polyphenols targeting the NO signaling pathway can be of major importance in the field of neurodegeneration and related complications. Here we comprehensively review the importance of NO and its production in the human body and afterwards highlight the importance of various natural products along with their mechanisms against various neurodegenerative diseases involving their effect on NO production.

[16] *Sarmah D, Datta A, Raut S et al.* **Role of Inflammasomes in Atherosclerosis and Stroke Pathogenesis**. Current pharmaceutical design 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32338208
ABSTRACT
Inflammation is a devastating outcome of cerebrovascular diseases (CVD), namely stroke and atherosclerosis. Numerous studies over the decade have shown that inflammasomes play a role in mediating inflammatory reactions post cellular injury occurring after stroke or a rupture of an atherosclerotic plaque. In view of this, targeting these inflammatory pathways using

different pharmacological therapies may improve outcomes in patients with CVD. Here we review the mechanisms by which inflammasomes drive the pathogenesis of stroke and atherosclerosis. Also discussed here are the possible treatment strategies available for inhibiting inflammasomes or their up-stream/down-stream mediators.

[17] *Kim NH, Kim SG*. **Fibrates Revisited: Potential Role in Cardiovascular Risk Reduction**. Diabetes Metab J 2020; 44:213-221.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32347023
ABSTRACT
Fibrates, peroxisome proliferator-activated receptor-alpha agonists, are potent lipid-modifying drugs. Their main effects are reduction of triglycerides and increase in high-density lipoprotein levels. Several randomized controlled trials have not demonstrated their benefits on cardiovascular risk reduction, especially as an "add on" to statin therapy. However, subsequent analyses by major clinical trials, meta-analyses, and real-world evidence have proposed their potential in specific patient populations with atherogenic dyslipidemia and metabolic syndrome. Here, we have reviewed and discussed the accumulated data on fibrates to understand their current status in cardiovascular risk management.

[18] *Cicero AFG, Pontremoli R, Fogacci F et al.* **Effect of Bempedoic Acid on Serum Uric Acid and Related Outcomes: A Systematic Review and Meta-analysis of the available Phase 2 and Phase 3 Clinical Studies**. Drug Saf 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32358698
ABSTRACT
INTRODUCTION: Bempedoic acid (ETC-1002) is a first-in-class lipid-lowering agent recently approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for commercialization. OBJECTIVE: The aim was to assess, through a systematic review of the literature and a meta-analysis of the available phase 2 and phase 3 clinical studies, the effect of treatment with bempedoic acid on serum uric acid (SUA) concentration. Secondary outcomes were treatment-related variations in creatinine serum level and incidence of gout. METHODS: A systematic literature search in SCOPUS, PubMed Medline, ISI Web of Science and Google Scholar databases was conducted up to November 13th, 2019, in order to identify clinical trials potentially eligible for the meta-analysis. Effect sizes were expressed as absolute mean differences (MDs) and 95% confidence intervals (CIs). RESULTS: Data were pooled from four clinical studies comprising ten arms, which included overall 3369 subjects, with 2213 in the active-treatment arm and 1156 in the control one. Meta-analysis of data suggested that treatment with bempedoic acid is related to a significant increase in SUA (MD 0.73, 95% CI 0.54-0.91, P < 0.001), serum creatinine (MD 0.04, 95% CI 0.03-0.05, P < 0.001) and the incidence of gout (odds ratio 3.56, 95% CI 1.24-10.19, P = 0.018). The relatively small number of subjects involved in the studies and the exclusion of patients with renal impairment from the clinical trials are important limitations of the meta-analysis. However, our data indicate potential safety issues with bempedoic acid and suggest that further studies are performed both to elucidate the pathogenetic mechanisms underlying these associations and to verify the long-term safety of this treatment. CONCLUSION: Bempedoic acid seems to have unfavourable effects on SUA, creatinine level and the incidence of gout. The ongoing Cardiovascular Outcomes Trial (CVOT) will explore the

longer-term safety of treatment with bempedoic acid and clarify its effect on cardiovascular events and mortality. PROSPERO DATABASE REGISTRATION: CRD42019146126.

[19] *Ou M, Li X, Zhao S et al.* **Long non-coding RNA CDKN2B-AS1 contributes to atherosclerotic plaque formation by forming RNA-DNA triplex in the CDKN2B promoter**. EBioMedicine 2020; 55:102694.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32335370
ABSTRACT
BACKGROUND: Atherosclerosis involves a slow process of plaque formation on the walls of arteries, and comprises a leading cause of cardiovascular disease. Long non-coding RNAs (lncRNAs) have been implicated in the pathogenesis of atherosclerosis. In this study, we aim to explore the possible involvement of lncRNA 'cyclin-dependent kinase inhibitor 2B antisense noncoding RNA' (CDKN2B-AS1) and CDKN2B in the progression of atherosclerosis. METHODS: Initially, we quantified the expression of CDKN2B-AS1 in atherosclerotic plaque tissues and, in THP-1 macrophage-derived, and human primary macrophage (HPM)-derived foam cells. Next, we established a mouse model of atherosclerosis using apolipoprotein E knockout (ApoE(-/-)) mice, where lipid uptake, lipid accumulation, and macrophage reverse cholesterol transport (mRCT) were assessed, in order to explore the contributory role of CDKN2B-AS1 to the progression of atherosclerosis. RIP and ChIP assays were used to identify interactions between CDKN2B-AS1, CCCTC-binding factor (CTCF), enhancer of zeste homologue 2 (EZH2), and CDKN2B. Triplex formation was determined by RNA-DNA pull-down and capture assay as well as EMSA experiment. FINDINGS: CDKN2B-AS1 showed high expression levels in atherosclerosis, whereas CDKN2B showed low expression levels. CDKN2B-AS1 accelerated lipid uptake and intracellular lipid accumulation whilst attenuating mRCT in THP-1 macrophage-derived foam cells, HPM-derived foam cells, and in the mouse model. EZH2 and CTCF were found to bind to the CDKN2B promoter region. An RNA-DNA triplex formed by CDKN2B-AS1 and CDKN2B promoter was found to recruit EZH2 and CTCF in the CDKN2B promoter region and consequently inhibit CDKN2B transcription by accelerating histone methylation. INTERPRETATION: The results demonstrated that CDKN2B-AS1 promotes atherosclerotic plaque formation and inhibits mRCT in atherosclerosis by regulating CDKN2B promoter, and thereby could be a potential therapeutic target for atherosclerosis.

[20] *Landmesser U, Poller W, Tsimikas S et al.* **From traditional pharmacological towards nucleic acid-based therapies for cardiovascular diseases**. European heart journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350510
ABSTRACT
Nucleic acid-based therapeutics are currently developed at large scale for prevention and management of cardiovascular diseases (CVDs), since: (i) genetic studies have highlighted novel therapeutic targets suggested to be causal for CVD; (ii) there is a substantial recent progress in delivery, efficacy, and safety of nucleic acid-based therapies; (iii) they enable effective modulation of therapeutic targets that cannot be sufficiently or optimally addressed using traditional small molecule drugs or antibodies. Nucleic acid-based therapeutics include (i) RNA-targeted therapeutics for gene silencing; (ii) microRNA-modulating and epigenetic therapies; (iii) gene therapies; and (iv) genome-editing approaches (e.g. CRISPR-Cas-based): (i) RNA-targeted therapeutics: several large-scale clinical development programmes, using

antisense oligonucleotides (ASO) or short interfering RNA (siRNA) therapeutics for prevention and management of CVD have been initiated. These include ASO and/or siRNA molecules to lower apolipoprotein (a) [apo(a)], proprotein convertase subtilisin/kexin type 9 (PCSK9), apoCIII, ANGPTL3, or transthyretin (TTR) for prevention and treatment of patients with atherosclerotic CVD or TTR amyloidosis. (ii) MicroRNA-modulating and epigenetic therapies: novel potential therapeutic targets are continually arising from human non-coding genome and epigenetic research. First microRNA-based therapeutics or therapies targeting epigenetic regulatory pathways are in clinical studies. (iii) Gene therapies: EMA/FDA have approved gene therapies for non-cardiac monogenic diseases and LDL receptor gene therapy is currently being examined in patients with homozygous hypercholesterolaemia. In experimental studies, gene therapy has significantly improved cardiac function in heart failure animal models. (iv) Genome editing approaches: these technologies, such as using CRISPR-Cas, have proven powerful in stem cells, however, important challenges are remaining, e.g. low rates of homology-directed repair in somatic cells such as cardiomyocytes. In summary, RNA-targeted therapies (e.g. apo(a)-ASO and PCSK9-siRNA) are now in large-scale clinical outcome trials and will most likely become a novel effective and safe therapeutic option for CVD in the near future. MicroRNA-modulating, epigenetic, and gene therapies are tested in early clinical studies for CVD. CRISPR-Cas-mediated genome editing is highly effective in stem cells, but major challenges are remaining in somatic cells, however, this field is rapidly advancing.

[21] *Lippi G, Favaloro EJ, Sanchis-Gomar F*. **Antisense lipoprotein[a] therapy: State-of-the-art and future perspectives**. European journal of internal medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32336611

ABSTRACT

Several lines of evidence now attest that lipoprotein[a] (Lp[a]) is a significant risk factor for many cardiovascular disorders. This enigmatic lipoprotein, composed of a single copy of apolipoprotein B (apoB) and apolipoprotein[a] (apo [a]), expresses peculiar metabolism, virtually independent from lifestyle interventions. Several therapeutic options have hence been proposed for lowering elevated Lp[a] values, with or without concomitant effect on low density lipoprotein (LDL) particles, mostly encompassing statins, ezetimibe, nicotinic acid, lipoprotein apheresis, and anti-PCSK9 monoclonal antibodies. Since all these medical treatments have some technical and clinical drawbacks, a novel strategy is currently being proposed, based on the use of antisense apo[a] and/or apoB inhibitors. Although the role of these agents in hypercholesterolemic patients is now nearby entering clinical practice, the collection of information on Lp[a] is still underway. Preliminary evidence would suggest that apo[a] antisense therapy seems more appropriate in patients with isolated Lp[a] elevations, while apoB antisense therapy is perhaps more advisable in patients with isolated LDL elevations. In patients with concomitant elevations of Lp[a] and LDL, either combining the two apo[a] and apoB antisense therapies (a strategy which has never been tested), or the combination of well-known and relatively inexpensive drugs such as statins with antisense apo[a] inhibitors can be theoretically suggested. The results of an upcoming phase 3 study with antisense apo[a] inhibitors will hopefully provide definitive clues as to whether this approach may become the standard of care in patients with increased Lp[a] concentrations.

[22] *Saito Y, Nakayama A, Sato T et al.* **Lipid-lowering statin therapy is beneficial in elderly female patients with hypercholesterolaemia and diabetic retinopathy**. European journal of preventive cardiology 2020:2047487320920761.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32340464
ABSTRACT

[23] *Sun Y, Chen L, Zhao S et al.* **Effects of nanoparticle-mediated delivery of pitavastatin on atherosclerotic plaques in ApoE-knockout mice and THP-1-derived macrophages**. Experimental and therapeutic medicine 2020; 19:3787-3797.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32346443
ABSTRACT
The treatment of atherosclerosis remains complex. Pitavastatin serves an important role in the prevention and treatment of atherosclerosis. The present study aimed to investigate the effects of nanoparticle (NP)-mediated delivery of pitavastatin into atherosclerotic plaques as a novel treatment method for atherosclerosis. The results of the present study demonstrated that pitavastatin-NP was more effective in attenuating the size of atherosclerotic plaques and enhancing the stability of plaques in vitro compared with pitavastatin alone. In an apolipoprotein E (ApoE)-knockout mouse model of atherosclerosis, a single intravenous injection of fluorescein isothiocyanate-NP resulted in the delivery of NP into atherosclerotic plaques for up to 7 days post-injection. In ApoE-knockout mice and THP-1-derived macrophages, pitavastatin-NP attenuated the development of atherosclerosis, which was associated with regulating lipid metabolism, and inhibited the secretion of inflammatory markers compared with pitavastatin alone. Additionally, the treatment advantages of pitavastatin-NP were independent of lipid lowering. The results demonstrated that pitavastatin-NP administration was more effective in attenuating the development of atherosclerotic plaques compared with systemic administration of pitavastatin.

[24] *Tromp TR, Stroes ESG, Hovingh GK*. **Gene-based therapy in lipid management: the winding road from promise to practice**. Expert opinion on investigational drugs 2020; 29:483-493.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32349563
ABSTRACT
INTRODUCTION: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality. High plasma low-density lipoprotein cholesterol (LDL-C) levels are a key CVD-risk factor. Triglyceride-rich remnant particles and lipoprotein(a) (Lp[a]) are also causally related to CVD. Consequently, therapeutic strategies for lowering LDL-C and triglyceride levels are widely used in routine clinical practice; however, specific Lp(a) lowering agents are not available. Many patients do not achieve guideline-recommended lipid levels with currently available therapies; hence, novel targets and treatment modalities are eagerly sought. AREAS COVERED: We discuss the milestones on the trajectory toward the full application of gene-based therapies in daily clinical practice. We describe the different methods, ranging from antisense oligonucleotides to liver-directed gene therapy and Crispr-cas9 modification to target the pivotal players in lipid metabolism: PCSK9, APOB, ANGPTL3, Lp(a), LDLR, and apoC-III. EXPERT OPINION: While acknowledging their different stages of development, gene-based therapies are likely to invoke a paradigm shift in lipid management because they allow us to target previously undruggable targets. Moreover, their low dosing frequency, high target

selectivity, and relatively predictable adverse event profile are considered major advantages over current lipid-lowering therapies.

[25] *Chaikijurajai T, Tang WHW*. **Myeloperoxidase: a potential therapeutic target for coronary artery disease**. Expert opinion on therapeutic targets 2020:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32336171
ABSTRACT
Introduction: Coronary artery disease (CAD) poses significant morbidity and mortality globally. Despite significant advances in treatment interventions, residual cardiovascular risks remain unchecked. Recent clinical trials have shed light on the potential therapeutic benefits of targeting anti-inflammatory pathways. Myeloperoxidase (MPO) plays an important role in atherosclerotic plaque formation and destabilization of the fibrous cap; both increase the risk of atherosclerotic cardiovascular disease and especially CAD.Areas covered: This article examines the role of MPO in the pathogenesis of atherosclerotic CAD and the mechanistic data from several key therapeutic drug targets. There have been numerous interesting studies on prototype compounds that directly or indirectly attenuate the enzymatic activities of MPO, and subsequently exhibit atheroprotective effects; these include aminobenzoic acid hydrazide, ferulic acid derivative (INV-315), thiouracil derivatives (PF-1355 and PF-06282999), 2-thioxanthines derivative (AZM198), triazolopyrimidines, acetaminophen, N-acetyl lysyltyrosylcysteine (KYC), flavonoids, and alternative substrates such as thiocyanate and nitroxide radical.Expert opinion: Future investigations must determine if the cardiovascular benefits of direct systemic inhibition of MPO outweigh the risk of immune dysfunction, which may be less likely to arise with alternative substrates or MPO inhibitors that selectively attenuate atherogenic effects of MPO.

[26] *Bi C, Fu Y, Zhang Z, Li B*. **Prostaglandin E2 confers protection against diabetic coronary atherosclerosis by stimulating M2 macrophage polarization via the activation of the CREB/BDNF/TrkB signaling pathway**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350920
ABSTRACT
It has been documented that M2 macrophage polarization plays a suppressive role in atherosclerosis in diabetes mellitus (DM). In addition, prostaglandin E2 (PGE2) is implicated in the development of M2 macrophage polarization. Therefore, the study aimed to investigate the specific mechanism of PGE2 in M2 macrophage polarization in diabetic coronary atherosclerosis (DMAS). Initially, clinical samples were obtained and DMAS mouse model was established. The expression of BDNF was determined, and M1 and M2 macrophage polarizations were evaluated. Then, the levels of BDNF and PGE2 were modified in DMAS mice and the serum indicator, atherosclerotic plaque, lipid uptake by PBMCs, as well as M1 and M2 macrophage polarization were determined. Macrophages were isolated and the effects of PGE2 and the CREB/BDNF/TrkB signaling pathway on M2 macrophage polarization were explored. BDNF was downregulated and macrophages were differentiated into M1 in DMAS patients and mice. BDNF and PGE2 were observed to promote M2 macrophage polarization, where atherosclerotic plaque and lipid uptake by PBMCs were reduced, and DMAS was alleviated in mice. Overexpression of BDNF activated the CREB/BDNF/TrkB signaling pathway and stimulated M2 macrophage polarization in macrophages. PGE2 stimulated M2

macrophage polarization by inducing KLF4 via the activation of the CREB/BDNF/TrkB signaling pathway. This study demonstrates that PGE2 promotes M2 macrophage polarization by activating the CREB/BDNF/TrkB signaling pathway, thus alleviating DMAS.

[27] *Pirillo A, Norata GD, Catapano AL*. **LDL-Cholesterol-Lowering Therapy**. Handbook of experimental pharmacology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350699
ABSTRACT
The causal relation between elevated levels of LDL-C and cardiovascular disease has been largely established by experimental and clinical studies. Thus, the reduction of LDL-C levels is a major target for the prevention of cardiovascular disease. In the last decades, statins have been used as the main therapeutic approach to lower plasma cholesterol levels; however, the presence of residual lipid-related cardiovascular risk despite maximal statin therapy raised the need to develop additional lipid-lowering drugs to be used in combination with or in alternative to statins in patients intolerant to the treatment. Several new drugs have been approved which have mechanisms of action different from statins or impact on different lipoprotein classes.

[28] *Suwa S, Ogita M, Takahashi N et al.* **Impact of LR11 as Residual Risk on Long-Term Clinical Outcomes in Patients with Coronary Artery Disease Treated with Statins after First Percutaneous Coronary Intervention**. Int Heart J 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350212
ABSTRACT
Cardiovascular events still occur despite statin-based lipid-lowering therapy in patients with coronary artery disease (CAD). LR11, a member of the low-density lipoprotein receptor family, is a novel marker for the proliferation of intimal smooth muscle cells, which are critical to atherosclerotic plaque formation. We evaluated the impact of LR11 on long-term clinical outcomes in CAD patients treated with statins after percutaneous coronary intervention (PCI).This study included 223 consecutive CAD patients (age, 64.5 +/- 9.6 years; male, 81.2%) treated with statin after first PCI between March 2003 and December 2004 at our institution. Patients were stratified to two groups according to LR11 levels (median). Composite cardiovascular disease (CVD) endpoints that included cardiovascular death, non-fatal acute coronary syndrome and non-fatal stroke were compared between groups.The rate of CVD endpoints was significantly higher in the high LR11 group (log-rank, P = 0.0029) during the median follow-up period of 2844 days. Multivariate Cox regression analysis showed that a higher LR11 level was significantly associated with adverse clinical outcomes (adjusted hazard ratio for composite CVD endpoints, 2.47; 95% confidence interval, 1.29-4.92; P = 0.006).Elevated levels of LR11 were significantly associated with long-term clinical outcomes among CAD patients treated with statins after first PCI.

[29] *Ce O, Rs P, Ab W et al.* **Potential Link Between Proprotein Convertase Subtilisin/Kexin Type 9 and Alzheimer's Disease**. International journal of biomedical investigation 2018; 1.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32352077
ABSTRACT
Alzheimer's disease [AD] is not only the most common neurodegenerative disease but is also currently incurable. Proprotein convertase subtilisin/kexin-9 [PCSK9] is an indirect regulator of

plasma low density lipoprotein [LDL] levels controlling LDL receptor expression at the plasma membrane. PCSK9 also appears to regulate the development of glucose intolerance, insulin resistance, abdominal obesity, inflammation, and hypertension, conditions that have been identified as risk factors for AD. PCSK9 levels also depend on age, sex, and ethnic background, factors associated with AD. Herein, we will review indirect evidence that suggests a link between PCSK9 levels and AD.

[30] *Cas MD, Roda G, Li F, Secundo F*. **Functional Lipids in Autoimmune Inflammatory Diseases**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32349258
ABSTRACT
Lipids are apolar small molecules known not only as components of cell membranes but also, in recent literature, as modulators of different biological functions. Herein, we focused on the bioactive lipids that can influence the immune responses and inflammatory processes regulating vascular hyperreactivity, pain, leukocyte trafficking, and clearance. In the case of excessive pro-inflammatory lipid activity, these lipids also contribute to the transition from acute to chronic inflammation. Based on their biochemical function, these lipids can be divided into different families, including eicosanoids, specialized pro-resolving mediators, lysoglycerophospholipids, sphingolipids, and endocannabinoids. These bioactive lipids are involved in all phases of the inflammatory process and the pathophysiology of different chronic autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, type-1 diabetes, and systemic lupus erythematosus.

[31] *Mushenkova NV, Summerhill VI, Zhang D et al.* **Current Advances in the Diagnostic Imaging of Atherosclerosis: Insights into the Pathophysiology of Vulnerable Plaque**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32340284
ABSTRACT
Atherosclerosis is a lipoprotein-driven inflammatory disorder leading to a plaque formation at specific sites of the arterial tree. After decades of slow progression, atherosclerotic plaque rupture and formation of thrombi are the major factors responsible for the development of acute coronary syndromes (ACSs). In this regard, the detection of high-risk (vulnerable) plaques is an ultimate goal in the management of atherosclerosis and cardiovascular diseases (CVDs). Vulnerable plaques have specific morphological features that make their detection possible, hence allowing for identification of high-risk patients and the tailoring of therapy. Plaque ruptures predominantly occur amongst lesions characterized as thin-cap fibroatheromas (TCFA). Plaques without a rupture, such as plaque erosions, are also thrombi-forming lesions on the most frequent pathological intimal thickening or fibroatheromas. Many attempts to comprehensively identify vulnerable plaque constituents with different invasive and non-invasive imaging technologies have been made. In this review, advantages and limitations of invasive and non-invasive imaging modalities currently available for the identification of plaque components and morphologic features associated with plaque vulnerability, as well as their clinical diagnostic and prognostic value, were discussed.

[32] *Kang HJ, Kim MH, Sung J et al.* **Effect of Probucol and/or Cilostazol on Carotid Intima Media Thickness in Patients with Coronary Heart Disease: A Randomized, Multicenter, Multinational Study**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32336696
ABSTRACT
AIM: In a prospective randomized multinational open blinded endpoint study, the long-term effects of probucol or probucol and cilostazol with statin on carotid mean intima media thickness (IMT) were evaluated for the first time. METHODS: Hypercholesterolemic patients with coronary artery disease were randomized to three groups and received study drugs for 3 years: the control with statin alone; the probucol group with statin and probucol; and the combo group with statin, probucol, and cilostazol. Primary efficacy endpoint was changes of mean carotid IMT at 3 years. Biomarkers, major adverse cerebro-cardiovascular events (MACCEs) and safety were secondary endpoints. RESULTS: Two hundred eighty-one patients were randomized into three groups. All three groups showed significant regression of carotid IMT at 3 years compared with baseline. Decrease in mean carotid IMT was significantly greater in the combo group than in the control group at 1 year. However, there were no significant differences in changes of mean carotid IMT between groups at 3 years (control; -0.12+/-0.36 mm vs. probucol; -0.11 +/-0.32 mm vs. combo; -0.16+/-0.38 mm). MACCEs were frequent in the control group, but the difference was not significant (control; 10.8% vs. probucol; 4.4% vs. combo; 6.9%, p=0.35). Probucol and cilostazol were well tolerated in long-term treatment without serious drug-related adverse reactions. CONCLUSION: Probucol or probucol and cilostazol with statin did not reduce carotid IMT in comparison with statin alone in this study. However, the clinical outcome of probucol-based treatment with current standard statin treatment may need further studies.

[33] *Tada H, Usui S, Sakata K et al.* **Low-Density Lipoprotein Cholesterol Level cannot be too Low: Considerations from Clinical Trials, Human Genetics, and Biology**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350167
ABSTRACT
LDL cholesterol is by far the best established "causal" cardiovascular risk. It is distributed normally, and the mean value ranges around 100~120 mg/dl. In terms of preventive cardiology, we now know very well that the lower the LDL cholesterol, the better. Clinical usefulness of aggressive LDL-lowering therapies using statin, ezetimibe, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have been shown in primary and in secondary prevention settings. Additionally, the idea, based on recent randomized controlled trials (RCT), that the lower LDL cholesterol the better appears to be true for LDL as low as ~ 30 mg/dl. According to those data, recent guidelines in Europe and in Japan suggest the lowering of LDL cholesterol level 70 mg/dl for high-risk patients. However, the attainment rates of such "strict" goals seem to be quite low, probably because most cardiologists still have a sense of anxiety of "low" LDL cholesterol level. But "low" indicates no more than "lower" than the "average" range, which is not always implying the optimal range. Additionally, Mendelian randomization studies focusing on individuals exhibiting "low" LDL cholesterol suggest that "normal" LDL cholesterol levels might be too much for us. Moreover, LDL cholesterol levels of other primates are substantially lower than those in humans. In this review article, based on a series of evidence from clinical trials, human genetics, and biology, we provide the idea that

we need to rethink what is the optimal range of LDL cholesterol level, instead of "normal" or "average" range.

[34] *Yamashita S, Arai H, Bujo H et al.* **Probucol Trial for Secondary Prevention of Atherosclerotic Events in Patients with Coronary Heart Disease (PROSPECTIVE)**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32336695
ABSTRACT
AIMS: Although intensive statin therapy reduced cardiovascular risks, cardiovascular events have not been completely prevented. Probucol is a potent antioxidant and reduces tendon xanthomas in familial hypercholesterolemia patients despite reduction of high-density lipoprotein (HDL)-cholesterol (HDL-C). We investigated whether probucol can reduce cardiovascular events on top of conventional lipid-lowering therapy in patients with coronary heart disease (CHD). METHODS: PROSPECTIVE is a multicenter, randomized, prospective study that recruited 876 Japanese patients with CHD and dyslipidemia with an low-density lipoprotein (LDL)-cholesterol (HDL-C) level of >/= 140 mg/dL without medication or those treated with lipid-lowering drugs. Lipid-lowering agents were administered during the study period in the control group (n=438), and probucol 500 mg/day was added to lipid-lowering therapy in the probucol group (n=438). Patients were randomly assigned to two treatment groups by adjusting the LDL-C level and presence of diabetes and hypertension and followed up for more than 3 years. The primary end point was a composite of cerebrovascular and cardiovascular events (cardiovascular disease death including sudden death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization). The secondary end point was carotid intima-media thickness in a subset of patients. RESULTS: The incidence of the primary end point showed a trend to be lower in the probucol group compared with that in the control group despite reduced HDL-C without serious adverse events. Anti-atherogenic effects of probucol may be attributed to its potent antioxidative function and enhancement of reverse cholesterol transport. CONCLUSION: Since there was no statistical significance between the probucol and control groups despite a marked reduction of HDL-C, further studies on the clinical outcomes of probucol on top of conventional therapy may be necessary in the future (UMIN000003307).

[35] *El-Sayyad HIH, El-Gallil HA, El-Ghaweet HA*. **Synergistic effects of pomegranate juice and atorvastatin for improving cerebellar structure and function of breast-feeding rats maternally fed on a high cholesterol diet**. J Chem Neuroanat 2020; 107:101798.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32339653
ABSTRACT
A highly cholesterol-diet is associated with atherosclerosis and little about the development of cerebellar cortex disorder. The study illustrated the changes of cerebellar cortex of rat neonate maternally fed on high cholesterol diet and the capacity of pomegranate alone or in combination with atorvastatin to improve it. Eighty-eight pregnant Wister rats were divided into eight groups (n = 11); control, pomegranate supplemented group (daily orally 0.4 mL (20 %), atorvastatin (10 mg/kg BT), hypercholesterolemia (dietary consumption 3% cholesterol for 6 weeks prior to conception and throughout gestation and lactation period), hypercholesterolemia and pomegranate or atorvastatin, hypercholesterolemia and atorvastatin and pomegranate. Dams and their offspring were sacrificed at 21 days post-partum. Sera of

mother and cerebellum of offspring were investigated biochemically as well as histo-cytological changes of cerebellar cortex of offspring. Offspring maternally fed on high cholesterol diet showed damage of the cerebellar Purkinje and granular cells associated with demyelination, increased caspase 3 immunohistochemistry and increased DNA damage. These were associated with decreased brain neurotransmitters and increase apoptic markers. Dams supplemented pomegranate and/or atorvastatin improved the assayed parameters more than that of atorvastatin alone. The authors concluded that pomegranate juice contains potent antioxidant nutrients capable of reducing the cytotoxicity of hypercholesterolemia and atorvastatin, and enhancing the structure and function of the cerebellar cortex.

[36] *Papaioannou TG, Alexandraki KI, Tousoulis D*. **Arterial stiffness improvement after adding on PCSK9 inhibitors in patients with familial hypercholesterolemia**. Journal of clinical lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32354688
ABSTRACT

[37] *Spinelli R, Parrillo L, Longo M et al.* **Molecular basis of ageing in chronic metabolic diseases**. Journal of endocrinological investigation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32358737
ABSTRACT
AIM: Over the last decades, the shift in age distribution towards older ages and the progressive ageing which has occurred in most populations have been paralleled by a global epidemic of obesity and its related metabolic disorders, primarily, type 2 diabetes (T2D). Dysfunction of the adipose tissue (AT) is widely recognized as a significant hallmark of the ageing process that, in turn, results in systemic metabolic alterations. These include insulin resistance, accumulation of ectopic lipids and chronic inflammation, which are responsible for an elevated risk of obesity and T2D onset associated to ageing. On the other hand, obesity and T2D, the paradigms of AT dysfunction, share many physiological characteristics with the ageing process, such as an increased burden of senescent cells and epigenetic alterations. Thus, these chronic metabolic disorders may represent a state of accelerated ageing. MATERIALS AND METHODS: A more precise explanation of the fundamental ageing mechanisms that occur in AT and a deeper understanding of their role in the interplay between accelerated ageing and AT dysfunction can be a fundamental leap towards novel therapies that address the causes, not just the symptoms, of obesity and T2D, utilizing strategies that target either senescent cells or DNA methylation. RESULTS: In this review, we summarize the current knowledge of the pathways that lead to AT dysfunction in the chronological ageing process as well as the pathophysiology of obesity and T2D, emphasizing the critical role of cellular senescence and DNA methylation. CONCLUSION: Finally, we highlight the need for further research focused on targeting these mechanisms.

[38] *Bergmark BA, O'Donoghue ML, Murphy SA et al.* **An Exploratory Analysis of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition and Aortic Stenosis in the FOURIER Trial**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32347887
ABSTRACT

Importance: Despite recent advances in treatment of severe aortic valve stenosis (AS), AS remains a life-threatening condition with no proven disease-modifying therapy. Low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp[a]) have been implicated in the pathobiology of AS. The proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab reduces circulating LDL-C concentrations by 50% to 60% and Lp(a) by 20% to 30%. Objective: To determine whether evolocumab reduces the risk of AS events in patients with atherosclerotic cardiovascular disease. Interventions: Patients were randomized 1:1 to evolocumab or placebo. Design, Setting, and Participants: Exploratory analysis of the FOURIER trial, which enrolled 27564 patients with stable atherosclerotic cardiovascular disease who were taking statin therapy at 1242 sites in 49 countries from February 2013 to November 2016. Patients were randomized to evolocumab or placebo and followed up for a median (interquartile range) of 2.2 (1.8-2.5) years. This post hoc analysis was performed from September 2019 to February 2020. Main Outcomes and Measures: Site-reported adverse events of new or worsening AS or aortic valve replacement (termed AS events). The adjusted risk of AS events was calculated with a multivariable model including concentrations of Lp(a) and LDL-C corrected for Lp(a) content, plus age, sex, diabetes, hypertension, current smoking, and estimated glomerular filtration rate. Evolocumab efficacy was tested using a Cox proportional hazards model. Results: Aortic stenosis events occurred in 63 patients (48 men [76%]; mean [SD] age, 69 [9] years) over a median of 2.2 years. Elevated Lp(a) concentration was associated with higher rates of AS events (adjusted hazard ratio [aHR], 1.55 [95% CI, 1.17-2.05] per SD; P = .002), including aortic valve replacement (aHR, 2.22 [95% CI, 1.38-3.58] per SD; P = .001), after multivariable adjustment. The corrected LDL-C concentration was not significantly associated with AS events (aHR, 1.23 [95% CI, 0.93-1.61] per SD; P = .14). The overall HR for AS events with evolocumab was 0.66 (95% CI, 0.40-1.09), with no apparent association in the first year (HR, 1.09 [95% CI, 0.48-2.47]) but an HR of 0.48 (95% CI, 0.25-0.93) after the first year of treatment. Conclusions and Relevance: In this exploratory analysis of the FOURIER trial, higher Lp(a) levels, but not Lp(a)-corrected LDL-C levels, were associated with a higher risk of subsequent AS events, including aortic valve replacement. Long-term therapy with evolocumab may reduce AS events, and this raises the possibility that specific pharmacologic lipid-lowering therapy could offer a means to prevent or slow the progression of AS. These exploratory findings merit further investigation with a dedicated randomized clinical trial. Trial Registration: ClinicalTrials.gov Identifier: NCT01764633.

[39] *Wiviott SD, Giugliano RP, Morrow DA et al.* **Effect of Evolocumab on Type and Size of Subsequent Myocardial Infarction: A Prespecified Analysis of the FOURIER Randomized Clinical Trial**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32347885
ABSTRACT
Importance: The PCSK9 inhibitor evolocumab reduced major vascular events in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, yet the types and sizes of myocardial outcomes in FOURIER have not been previously explored. Objective: To assess the types and sizes of myocardial infarction (MI) and the effect of evolocumab on MI by subtype. Design, Setting, and Participants: A prespecified analysis of a multicenter double-blind randomized clinical trial. Patients were randomized to evolocumab or placebo and followed up for a median of 2.2 years. The study included 27564 patients with stable atherosclerotic disease receiving statin therapy. Clinical end points were

evaluated by the Thrombolysis in Myocardial Infarction clinical events committee. Rates presented are 3-year Kaplan-Meier estimates. Data were collected from 2013 to 2016 and analyzed from June 2017 to December 2019. Main Outcomes and Measures: Myocardial infarction was defined based on the third universal MI definition, and further classified according to MI type (universal MI subclass, ST-segment elevation myocardial infarction [STEMI] vs non-STEMI) and by MI size (determined by peak troponin level). Results: A total of 27564 patients were randomized, with a mean (SD) age of 62.5 (9.0) years, and 20795 (75%) were male. Of these, 1107 patients experienced a total of 1288 MIs. Most MIs (68%) were atherothrombotic (type 1), with 15% from myocardial oxygen supply-demand mismatch (type 2) and 15% percutaneous coronary intervention-related (type 4). Sudden death (type 3) and coronary artery bypass grafting-related (type 5) accounted for a total of 21 MIs (<2%). Evolocumab significantly reduced the risk of first MI by 27% (4.4% vs 6.3%; hazard ratio [HR], 0.73; 95% CI, 0.65-0.82; P < .001), type 1 by 32% (2.9% vs 4.5%; HR, 0.68; 95% CI, 0.59-0.79; P < .001), and type 4 by 35% (0.8% vs 1.1%; HR, 0.65; 95% CI, 0.48-0.87; P = .004), with no effect on type 2 (0.9% vs 0.8%; HR, 1.09; 95% CI, 0.82-1.45; P = .56). Most MIs (688 [59.8%]) had troponin levels greater than or equal to 10 times the upper limit of normal. The benefit was highly significant and consistent regardless of the size of MI with a 34% reduction in MIs with troponin level greater than or equal to 10 times the upper limit of normal (2.6% vs 3.7%; HR, 0.66; 95% CI, 0.56-0.77; P < .001) and a 36% reduction in the risk of STEMI (1.0% vs 1.5%; HR, 0.64; 95% CI, 0.49-0.84; P < .001). Conclusions and Relevance: Low-density lipoprotein cholesterol lowering with evolocumab was highly effective in reducing the risk of MI. This reduction with evolocumab included benefit across multiple subtypes of MI related to plaque rupture, smaller and larger MIs, and both STEMI and non-STEMI. These data are consistent with the known benefit of low-density lipoprotein cholesterol lowering and underscore the reduction in clinically meaningful events. Trial Registration: ClinicalTrials.gov Identifier: NCT01764633.

[40] *Kochergin NA, Kochergina AM, Khorlampenko AA et al.* **[Vulnerable atherosclerotic plaques of coronary arteries in patients with stable coronary artery disease: 12-months follow-up]**. Kardiologiia 2019; 60:69-74.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32345201
ABSTRACT
RELEVANCE: A key objective of modern cardiology is the assessment of acute coronary syndrome (ACS) risk in patients with coronary artery disease (CAD) to develop preventive measures and choose optimal treatment strategies. OBJECTIVE: Detect vulnerable plaques of non-target coronary arteries in patients with stable CAD during routine percutaneous coronary intervention using virtual-histology intravascular ultrasound (VH-IVUS) and view their morphology over time. MATERIALS AND METHODS: The prospective observational cohort study included 58 patients with stable CAD. After stenting of a target vessel, VH-IVUS was carried out in proximal and middle segments (6-8 cm) of a non-target coronary artery with no significant stenosis according to coronary angiography. Twelve months later, all patients underwent coronary angiography with re-IVUS of previously detected lesions. Death, myocardial infarction, rehospitalization, and unplanned myocardial revascularization due to vulnerable plaques were the endpoints of the study. RESULTS: IVUS with virtual histology revealed 58 lesions of non-target coronary arteries in 56 (96.5 %) patients. Two patients had no lesions in non-target coronary arteries. A large necrotic core with thin cap (thin-cap

fibroatheroma) was detected in 12 (20.7 %) plaques, six of which had additional ACS risk criteria (stenosis area >70 % and / or lumen area <4 mm2). Within the 12month follow-up period, three patients (one with a vulnerable plaque in IVUS) were hospitalized with a clinical picture of ACS. One cardiac death was registered in a patient with the IVUS vulnerable plaque. 7 of 12 vulnerable plaques stabilized in 12 months. CONCLUSION: 1) The data presented indicate a high rate (20.7 %) of vulnerable plaques of non-target coronary arteries in patients with stable CAD who underwent stenting; 2) Two (16.6 %) patients with vulnerable plaques reached endpoints (death and rehospitalization) within the 12month follow-up period; 3) An analysis of atherosclerotic plaques in non-target coronary arteries over time showed that vulnerable plaques stabilized and did not cause ACS in more than half of cases (7 of 12); 4) Plaques that were not vulnerable according to IVUS were not likely to destabilize within the 12month follow-up period.

[41] *Pogosova NV, Yufereva YM, Kachanova NP et al.* **[Prediction of Subclinical Coronary Atherosclerosis in Patients with High and Very High Cardiovascular Risk]**. Kardiologiia 2020; 60:75-82.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32345202
ABSTRACT
Objective To develop a diagnostic rule for detection of patients (pts) with high probability of subclinical atherosclerosis among those with high or very high cardiovascular (CV) risk.Materials and Methods This cross-sectional study enrolled 52 pts (32 men [62 %]), aged 40 to 65 years [mean age 54.6+/-8.0]) with high or very high CV risk (5-9 and >/=10 % by The Systematic Coronary Risk Estimation Scale [SCORE], respectively). All participants underwent cardiac computed tomography (CT) angiography and calcium scoring. Traditional risk factors (RFs) (family history of premature CVD, smoking, overweight / obesity and abdominal obesity, hypertension, type 2 diabetes mellitus, lipids parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) and lipids-related markers (apolipoprotein A1, apolipoprotein B, ApoB / ApoA1 ratio), biomarkers of inflammation (high-sensitivity C-reactive protein [hs CRP], fibrinogen), indicator carbohydrate metabolism (glucose), ankle-brachial index, stress-test, carotid plaques according to ultrasound were evaluated in all pts. Psychological RFs were evaluated using Hospital Anxiety and Depression Scale and DS-14 for type D personality.Results All pts were divided into 2 groups according to the CT angiography results: pts in the main group (n=21) had any non-obstructive lesions or calcium score >0, pts in the control group (n=31) had intact coronary arteries. The groups did not differ in age or gender. 26 multiple linear logistic models for any subclinical atherosclerosis were developed based on obtained diagnostic features. Taking into account R-square = 0.344 (p=0.0008), the best fitting model was follows: subclinical coronary atherosclerosis= -1.576 + 0.234 x SCORE >/=5 % + 0.541 x hs CRP >2 g / l +0.015 x heart rate (bpm) +0.311 family history of premature CVD. The developed algorithm had sensitivity of 63 % and specificity of 80 %.Conclusion The created diagnostic model diagnostic model suggests the presence of subclinical coronary atherosclerosis in patients with high / very high CV risk with a high degree of probability. This easy-to-use method can be used in routine clinical practice to improve risk stratification and management choices in high-risk pts.

[42] *Ragino YI, Kashtanova EV, Murashov IS et al.* **[The Study of Biochemical Factors of Calcification of Stable and Unstable Plaques in the Coronary Arteries of Man]**. Kardiologiia 2020; 60:83-88.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32345203
ABSTRACT
OBJECTIVE: The aim of the study was to study biochemical factors of calcification in stable and unstable plaques of coronary arteries and in the blood of patients with severe coronary atherosclerosis, to find associations of biochemical factors of calcification with the development of unstable atherosclerotic plaque. MATERIALS AND METHODS: The study included 25 men aged 60,4+/-6,8 years who received coronary bypass surgery. In the course of the operation intraoperative indications in men were from coronary endarteriectomy (s) artery (a - d) and histological and biochemical analyses of the samples of the intima / media. Out of 85 fragments of intima / media of coronary arteries, 15 fragments of unchanged intima / media, 39 fragments of stable atheromatous plaque and 31 fragments of unstable plaque were determined. In homogenates of samples of intima / media (after measurement of protein by the method of Lowry) and in blood by ELISA were determined by biochemical factors of calcification: osteoprotegerin, osteocalcin, an osteopontin, osteonectin, as well as inflammatory factors (cytokines, chemokines). RESULTS: A significant direct correlation (Spearman coefficient =0.607, p<0.01) between the stages of atherosclerotic focus development to unstable plaque and the degree of calcification of atherosclerotic focus development samples was found. There was an increased content of osteocalcin in stable and unstable plaques by 3.3 times in comparison with the unchanged tissue of intima / media of coronary arteries, as well as in samples with small and dust-like, with coarse-grained calcifications in comparison with samples without calcifications by 2.8 and 2.1 times, respectively. According to multivariate logistic regression analysis, the relative risk of unstable atherosclerotic plaque in the coronary artery is associated with a reduced content of osteocalcin (OR=0.988, 95 % CI 0.978-0.999, p=0.028). Also, the relative risk of calcifications in the atherosclerotic plaque in the coronary artery is associated with an increased content of osteocalcin (OR=1,008, 95 % CI 1,001-1,015, p=0,035). In men with severe coronary atherosclerosis, a significant inverse correlation was found (Spearman coefficient -0.386, p=0.022) between the content of osteoprotegerin in the vascular wall and in the blood.

[43] *Zhou L, Yan Y, Du H et al.* **Plaque features and vascular geometry in basilar artery atherosclerosis**. Medicine (Baltimore) 2020; 99:e19742.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32358348
ABSTRACT
Hemodynamic changes occurring at the segments of arterial bifurcations, up and down stream of stenotic vessels appear to play a critical role in the development of atherosclerosis. Therefore, we hypothesized that basilar artery (BA) geometry may be related to the distribution of atherosclerotic plaque.In this retrospective cross-sectional study, all patients hospitalized with ischemic stroke and intracranial atherosclerotic disease were sifted from March 2017 to October 2017. Sixty-seven patients with intracranial atherosclerotic disease (39 with and 28 without BA atherosclerosis) were analyzed. Magnetic resonance imaging, magnetic resonance angiography, and high-resolution black-blood MRI were performed within 7 days after symptoms onset. BA tortuosity, plaque location, and plaque enhancement were assessed. Plaque burden and vascular remodeling were measured.Of the 39 patients with BA

atherosclerosis, plaques preferred to be formed at the inner arc than the outer arc (27/39, 69% vs 12/39, 31%) in the tortuous BA. In addition, patients with BA plaque had a greater vascular tortuosity compared with those without plaque (113.1 +/- 10.2 vs 107 +/- 4.6; P = .034). Finally, patients with apparent BA plaque had greater plaque enhancement (14/21, 67% vs 5/18, 28%; P = .017) and plaque burden (0.76 +/- 0.15 vs 0.70 +/- 0.09; P = .036) compared with those with minimal plaque.Plaque may be more likely to form at the inner arc of tortuous BA with atherosclerotic disease, and increased BA tortuosity is associated with its likelihood to form plaque.

[44] *Ishii M, Iadecola C*. **Risk factor for Alzheimer's disease breaks the blood-brain barrier**. Nature 2020; 581:31-32.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32350425
ABSTRACT

[45] *Garcia Calvo S, Diaz-Soto G, Torres Torres B et al.* **[Metabolic control, cardiovascular profile, and adherence to the Mediterranean diet in a familial hypercholesterolemia cohort in a Public Health Program]**. Nutricion hospitalaria 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32338018
ABSTRACT
INTRODUCTION AND OBJECTIVE: familial heterozygous hypercholesterolemia (HFH) is the most common monogenic lipid metabolism disorder that associates premature cardiovascular disease. Our aim was to describe the degree of metabolic control, cardiovascular profile, and adherence to the Mediterranean diet in a cohort of HFH patients. SUBJECTS AND METHODS: a retrospective cohort study of the index cases and their relatives genetically diagnosed with HFH by the Endocrinology and Nutrition Service in the HCUV from 2009 to 2017. Anthropometric, clinical, laboratory, genetic, and treatment data were analyzed. RESULTS: a total of 138 subjects were studied, with a mean age of 48.8 (17.7) years, 55.8% of them women. A gene mutation was found in 55.8%, and 10.1% had previous ischemic heart disease. At diagnosis mean total cholesterol was 281.1 (68.4) mg/dL, and LDL-C was 204 (65) mg/dL. Among family cases, at diagnosis, a lower mean age was observed [32.89 (19.2) years vs 50.3 (17.6) years, $p < 0.001$] as well as lower LDL values [181.9 (64.3) mg/dL vs 226.8 (52) mg/dL, $p < 0.005$] as compared to index cases. A positive correlation was observed between lipid-lowering treatment dose and LDL level reduction ($r = 0.254$, $p < 0.05$), although only 30% of patients reached their LDL target. Patients with HFH were highly adherent to Mediterranean diet, with an average score of 9.5 (1.9) in the Predimed test. CONCLUSIONS: early HFH detection is necessary to prevent premature cardiovascular events. A diagnosis of cases among family members anticipates the treatment of patients with HFH. Patients with HFH are more sensitive to heart-healthy diets.

[46] *Shala-Haskaj P, Krahenmann F, Schmidt D*. **[CME: Familial Hypercholesterolemia - Statin Treatment during Pregnancy and Breastfeeding]**. Praxis 2020; 109:405-410.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32345186
ABSTRACT
CME: Familial Hypercholesterolemia - Statin Treatment during Pregnancy and Breastfeeding Abstract. Patients with familial hypercholesterolemia have a permanent increased cardiovascular risk. Thus, early detection and intensive treatment with statins is vital. However,

treatment during pregnancy using statins remains unclear and limited. According to the NICE guidelines, women should stop statins three months before conception in order to avoid teratogenicity. In addition, contraception during statin treatment is recommended. Moreover, women should not take lipid-lowering drugs until the end of lactation. In the event of an unplanned pregnancy, a woman with familial hypercholesterolemia should discontinue the statins and consult her doctor.

[47] *Santos HO, Earnest CP, Tinsley GM et al.* **Small dense low-density lipoprotein-cholesterol (sdLDL-C): Analysis, effects on cardiovascular endpoints and dietary strategies**. Prog Cardiovasc Dis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32353373
ABSTRACT
Lipid profile screening is crucial for the prevention, evaluation and treatment of cardiovascular (CV) disease (CVD). Small dense low-density lipoprotein-cholesterol (sdLDL-C) is an emerging biomarker associated with CVD and several comorbidities. The aim of this literature review is to discuss the potential importance of sdLDL-C as a surrogate biomarker for managing CVD by explaining its pathophysiology and promising treatments. The current synthesis demonstrates the impact of sdLDL-C on CV ailments, which are related to arterial pathologies and dysregulated lipid profiles. Several drug classes used for the treatment of dyslipidemia decrease the sdLDL-C concentrations. For instance, statins, fibrates, ezetimibe, nicotinic acid, resin and orlistat are pharmacological sdLDL-C-lowering agents. Regarding nutritional strategies, simple carbohydrate types, such as fructose, are common in Western diets and should be reduced or avoided due to their potential in increasing synthesis of sdLDL-C subclasses. Dairy products, avocado, pistachios, soy-based diet (except for hydrogenated soybean oil) and corn oil seem to be suitable food choices for a therapeutic diet aiming to control sdLDL-C concentrations. However, thus far dietary supplementation with omega-3 fatty acids is unsubstantiated for decreasing sdLDL-C concentration. In conclusion, coupled with the traditional lipid profile, measurement or even the estimation of sdLDL-C as a routine screening should be encouraged, whereas more insights into the control of sdLDL-C are imperative. Appropriate clinical reference ranges for sdLDL-C are also needed.

[48] *Shen H, Feng S, Lu Y et al.* **Correlation between plasma proprotein convertase subtilisin/kexin type 9 and blood lipids in patients with newly diagnosed primary nephrotic syndrome**. Renal failure 2020; 42:405-412.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32349585
ABSTRACT
Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a major post-transcriptional regulator of low-density lipoprotein receptor degradation. Recently, PCSK9 was shown to be overexpressed by liver cells in rats with proteinuria. However, the levels of PCSK9 in newly diagnosed primary nephrotic syndrome (PNS) patients and correlations involving PCSK9 and blood lipids are not clearly understood.Methods: One hundred and sixteen patients who were newly diagnosed with PNS were enrolled in this study.Results: Plasma PCSK9 levels in PNS patients were significantly higher than those in healthy controls [310.86 (250.87, 390.25) ng/ml vs 255.67 (202.26, 320.26) ng/ml, p = 0.002]. Plasma PCSK9 in PNS patients was positively correlated with total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) (gamma = 0.246, p = 0.008, and gamma = 0.183, p = 0.049). When

plasma PCSK9 was >267.60 ng/ml, the risk of developing hypercholesterolemia significantly increased in PNS patients (OR = 6.40, 95% CI 2.06-19.87, p = 0.001). When plasma PCSK9 was >255.05 ng/ml, the risk of developing higher levels of LDL-C significantly increased in PNS patients (OR = 3.83, 95%CI 1.25-11.68, p = 0.018).Conclusions: Plasma PCSK9 levels in newly diagnosed PNS patients were markedly increased, and elevated PCSK9 abundance was positively correlated with elevated serum TC and LDL-C levels, suggesting that PCSK9 may emerge as a novel therapeutic target in NS-associated hypercholesterolemia.

[49] *Lipsky ZW, Marques CNH, German GK*. **Lipid depletion enables permeation of Staphylococcus aureus bacteria through human stratum corneum**. Tissue barriers 2020:1754706.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32338129
ABSTRACT
Atopic dermatitis (AD) is a chronic inflammatory disease that affects approximately 2-5% of adults worldwide. The pathogenesis of AD continues to be a well-debated point of conjecture, with numerous hypotheses having been proposed. AD conditions are associated with increased populations of Staphylococcus aureus and reduced skin lipids. In this study, we evaluate the ability of S. aureus to permeate across human stratum corneum (SC) exhibiting both normal and depleted lipid conditions consistent with AD. This permeation would enable bacteria to interact with underlying viable epidermal cells, which could serve as a trigger for inflammation and disease onset. Our results indicate that permeation of S. aureus through SC exhibiting normal lipid conditions is not statistically significant. However, bacteria can readily permeate through lipid depleted tissue over a 9-d period. These findings suggest that S. aureus may potentially act as the mechanistic cause, rather than merely the result of AD.Abbreviations: AD: Atopic dermatitis; SC: Stratum Corneum; AMP: Antimicrobial peptide; DIW: Deionized water; PDMS: Polydimethylsiloxane; GFP: Green fluorescent protein; BHI: Brain heart infusion medium.

[50] *Kul S, Caliskan Z, Guvenc TS et al.* **Plasma lipids in patients with inflammatory bowel disease : Observations on the associations between lipid indices and coronary flow reserve**. Wien Klin Wochenschr 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32347376
ABSTRACT
BACKGROUND AND AIMS: Patients with inflammatory bowel disease (IBD) are at increased risk for coronary artery disease (CAD), even after adjusting for traditional risk factors for atherosclerosis. While inflammation is widely regarded as the pathophysiologic link between IBD and CAD, the exact mechanisms are largely unknown. This study was conducted to investigate the association of lipid parameters and indices with coronary flow reserve and markers of inflammation in IBD patients. METHODS: A total of 73 patients with IBD and 26 healthy controls were enrolled. Patients in the IBD arm were either in remission or had mild disease activity. Lipid parameters, Creactive protein (CRP) and erythrocyte sedimentation rate (ESR) were analyzed using standard laboratory techniques. Coronary flow reserve (CFR) was measured using two-dimensional echocardiography. RESULTS: Both CRP and ESR were higher and CFR was significantly lower in IBD patients, but there were no differences in terms of lipid parameters or indices; however, patients with IBD and a CFR <2.0 had significantly higher triglyceride (TG) level (155.0 (80.0)mg/dl vs. 108.0 (68.0)mg/dl, p< 0.001) and there

was a strong trend towards lower high-density lipoprotein (HDL) cholesterol (40.0 (8.5)mg/dl vs. 45.0 (10.0)mg/dl, p= 0.05) level in the latter group when compared to patients with a CFR >/=2.0. The atherogenic index of plasma (AIP), measured as log(TG/HDL-C) had the best predictive value for CFR in IBD group and was an independent predictor of CFR after multivariate adjustment for confounders (unstandardized coefficient: -0.75, 95% CI: (-1.13)-(-0.37)), beta= -0.41, p= <0.001). CONCLUSION: The atherogenic index of plasma is a marker for reduced CFR in IBD patients and could be useful to screen those at risk for early atherogenesis and CAD.