[1] *Shibutani H, Fujii K, Shirakawa M et al.* **Diagnostic Accuracy of Optical Frequency Domain Imaging for Identifying Necrotic Cores with Intraplaque Hemorrhage in Advanced Human Carotid Plaques**. The American journal of cardiology 2021; 156:123-128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34344514

ABSTRACT

This study investigated whether optical frequency domain imaging (OFDI) can identify carotid artery vulnerable plaque characteristics, focusing on lipid-rich necrotic core (NC) and intraplaque hemorrhage (IPH). Fourteen patients scheduled for carotid endarterectomy underwent OFDI scan during preoperative angiography. Atherosclerotic plaque specimens obtained from carotid endarterectomy were cut every 3-4 mm into 4-μm transverse cross-sections and stained with standard methods. Each cross-section was matched with OFDI, and histologically classified into either fibrous, calcific, pathological intimal thickening (PIT), and NC. Of 75 histologic cross-sections, 6 were categorized as fibrous (8%), 18 as calcific (24%), 9 as PIT (12%), and 42 as NC (56%). Tissues categorized as NC had significantly higher OFDI signal attenuation rates than the other tissues ($p < 0.001$), followed by PIT, calcific, and fibrous tissues. The receiver operating characteristic analysis indicated that attenuation rates of >0.023 and >0.031 predicted the presence of NC and IPH with high areas under the curve of 0.91 and 0.88, respectively. OFDI provides potential capability for the detection of NCs with IPH of carotid artery plaques by quantitatively analyzing the attenuation rate.

[2] *de Luis DA, Izaola O, Primo D, Aller R.* **APOA5 Variant rs662799, Role in Cardiovascular Traits and Serum Adipokine Levels in Caucasian Obese Subjects**. Annals of nutrition & metabolism 2021:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34350864

ABSTRACT

BACKGROUND AND AIMS: This ApoA5-1131C allele of rs662799 variant is related with a higher serum triglyceride levels, and it contributes to increase risk of cardiovascular disease. The aim of the present investigation was to evaluate single nucleotide polymorphism rs662799 in APOA5 gene and its associations with cardiovascular risk factors, MS, and serum adipokine levels. METHODS: The study involved a population of 1,002 Caucasian obese subjects. Measurements of body weight, waist circumference, fat mass, arterial blood pressure, blood glucose, C-reactive protein, insulin levels, insulin resistance (HOMA-IR), lipid profile, and adipokines levels were recorded. Genotype of ApoA5 gene polymorphism (rs662799) and prevalence of metabolic syndrome (MS) were evaluated. RESULTS: The distribution of the rs662799 polymorphism in this adult population (n = 1,002) was 88.3% (n = 885) (TT), 11.4% (n = 114) (TC), and 0.3% (n = 3) (CC). No significant differences were found between the 2 genotypes in the anthropometric data, MS, or blood pressure. Triglyceride levels were higher in C-allele carriers (delta total group: 19.7 ± 2.1 mg/dL: p = 0.02) than non C-allele carriers. HDL-cholesterol levels were lower in C-allele carriers (delta total group: -6.7 ± 1.1 mg/dL: p = 0.02) than non C-allele carriers. Adiponectin levels were lower in C-allele carriers (delta total group: -11.6 ± 1.0 mg/dL: p = 0.02) too. In C-allele carriers, logistic regression analysis showed an increased risk of hypertriglyceridemia (odds ratio [OR] = 2.1, 95% confidence interval [CI] = 1.2-3.4, p = 0.001) and percentage of low-HDL-C (OR = 2.2, 95% CI = 1.3-3.7, p = 0.002) after adjusting by body mass index and age. CONCLUSIONS: C-allele carriers of rs662799 of APOA5 gene showed high rates of low levels of HDL and hypertriglyceridemia, with differences in triglyceride, HDL cholesterol, and adiponectin levels in Caucasian obese subjects.

[3] *Chen Y, Feng X, Qi C et al.* **Efficacy and safety of Xa inhibitors in patients with heart failure and coronary or peripheral artery disease: a systematic review and meta-analysis of randomized controlled trials**. Ann Palliat Med 2021; 10:8082-8093.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34353093

ABSTRACT

BACKGROUND: To evaluate the efficacy and safety of Xa inhibitors in patients with heart failure (HF) and coronary artery disease (CAD) or peripheral artery disease (PAD). METHODS: A systematic electronic literature search was performed using the PubMed, Web of Science, EMBASE, and Cochrane Library databases from inception to June 26, 2019. A total of four randomized controlled trials involving 14,694 patients were included in this meta-analysis. RESULTS: The meta-analysis showed that there was no statistical difference between the Xa inhibitor and control group regarding the primary efficacy outcome [rivaroxaban 2.5 mg group: relative risk (RR) 0.82, 95% CI: 0.66-1.01, P=0.06; rivaroxaban 5 mg group: RR 0.86, 95% CI: 0.73-1.02, P=0.08]. The risk of the primary safety outcome was significantly increased among patients who received Xa inhibitors compared with the control group (rivaroxaban 2.5 mg group: RR 1.55, 95% CI: 1.21-1.98, P=0.0006; rivaroxaban 5 mg group: RR 1.66, 95% CI: 1.30-2.12, P<0.0001). There was no significant difference in the risk of cardiovascular death between the Xa inhibitor and control group (rivaroxaban 2.5 mg group: RR 0.79, 95% CI: 0.54-1.14, P=0.21; rivaroxaban 5 mg group: RR 0.89, 95% CI: 0.73-1.08, P=0.24). The risk of myocardial infarction (MI) in the rivaroxaban 5 mg group was significantly lower than that of the control group (RR 0.83, 95% CI: 0.69-0.99, P=0.04). However, the risk of MI in the rivaroxaban 2.5 mg group was similar to that of the control group (RR 0.85, 95% CI: 0.71-1.01, P=0.07). DISCUSSION: Xa inhibitors were associated with a higher risk of major adverse cardiovascular events and bleeding among HF and CAD or PAD patients. Therefore, Xa inhibitors should be used cautiously in patients with HF and CAD or PAD.

[4] *Shen N, Pan J, Miao H et al.* **Fibrates for the treatment of pruritus in primary biliary cholangitis: a systematic review and meta-analysis**. Ann Palliat Med 2021; 10:7697-7705.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34353058

ABSTRACT

BACKGROUND: This meta-analysis aimed to evaluate the effectiveness of fibrates in the treatment of pruritus in patients with primary biliary cholangitis (PBC), so as to guide the clinical treatment of such cases. METHODS: Searches of the PubMed, Google Scholar, and Cochrane Library databases were performed to identify randomized controlled trials (RCTs) and prospective studies published up to December 2020 that used bezafibrate and fenofibrate as treatments for pruritus in patients with PBC. Data extraction and quality evaluation of the included literature were performed. Review Manager 5.3 software was employed for statistical analysis of the data. RESULTS: This meta-analysis included 7 studies, comprising 382 patients with PBC, which assessed the efficacy of bezafibrate and fenofibrate for treating pruritus. The results showed that treatment with fibrates significantly improved pruritus symptoms in patients with PBC [relative risk (RR) =6.52, 95% confidence interval (CI): 3.26-13.06, P<0.00001]. Subgroup analysis revealed that in comparison with fenofibrate (RR =5.34, 95% CI: 0.88-32.62, P=0.07), bezafibrate (RR =25.87, 95% CI: 7.93-84.42, P<0.00001) was more effective in improving pruritic symptoms in patients with PBC. Bezafibrate was also superior to fenofibrate in reducing the degree of pruritus in patients (mean difference =3.36, 95%

CI: 2.62-4.09, P=0.05, I2=73%). CONCLUSIONS: Fibrates can significantly improve pruritus symptoms in patients with PBC but only in a subset of patients. Further studies are needed to elucidate the pathophysiological mechanisms underlying the effect of fibrates on pruritus in PBC, and thus guide future treatment regimens.

[5] *Fras Z, Tršan J, Banach M*. **On the present and future role of Lp-PLA(2) in atherosclerosis-related cardiovascular risk prediction and management**. Archives of medical science : AMS 2021; 17:954-964.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34336025
ABSTRACT
Circulating concentration and activity of secretory phospholipase A(2) (sPLA(2)) and lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) have been proven as biomarkers of increased risk of atherosclerosis-related cardiovascular disease (ASCVD). Lp-PLA(2) might be part of the atherosclerotic process and may contribute to plaque destabilisation through inflammatory activity within atherosclerotic lesions. However, all attempts to translate the inhibition of phospholipase into clinically beneficial ASCVD risk reduction, including in randomised studies, by either non-specific inhibition of sPLA(2) (by varespladib) or specific Lp-PLA(2) inhibition by darapladib, unexpectedly failed. This gives us a strong imperative to continue research aimed at a better understanding of how Lp-PLA(2) and sPLA(2) regulate vascular inflammation and atherosclerotic plaque development. From the clinical viewpoint there is a need to establish and validate the existing and emerging novel anti-inflammatory therapeutic strategies to fight against ASCVD development, by using potentially better animal models and differently designed clinical trials in humans.

[6] *Hutanu A, Iancu M, Dobreanu M et al.* **Extended lipid profile in Romanian ischemic stroke patients in relation to stroke severity and outcome: a path analysis model**. Archives of medical science : AMS 2021; 17:864-873.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34336014
ABSTRACT
INTRODUCTION: Our aim was to evaluate the extended lipid profile in ischemic stroke patients and the relationship with stroke type, severity and outcome. MATERIAL AND METHODS: We prospectively enrolled 124 ischemic stroke patients and 40 healthy controls; baseline plasma and erythrocyte membrane fatty acids concentrations and common lipid profile were analysed. Stroke severity was evaluated by NIHSS on admission, while the functional outcome was defined by mRS at discharge and after 3 months. RESULTS: Total cholesterol, triglycerides, HDL-cholesterol, DHA, adrenic, stearic and lauric acid were all lower in patients, taking into account that 87.7% of patients did not receive statins before admission. There was a different pattern in plasma and erythrocyte membrane of fatty acids between patients and controls, also omega-3 index was significantly lower in patients. Patients with poor outcome without statins had significantly lower triglyceride ($p = 0.028$), while the total cholesterol levels were significantly lower in patients with poor outcome ($p = 0.03$) but with treatment initiated after admission. Bivariate analysis revealed that patients with poor outcome had significantly lower triglyceride levels regardless the statins use, while the total cholesterol and HDL-cholesterol levels were significantly lower in patients with poor outcome under statin treatment. The long-term outcome were positively influenced by age ($\beta = 0.22$, $p = 0.001$), and NIHSS score at admission ($\beta = 0.55$, $p < 0.001$), and negatively by cholesterol levels ($\beta = -0.17$, $p = 0.031$).

CONCLUSIONS: DHA, adrenic, stearic and lauric acid were lower in stroke patients; plasma adrenic acid was consumed during the acute phase. The most important predictors for long-term outcome was NIHSS at admission followed by age and total cholesterol.

[7] *Dhawan UK, Bhattacharya P, Narayanan S et al.* **Hypercholesterolemia Impairs Clearance of Neutrophil Extracellular Traps and Promotes Inflammation and Atherosclerotic Plaque Progression**. Arteriosclerosis, thrombosis, and vascular biology 2021:Atvbaha120316389.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34348488

ABSTRACT

OBJECTIVE: Hypercholesterolemia-induced NETosis and accumulation of neutrophil extracellular traps (NETs) in the atherosclerotic lesion exacerbates inflammation and is causally implicated in plaque progression. We investigated whether hypercholesterolemia additionally impairs the clearance of NETs mediated by endonucleases such as DNase1 and DNase1L3 and its implication in advanced atherosclerotic plaque progression. Approach and Results: Using a mouse model, we demonstrate that an experimental increase in the systemic level of NETs leads to a rapid increase in serum DNase activity, which is critical for the prompt clearance of NETs and achieving inflammation resolution. Importantly, hypercholesterolemic mice demonstrate an impairment in this critical NET-induced DNase response with consequent delay in the clearance of NETs and defective inflammation resolution. Administration of TUDCA, a chemical chaperone that relieves endoplasmic reticulum stress, rescued the hypercholesterolemia-induced impairment in the NET-induced DNase response suggesting a causal role for endoplasmic reticulum stress in this phenomenon. Correction of the defective DNase response with exogenous supplementation of DNase1 in Apoe(-/-) mice with advanced atherosclerosis resulted in a decrease in plaque NET content and significant plaque remodeling with decreased area of plaque necrosis and increased collagen content. From a translational standpoint, we demonstrate that humans with hypercholesterolemia have elevated systemic extracellular DNA levels and decreased plasma DNase activity. CONCLUSIONS: These data suggest that hypercholesterolemia impairs the NET-induced DNase response resulting in defective clearance and accumulation of NETs in the atherosclerotic plaque. Therefore, strategies aimed at rescuing this defect could be of potential therapeutic benefit in promoting inflammation resolution and atherosclerotic plaque stabilization.

[8] *Kaur D, Negi G, Walia R et al.* **Just not cosmesis! Role of low-density lipoprotein apheresis in familial hypercholesterolemia: Experience at a newly developed tertiary care institution in Northern India**. Asian journal of transfusion science 2021; 15:104-108.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34349468

ABSTRACT

Familial hypercholesterolemia (FH) is characterized by an increase in plasma low-density lipoprotein-cholesterol (LDL-C) levels. It presents with tendon/skin xanthomas and premature atherosclerotic cardiovascular disease. The most available treatment options for FH are lipid-lowering medications such as statins, lifestyle modification, and LDL apheresis. As per American Society for Apheresis guidelines 2019, the treatment of FH using LDL apheresis falls under Category I. Here, we are reporting an interesting case of a young patient who presented with chief complaints of progressively increasing yellowish lesions around eyes, neck, hands, and legs. She was thoroughly investigated and was diagnosed provisionally as a case of Type 2 FH. Her total serum cholesterol and LDL-C

were 717.2 mg/dl and 690.6 mg/dl, respectively, at presentation. One cycle of LDL apheresis was planned for her. We found immediate post-procedural reduction of 55.8% and 55.3% for total serum and LDL cholesterol levels respectively while 70.58% and 77.41% reduction in the levels from the day of presentation to the hospital.

[9] *Coggi D, Frigerio B, Bonomi A et al.* **Relationship between Circulating PCSK9 and Markers of Subclinical Atherosclerosis-The IMPROVE Study**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34356905

ABSTRACT

Background and purpose: circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) is one of the key regulators of cholesterol metabolism. Despite this, its role as a player in atherosclerosis development is still matter of debate. Here, we investigated the relationships between this protein and several markers of subclinical atherosclerosis. (2) Methods: the IMPROVE study enrolled 3703 European subjects (54-79 years; 48% men; with ≥3 vascular risk factors), asymptomatic for cardiovascular diseases. PCSK9 levels were measured by ELISA. B-mode ultrasound was used to measure markers of carotid subclinical atherosclerosis. (3) Results: in the crude analysis, PCSK9 levels were associated with several baseline measures of carotid intima-media thickness (cIMT) (all $p < 0.0001$); with cIMT change over time (Fastest-IMTmax-progr) ($p = 0.01$); with inter-adventitia common carotid artery diameter (ICCAD) ($p < 0.0001$); and with the echolucency (Grey Scale Median; GSM) of both carotid plaque and plaque-free common carotid IMT (both $p < 0.0001$). However, after adjustment for age, sex, latitude, and pharmacological treatment, all the afore-mentioned correlations were no longer statistically significant. The lack of correlation was also observed after stratification for sex, latitude, and pharmacological treatments. (4) Conclusions: in subjects who are asymptomatic for cardiovascular diseases, PCSK9 plasma levels do not correlate with vascular damage and/or subclinical atherosclerosis of extracranial carotid arteries.

[10] *Iannuzzo G, Tripaldella M, Mallardo V et al.* **Lipoprotein(a) Where Do We Stand? From the Physiopathology to Innovative Terapy**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34356902

ABSTRACT

A number of epidemiologic studies have demonstrated a strong association between increasing lipoprotein a [Lp(a)] and cardiovascular disease. This correlation was demonstrated independent of other known cardiovascular (CV) risk factors. Screening for Lp(a) in the general population is not recommended, although Lp(a) levels are predominantly genetically determined so a single assessment is needed to identify patients at risk. In 2019 ESC/EAS guidelines recommend Lp(a) measurement at least once a lifetime, fo subjects at very high and high CV risk and those with a family history of premature cardiovascular disease, to reclassify patients with borderline risk. As concerning medications, statins play a key role in lipid lowering therapy, but present poor efficacy on Lp(a) levels. Actually, treatment options for elevated serum levels of Lp(a) are very limited. Apheresis is the most effective and well tolerated treatment in patients with high levels of Lp(a). However, promising new therapies, in particular antisense oligonucleotides have showed to be able to

significantly reduce Lp(a) in phase II RCT. This review provides an overview of the biology and epidemiology of Lp(a), with a view to future therapies.

[11] *O'Brien ST, Neylon OM, O'Brien T*. **Dyslipidaemia in Type 1 Diabetes: Molecular Mechanisms and Therapeutic Opportunities**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34356890
ABSTRACT
Cardiovascular disease (CVD) is the leading cause of death in Type 1 Diabetes (T1D). The molecular basis for atherosclerosis in T1D is heavily influenced by hyperglycaemia and its atherogenic effects on LDL. Ongoing research into the distinct pathophysiology of atherosclerosis in T1D offers exciting opportunities for novel approaches to calculate CVD risk in patients with T1D and to manage this risk appropriately. Currently, despite the increased risk of CVD in the T1D population, there are few tools available for estimating the risk of CVD in younger patients. This poses significant challenges for clinicians in selecting which patients might benefit from lipid-lowering therapies over the long term. The current best practice guidance for the management of dyslipidaemia in T1D is generally based on evidence from patients with T2D and the opinion of experts in the field. In this review article, we explore the unique pathophysiology of atherosclerosis in T1D, with a specific focus on hyperglycaemia-induced damage and atherogenic LDL modifications. We also discuss the current clinical situation of managing these patients across paediatric and adult populations, focusing on the difficulties posed by a lack of strong evidence and various barriers to treatment.

[12] *Sundararaman SS, Döring Y, van der Vorst EPC*. **PCSK9: A Multi-Faceted Protein That Is Involved in Cardiovascular Biology**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34356856
ABSTRACT
Pro-protein convertase subtilisin/kexin type 9 (PCSK9) is secreted mostly by hepatocytes and to a lesser extent by the intestine, pancreas, kidney, adipose tissue, and vascular cells. PCSK9 has been known to interact with the low-density lipoprotein receptor (LDLR) and chaperones the receptor to its degradation. In this manner, targeting PCSK9 is a novel attractive approach to reduce hyperlipidaemia and the risk for cardiovascular diseases. Recently, it has been recognised that the effects of PCSK9 in relation to cardiovascular complications are not only LDLR related, but that various LDLR-independent pathways and processes are also influenced. In this review, the various LDLR dependent and especially independent effects of PCSK9 on the cardiovascular system are discussed, followed by an overview of related PCSK9-polymorphisms and currently available and future therapeutic approaches to manipulate PCSK9 expression.

[13] *Kryczka KE, Kruk M, Demkow M, Lubiszewska B*. **Fibrinogen and a Triad of Thrombosis, Inflammation, and the Renin-Angiotensin System in Premature Coronary Artery Disease in Women: A New Insight into Sex-Related Differences in the Pathogenesis of the Disease**. Biomolecules 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34356659
ABSTRACT
Coronary artery disease (CAD) is the leading cause of morbidity and mortality in women worldwide. Its social impact in the case of premature CAD is particularly devastating. Many differences in the

presentation of the disease in women as compared to men, including atypical symptoms, microvascular involvement, and differences in pathology of plaque formation or progression, make CAD diagnosis in women a challenge. The contribution of different risk factors, such as smoking, diabetes, hyperlipidemia, or obesity, may vary between women and men. Certain pathological pathways may have different sex-related magnitudes on CAD formation and progression. In spite of the already known differences, we lack sufficiently powered studies, both clinical and experimental, that assess the multipathogenic differences in CAD formation and progression related to sex in different age periods. A growing quantity of data that are presented in this article suggest that thrombosis with fibrinogen is of more concern in the case of premature CAD in women than are other coagulation factors, such as factors VII and VIII, tissue-type plasminogen activator, and plasminogen inhibitor-1. The rise in fibrinogen levels in inflammation is mainly affected by interleukin-6 (IL-6). The renin-angiotensin (RA) system affects the inflammatory process by increasing the IL-6 level. Unlike in men, in young women, the hypertensive arm of the RA system is naturally downregulated by estrogens. At the same time, estrogens promote the fibrinolytic path of the RA system. In young women, the promoted fibrinolytic process upregulates IL-6 release from leukocytes via fibrin degradation products. Moreover, fibrinogen, whose higher levels are observed in women, increases IL-6 synthesis and exacerbates inflammation, contributing to CAD. Therefore, the synergistic interplay between thrombosis, inflammation, and the RA system appears to have a more significant influence on the underlying CAD atherosclerotic plaque formation in young women than in men. This issue is further discussed in this review. Fibrinogen is the biomolecule that is central to these three pathways. In this review, fibrinogen is shown as the biomolecule that possesses a different impact on CAD formation, progression, and destabilization in women to that observed in men, being more pathogenic in women at the early stages of the disease than in men. Fibrinogen is a three-chain glycoprotein involved in thrombosis. Although the role of thrombosis is of great magnitude in acute coronary events, fibrinogen also induces atherosclerosis formation by accumulating in the arterial wall and enabling low-density lipoprotein cholesterol aggregation. Its level rises during inflammation and is associated with most cardiovascular risk factors, particularly smoking and diabetes. It was noted that fibrinogen levels were higher in women than in men as well as in the case of premature CAD in women. The causes of this phenomenon are not well understood. The higher fibrinogen levels were found to be associated with a greater extent of coronary atherosclerosis in women with CAD but not in men. Moreover, the lysability of a fibrin clot, which is dependent on fibrinogen properties, was reduced in women with subclinical CAD compared to men at the same stage of the disease, as well as in comparison to women without coronary artery atherosclerosis. These findings suggest that the magnitude of the pathological pathways contributing to premature CAD differs in women and men, and they are discussed in this review. While many gaps in both experimental and clinical studies on sex-related differences in premature CAD exist, further studies on pathological pathways are needed.

[14] *Yuan Y, Wang W, Shang X et al.* **Association between statin use and the risks of glaucoma in Australia: a 10-year cohort study**. The British journal of ophthalmology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34348924

ABSTRACT

SYNOPSIS: In a cohort of middle-aged and elderly Australians, we found that long-term statin use was associated with a higher risk of glaucoma onset. As to subtypes of statins, the increased risk was only found in rosuvastatin users. PURPOSE: To investigate the relationship between statin use and

glaucoma onset in a 10-year longitudinal study. METHODS: This nested case-control study was based on data from a large-scale cohort of Australians aged over 45 years old. Medication exposure was identified by claims records from the Pharmaceutical Benefits Scheme during the follow-up period (2009-2016). The onset of glaucoma was defined as the people with at least three claims of antiglaucoma medications. Controls matched by age, gender and cardiovascular diseases were selected from participants without prescription of antiglaucoma medications. A conditional logistic regression model was used to assess the association between statin use and glaucoma onset. RESULTS: The proportion of statin users was higher in the case group (40.5%) than that in the control group (38.4%). After adjusting for baseline characteristics and longitudinal claims records, statin use was not associated with glaucoma onset (OR 1.04, 95% CI 0.97 to 1.11). However, an increased risk of glaucoma onset was observed in participants with a longer duration of statin use (>3 years vs <1 year: OR 1.12, 95% CI 1.04 to 1.21). With respect to specific types of statins, participants taking rosuvastatin were more likely to suffer from glaucoma (OR 1.11, 95%CI 1.01 to 1.22). The use of other statins was not significantly associated with glaucoma onset. CONCLUSIONS: Long-term statin use was found to be associated with a higher risk of glaucoma onset in this study. Regarding specific types of statins, the increased risk of glaucoma onset was only observed in users of rosuvastatin.

[15] *Hu Z, Cui J, Li X et al.* **High-Density Lipoprotein Cholesterol in Young Nondiabetic Coronary Heart Disease Patients**. Cardiology research and practice 2021; 2021:2970568.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34336270

ABSTRACT

OBJECTIVE: To investigate the association between the lipid profiles and coronary heart disease (CHD) in nondiabetic patients younger than 65 years of age. METHOD: 424 patients were enrolled in this study from January 2019 to December 2020. All the patients were screened for clinically indicated coronary angiography. They were divided into two groups according to the coronary angiography results: 340 patients with the presence of CHD (at least one coronary artery stenosis ≥50%) were classified as the CHD group, and the rest with the absence of CHD comprised the normal group. The demographic data and lipid profiles were compared. RESULT: CHD was higher in males than females (84.5% vs. 62.2%, $P < 0.001$). In the CHD group, the level of high-density lipoprotein cholesterol (HDL-C) was lower ($P < 0.001$), while the triglyceride (TG)/HDL-C ratio was higher (P=0.022). No significant differences were shown between the two groups in terms of age, family history of CHD, hypertension, and the levels of TC, TG, and LDL-C. Gender differences were further explored. In men, except for the level of HDL-C which was significantly lower in the CHD group than that in the normal group (P=0.017), parameters were comparable. A binary logistic regression model further indicated that HDL-C was associated with CHD (OR = 0.137, 95%CI: 0.031-0.594, P=0.008). Also, with the increase of the number of coronary artery with lesions, the levels of HDL-C decreased significantly in men. In women, no differences were observed between the CHD group and normal group. CONCLUSION: HDL-C may be inversely associated with the risk of CHD in young nondiabetes patients, especially in men. More research is needed to confirm it.

[16] *Kadoglou NPE, Stasinopoulou M*. **How to Use Statins in Secondary Prevention of Atherosclerotic Diseases: from the Beneficial Early Initiation to the Potentially Unfavorable**

Discontinuation. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34347204
ABSTRACT
Statins, a class of lipid-lowering drugs, reduce morbidity and mortality in patients with established atherosclerosis-related cardiovascular disease. Early initiation of statin therapy after admission for acute coronary syndromes (ACS), stroke, or transient ischemic attack (TIA) is associated with improved cardiovascular outcomes. Moreover, high-dose statin treatment prior to coronary or carotid revascularization has been shown to reduce cardiovascular events in these patients. However, many patients may be undertreated, and a residual cardiovascular risk remains in current clinical practice. Despite the beneficial role of statins, their discontinuation rate among patients is still elevated leading to severe adverse cardiovascular events due to atherosclerotic plaque destabilization. In this review, we summarized the impact of statin treatment among patients, focusing on the initiation time-points as well as the potential harm derived by their discontinuation.

[17] *Sagris M, Antonopoulos AS, Theofilis P et al.* **Risk factors profile of young and older patients with Myocardial Infarction**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34358302
ABSTRACT
Myocardial infarction (MI) among young adults (< 45 years) represents a considerable proportion of the total heart attack incidents. The underlying pathophysiologic characteristics, atherosclerotic plaque features and risk factors profile differ between young and older patients with MI. This review article discusses the main differences between the younger and elderly MI patients as well as the different pathogenic mechanisms underlying the development of MI in the younger. Young patients with MI often have eccentric atherosclerotic plaques with inflammatory features but fewer lesions, and are more likely to be smokers, obese, and have poor lifestyle, such as inactivity and alcohol intake. Compared to older MI patients, younger are more likely to be men, have familial-combined hyperlipidemia and increased levels of lipoprotein-a. In addition, MI in younger patients may be related to use of cannabis, cocaine use and androgenic anabolic steroids. Genomic differences especially in the pathways of coagulation and lipid metabolism have also been identified between young and older patients with MI. Better understanding of the risk factors and the anatomic and pathophysiologic processes in young adults can improve MI prevention and treatment strategies in this patient group. Awareness could help identify young subjects at increased risk and guide primary prevention strategies. Additional studies focusing on gene pathways related to lipid metabolism, inflammation and coagulation are needed.

[18] *Kim Y, Lee S, Lee Y et al.* **Predictive value of triglyceride/high-density lipoprotein cholesterol for major clinical outcomes in advanced chronic kidney disease: a nationwide population-based study**. Clinical kidney journal 2021; 14:1961-1968.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34345420
ABSTRACT
BACKGROUND: Dyslipidemia is an essential parameter in the prediction of cardiovascular disease (CVD). We aimed to explore whether lipid profiles could predict major outcomes in patients with advanced chronic kidney disease (CKD). METHODS: We retrospectively reviewed the National

Health Insurance Service database for people who received nationwide health screening in 2009. All subjects exposed to a lipid-lowering agent before screening were excluded. The population was divided into control, early [estimated glomerular filtration rate (eGFR) 45-59 mL/min/1.73 m(2)] and advanced (eGFR <45 mL/min/1.73 m(2)) CKD groups. The hazard ratios (HRs) of outcomes were calculated using multivariate Cox regression models. RESULTS: A total of 3 634 873 participants were included in this study, with 404 298 (11.1%) and 66 805 (1.8%) having early and advanced CKD, respectively. For all populations, levels of triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) showed a linear association with major cardiovascular and cerebrovascular events (MACCEs) and all-cause mortality, while low-density lipoprotein cholesterol (LDL-C) showed a different pattern of association with MACCEs (linear association) from all-cause mortality (U-shaped association). The significance between the levels of LDL-C and outcomes was attenuated in the advanced CKD group. For TG/HDL-C, although the significance was decreased, the linear patterns with both MACCEs and all-cause mortality were maintained in the advanced CKD group. CONCLUSIONS: The pattern and significance of lipid profiles were different according to the grade of kidney function. TG/HDL-C should be additionally considered as a predictive marker for CVD and mortality along with LDL-C in patients with CKD.

[19] *Mal M, Kumar A, Meraj A et al.* **Role of Cod Liver Oil in Preventing Myocardial Infarction**. Cureus 2021; 13:e16067.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34345552
ABSTRACT
INTRODUCTION: Omega-3 fatty acids have for long been shown to reduce the incidence of cardiovascular (CV) diseases. Omega-3 fatty acids mainly exist in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid in fish oils. Cod liver oil is found to have a high concentration of these omega-3 fatty acids. This study aims to explore the benefits of using cod liver oil in reducing the incidence of myocardial infarction (MI) among at-risk patients. Method: This open-label placebo-controlled two-arm interventional study was conducted in the internal medicine and cardiology unit of tertiary care hospital between January 2018 to January 2021. During this period, 870 patients at risk of CV events were enrolled in the study after obtaining informed consent. The study group received 415 mg cod liver oil daily, in addition to their current treatment, in a bottle without label and the control group received no additional treatment to their standard treatment. Patients were followed up for 12 months or till the development of MI. RESULT: Patients treated with cod liver oil had comparatively fewer incidences of MI; however, the difference was not significant (p-value: 0.09). Furthermore, the difference was non-significant for both fatal and non-fatal MI. The relative risk for total MI incidence was 0.70 (0.44-1.10). CONCLUSION: According to our study, adding cod liver oil to the diet does not play a major role in reducing the risk of MI. Further large-scale studies are needed to understand the role of cod liver oil in reducing the risk of CV events, including MI.

[20] *Paul M, Paul P, Dey D et al.* **A Case of Statin-Associated Immune-Mediated Necrotizing Myopathy, Successfully Treated With Intravenous Immunoglobulin**. Cureus 2021; 13:e16001.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34336492
ABSTRACT
Statins have become the commonest lipid-lowering agent worldwide and have significantly reduced morbidity and mortality associated with cardiovascular diseases. Overall, statins are very well

tolerated. However, in clinical practice, a wide variety of skeletal myopathic effects have been observed, ranging from asymptomatic patients with high creatine phosphokinase (CPK) to fatal cases of acute rhabdomyolysis. Recent reports suggest that statins are associated with immune-mediated necrotizing myopathy (IMNM), a unique autoimmune myopathy. Unlike other drug reactions, this can occur months to years after initiation of statin. It is a distinctive autoimmune myopathy where symptoms persist or even progress after statin discontinuation and requires immunosuppressive therapy. The presence of anti-hydroxy-methyl-glutaryl coenzyme-A reductase (HMGCR) antibody in serum strengthens the diagnosis of statin-associated necrotizing myopathy. Here we present a case of statin-associated IMNM in a 43-year-old Caucasian female who had statin-induced progressive deterioration of proximal muscle weakness with poor response to high-dose steroids and required further immunosuppressive therapy.

[21] *Cicero AFG, Fogacci F, Stoian AP et al.* **Nutraceuticals in the Management of Dyslipidemia: Which, When, and for Whom? Could Nutraceuticals Help Low-Risk Individuals with Non-optimal Lipid Levels?** Current atherosclerosis reports 2021; 23:57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34345932

ABSTRACT

PURPOSE OF REVIEW: The aim of this review is to summarize the available clinical efficacy and safety data related to the most studied and used lipid-lowering nutraceuticals. RECENT FINDINGS: A growing number of meta-analyses of randomized clinical trials supports the effectiveness and tolerability of some lipid-lowering nutraceuticals such as red yeast rice, plant sterols and stanols, soluble fibers, berberine, artichoke extracts, bergamot polyphenol fraction, garlic, green tea, and spiruline. No significant safety concern has been raised for the use of such products. Association of more lipid-lowering nutraceuticals and of some nutraceuticals with lipid-lowering drugs has been tested as well. Current evidence suggests that some clinically tested lipid-lowering nutraceuticals could be safely used to improve plasma lipid levels in subjects affected by mild-to-moderate dyslipidaemia with low cardiovascular risk.

[22] *Gencer B, Mach F*. **PCSK9 inhibition could be effective for acute myocardial infarction**. Curr Med Chem 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34348606

ABSTRACT

In this review, we will explore the role of PCSK9 and inhibition of PCSK9 in patients after acute myocardial infarction (MI). Despite the implementation of evidence-based therapies to improve outcomes, mortality at one-year remains at 12-15% and the need to further reduce complications related to MI persists. Mechanistic and epidemiologic studies suggest that the naturally occurring PCSK9 protein increases coronary plaque vulnerability through several pathways, including pro-inflammatory LDL-C oxidation and direct modification of plaque composition. PCSK9 inhibitors are a class of drugs with proven efficacy in patients with recent MI. The latest guidelines recommend the use of PCSK9 in patients with recent MI early in the process of care to reduce LDL-C values and associated morbidity. The use of PCSK9 inhibition could be beneficial for mortality reduction after an acute MI and should be tested in an appropriately powered randomized controlled trial.

[23] *Patterson MT, Williams JW*. **Metabolic regulation of macrophage proliferation and function in atherosclerosis**. Current opinion in lipidology 2021; 32:293-300.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34334628
ABSTRACT
PURPOSE OF REVIEW: Macrophage accumulation within atherosclerotic plaque is a primary driver of disease progression. However, recent advances in both phenotypic and functional heterogeneity of these cells have allowed for improved insight into potential regulation of macrophage function within lesions. In this review, we will discuss recent insights on macrophage heterogeneity, lipid processing, metabolism, and proliferation in atherosclerosis. Furthermore, we will identify outstanding questions in the field that are pertinent to future studies. RECENT FINDINGS: With the recent development of single-cell RNA sequencing, several studies have highlighted the diverse macrophage populations within plaques, including pro-inflammatory, anti-inflammatory, lipid loaded and tissue resident macrophages. Furthermore, new data has suggested that differential activation of metabolic pathways, including glycolysis and fatty acid oxidation, may play a key role in determining function. Recent works have highlighted that different populations retain varying capacity to undergo proliferation; regulating the proliferation pathway may be highly effective in reducing plaque in advanced lesions. SUMMARY: Macrophage populations within atherosclerosis are highly heterogeneous; differences in cytokine production, lipid handling, metabolism, and proliferation are seen between subpopulations. Understanding the basic cellular mechanisms that drive this heterogeneity will allow for the development of highly specific disease modulating agents to combat atherosclerosis.

[24] *Rahhal A, Khir F, Orabi B et al.* **A Comparative Study of High-intensity Rosuvastatin Versus Atorvastatin Therapy Post-acute Coronary Syndrome Using Real-world Data**. Current problems in cardiology 2021:100956.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34363847
ABSTRACT
A high-intensity statin is recommended for the secondary prevention of cardiovascular diseases (CVD). However, real-world evidence of the effectiveness of rosuvastatin following acute coronary syndrome (ACS) is scarce. This retrospective cohort study included patients diagnosed with ACS to compare between the 2 high-intensity statin therapies (rosuvastatin vs atorvastatin) in terms of a primary composite outcome of CVD-associated death, non-fatal ACS, and non-fatal stroke at 1 month and 12 months post discharge. The primary effectiveness outcome did not differ between the 2 groups at 1 month (1.3% vs 1%; aHR = 1.64, 95% CI 0.55-4.94, P= 0.379) and at 12 months (4.8% vs 3.5%; aHR = 1.48, 95% CI 0.82-2.67, P= 0.199). Similarly, the 2 groups had comparable safety outcomes. In conclusion, the use of high-intensity rosuvastatin compared to high-intensity atorvastatin therapy in patients with ACS had resulted in comparable cardiovascular effectiveness and safety outcomes.

[25] *Wu Q, Taboureau O, Audouze K*. **Development of an adverse drug event network to predict drug toxicity**. Curr Res Toxicol 2020; 1:48-55.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34345836
ABSTRACT

Despite of their therapeutic effects, drug's exposure may have negative effects on human health such as adverse drug reaction (ADR) and side effects (SE). Adverse drug events (ADEs), that correspond to an event occurring during the drug treatment (i.e. ADR and SE), is not necessarily caused by the drug itself, as this is the case with medical errors and social factors. Due to the complexity of the biological systems, not all ADEs are known for marketed drugs. Therefore, new and effective methods are needed to determine potential risks, including the development of computational strategies. We present an ADE association network based on 90,827 drug-ADE associations between 930 unique drug and 6221 unique ADE, on which we implemented a scoring system based on a pull-down approach for prediction of drug-ADE combination. Based on our network, ADEs proposed for three drugs, safinamide, sonidegib, rufinamide are further discussed. The model was able to identify, already known drug-ADE associations that are supported by the literature and FDA reports, and also to predict uncharacterized associations such as dopamine dysregulation syndrome, or nicotinic acid deficiency for the drugs safinamide and sonidegib respectively, illustrating the power of such integrative toxicological approach.

[26] *Sommariva E, Stadiotti I, Casella M et al.* **Oxidized LDL-dependent pathway as new pathogenic trigger in arrhythmogenic cardiomyopathy**. EMBO molecular medicine 2021; 13:e14365.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34337880

ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) is hallmarked by ventricular fibro-adipogenic alterations, contributing to cardiac dysfunctions and arrhythmias. Although genetically determined (e.g., PKP2 mutations), ACM phenotypes are highly variable. More data on phenotype modulators, clinical prognosticators, and etiological therapies are awaited. We hypothesized that oxidized low-density lipoprotein (oxLDL)-dependent activation of PPARγ, a recognized effector of ACM adipogenesis, contributes to disease pathogenesis. ACM patients showing high plasma concentration of oxLDL display severe clinical phenotypes in terms of fat infiltration, ventricular dysfunction, and major arrhythmic event risk. In ACM patient-derived cardiac cells, we demonstrated that oxLDLs are major cofactors of adipogenesis. Mechanistically, the increased lipid accumulation is mediated by oxLDL cell internalization through CD36, ultimately resulting in PPARγ upregulation. By boosting oxLDL in a Pkp2 heterozygous knock-out mice through high-fat diet feeding, we confirmed in vivo the oxidized lipid dependency of cardiac adipogenesis and right ventricle systolic impairment, which are counteracted by atorvastatin treatment. The modulatory role of oxidized lipids on ACM adipogenesis, demonstrated at cellular, mouse, and patient levels, represents a novel risk stratification tool and a target for ACM pharmacological strategies.

[27] *Stiekema LCA, Willemsen L, Kaiser Y et al.* **Impact of cholesterol on proinflammatory monocyte production by the bone marrow**. European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34343254

ABSTRACT

AIM: Preclinical work indicates that low-density lipoprotein cholesterol (LDL-C) not only drives atherosclerosis by directing the innate immune response at plaque level but also augments proinflammatory monocyte production in the bone marrow (BM) compartment. In this study, we aim to unravel the impact of LDL-C on monocyte production in the BM compartment in human subjects.

METHODS AND RESULTS: A multivariable linear regression analysis in 12 304 individuals of the EPIC-Norfolk prospective population study showed that LDL-C is associated with monocyte percentage (β = 0.131 [95% CI: 0.036-0.225]; P = 0.007), at the expense of granulocytes (β = -0.876 [95% CI: -1.046 to -0.705]; P < 0.001). Next, we investigated whether altered haematopoiesis could explain this monocytic skewing by characterizing CD34+ BM haematopoietic stem and progenitor cells (HSPCs) of patients with familial hypercholesterolaemia (FH) and healthy normocholesterolaemic controls. The HSPC transcriptomic profile of untreated FH patients showed increased gene expression in pathways involved in HSPC migration and, in agreement with our epidemiological findings, myelomonocytic skewing. Twelve weeks of cholesterol-lowering treatment reverted the myelomonocytic skewing, but transcriptomic enrichment of monocyte-associated inflammatory and migratory pathways persisted in HSPCs post-treatment. Lastly, we link hypercholesterolaemia to perturbed lipid homeostasis in HSPCs, characterized by lipid droplet formation and transcriptomic changes compatible with increased intracellular cholesterol availability. CONCLUSIONS: Collectively, these data highlight that LDL-C impacts haematopoiesis, promoting both the number and the proinflammatory activation of circulating monocytes. Furthermore, this study reveals a potential contributory role of HSPC transcriptomic reprogramming to residual inflammatory risk in FH patients despite cholesterol-lowering therapy.

[28] *Melexopoulou C, Marinaki S, Oikonomou E et al.* **PCSK9 and inflammatory biomarkers in the early post kidney transplantation period**. European review for medical and pharmacological sciences 2021; 25:4762-4772.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34337724

ABSTRACT

OBJECTIVE: Various biomarkers have been studied in the early post-kidney transplantation (post-KTx) period in order to identify potential therapeutic targets for improving long-term graft survival. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a biomarker that has recently gained interest in cardiovascular disease but its role still remains to be defined post-KTx. PATIENTS AND METHODS: We prospectively evaluated the levels of PCSK9, interleukin (IL)-6, WBC and C-reactive protein in seventy-three hemodialysis patients undergoing KTx, at 3 time-points; pre-transplantation (day 0) and at 1 and 6-months post-KTx. All data were also analyzed according to donor-type (living or deceased) and compared with hemodialysis patients on transplant waiting list. RESULTS: At Day 0 there was no difference in WBC, CRP, IL-6 and PCSK9 levels between patients scheduled for transplantation and those who remained on hemodialysis. In transplanted patients WBC, CRP and IL-6 levels were significantly reduced early post-KTx [logIL-6 Day 0: 0.68 (0.33, 0.85) vs. 1-month: 0.57 (0.37, 0.75) vs. 6-months: 0.50 (0.32, 0.69) pg/ml, p=0.01], while PCSK9 levels were significantly increased (Day 0: 199.8±63.0 vs. 1-month: 276.2±79.4 vs. 6-months: 245.9±62.5 ng/ml, p<0.001). In contrast, no change of WBC, CRP, IL-6 and PCSK9 levels was observed in hemodialysis patients on follow-up (p=NS for all). Between living-donor and deceased-donor recipients, analysis showed reduced CRP and increased PCSK9 levels in both groups (p<0.05 for all), while IL-6 levels were reduced in living-donor and increased in deceased-donor recipients 1-month post-KTx. PCSK9 levels were not correlated with renal function, delayed graft function, rejection episodes or inflammatory biomarkers. CONCLUSIONS: PCSK9 levels were increased post-KTx independently from renal function and inflammatory biomarkers, in both living and deceased-donor recipients.

[29] *Cheng Q, Liu XC, Chen CL et al.* **The U-Shaped Association of Non-High-Density Lipoprotein Cholesterol Levels With All-Cause and Cardiovascular Mortality Among Patients With Hypertension**. Frontiers in cardiovascular medicine 2021; 8:707701.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34336961

ABSTRACT

Background: Non-high-density lipoprotein cholesterol (non-HDL-C) is a valuable indicator in routine blood lipid tests, but the associations of non-HDL-C with mortality in hypertensive population still remain uncertain. Methods: In the National Health and Nutrition Examination Surveys from 1999 to 2014, participants having hypertension were included and grouped by non-HDL-C levels (<130, 130-159, 160-189, 190-219, and ≥220 mg/dl). Multivariate Cox regression was conducted for calculation of hazard ratios (HR) and 95% confidence interval (CI). To reveal the relationship between non-HDL-C and mortality, Kaplan-Meier survival curves, restricted cubic spline, linear regression, and subgroup analysis were also applied. Results: A total of 12,169 participants (47.52% males, mean age 57.27 ± 15.79 years) were included. During average follow-up of 92.5 months, 1,946 (15.99%) all-cause deaths and 422 (3.47%) cardiovascular deaths occurred. After adjusting for confounders, the association of non-HDL-C with mortality was detected as U-shaped. Threshold values were observed at 158 mg/dl for all-cause mortality and 190 mg/dl as to cardiovascular mortality. Below the threshold, every 10 mg/dl increment in non-HDL-C attributed to relatively low all-cause mortality significantly (HR = 0.94, 95% CI: 0.92-0.96). Above the threshold, non-HDL-C has significant positive associations with both all-cause (HR = 1.03, 95% CI: 1.01-1.05) and cardiovascular mortality (HR = 1.09, 95% CI: 1.05-1.14). For subgroups analysis, similar results were found among participants age <65 years old, non-white population, those were not taking lipid-lowering drugs, and subjects with body mass index (BMI) ≥25 kg/m(2). Conclusion: The U-shaped association was detected between non-HDL-C and mortality among hypertensive population.

[30] *Murdock DR, Venner E, Muzny DM et al.* **Genetic testing in ambulatory cardiology clinics reveals high rate of findings with clinical management implications**. Genetics in medicine : official journal of the American College of Medical Genetics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34363016

ABSTRACT

PURPOSE: Cardiovascular disease (CVD) is the leading cause of death in adults in the United States, yet the benefits of genetic testing are not universally accepted. METHODS: We developed the "HeartCare" panel of genes associated with CVD, evaluating high-penetrance Mendelian conditions, coronary artery disease (CAD) polygenic risk, LPA gene polymorphisms, and specific pharmacogenetic (PGx) variants. We enrolled 709 individuals from cardiology clinics at Baylor College of Medicine, and samples were analyzed in a CAP/CLIA-certified laboratory. Results were returned to the ordering physician and uploaded to the electronic medical record. RESULTS: Notably, 32% of patients had a genetic finding with clinical management implications, even after excluding PGx results, including 9% who were molecularly diagnosed with a Mendelian condition. Among surveyed physicians, 84% reported medical management changes based on these results, including specialist referrals, cardiac tests, and medication changes. LPA polymorphisms and high polygenic risk of CAD were found in 20% and 9% of patients, respectively, leading to diet, lifestyle, and other changes. Warfarin and simvastatin pharmacogenetic variants were present in roughly half of the

cohort. CONCLUSION: Our results support the use of genetic information in routine cardiovascular health management and provide a roadmap for accompanying research.

[31] *Takeshige R, Otake H, Kawamori H et al.* **Progression from normal vessel wall to atherosclerotic plaque: lessons from an optical coherence tomography study with follow-up of over 5 years**. Heart Vessels 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34338851
ABSTRACT
The initial process of atherosclerotic development has not been systematically evaluated. This study aimed to observe atherosclerotic progression from normal vessel wall (NVW) to atherosclerotic plaque and examine local factors associated with such progression using>5-year long-term follow-up data obtained by serial optical coherence tomography (OCT). A total of 49 patients who underwent serial OCT for lesions with NVW over 5 years (average: 6.9 years) were enrolled. NVW was defined as a vessel wall with an OCT-detectable three-layer structure and intimal thickness≤300 μm. Baseline and follow-up OCT images were matched, and OCT cross sections with NVW>30° were enrolled. Cross sections were diagnosed as "progression" when the NVW in these cross sections was reduced by>30° at>5-year follow-up. Atherogenic progression from NVW to atherosclerotic plaque was observed in 40.8% of enrolled cross sections. The incidence of microchannels in an adjacent atherosclerotic plaque within the same cross section (6.7 vs. 3.3%; p=0.046) and eccentric distribution of atherosclerotic plaque (25.0 vs. 12.6%; p<0.001) at baseline was significantly higher in cross sections with progression than in those without. Cross sections with progression exhibited significantly higher NVW intimal thickness at baseline than cross sections without progression (200.1±53.7 vs. 180.2±59.6 μm; p<0.001). Multivariate analysis revealed that the presence of microchannels in an adjacent atherosclerotic plaque, eccentric distribution of atherosclerotic plaque, and greater NVW intimal thickness at baseline were independently associated with progression at follow-up. The presence of microchannels in an adjacent atherosclerotic plaque, eccentric distribution of atherosclerotic plaque, and greater NVW intimal thickness were potentially associated with initial atherosclerotic development from NVW to atherosclerotic plaque.

[32] *Kamon T, Kaneko H, Itoh H et al.* **Possible Gender Difference in the Association Between Abdominal Obesity, Chronic Inflammation, and Preclinical Atherosclerosis in the General Population**. Int Heart J 2021; 62:837-842.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34334582
ABSTRACT
Chronic inflammation due to abdominal obesity plays a major role in the development of cardiovascular disease (CVD). Gender differences are well characterized in the development of CVD; however, in the association among abdominal obesity, chronic inflammation, and preclinical atherosclerosis, gender differences in the general population remain to be clarified. We retrospectively analyzed 1,163 subjects who underwent voluntary health checkups at our institute. We defined carotid artery plaque formation as carotid intima-media thickness ≥ 1.1 mm. Multiple regression analysis showed that waist circumference was a major independent predictor of increase in serum C-reactive protein (CRP) level in both men and women. Serum CRP level was significantly increased in men with carotid artery plaque formation, but not in women. Multivariable logistic regression analysis demonstrated that serum CRP level, as well as age and hypertension, was

independently associated with carotid artery plaque formation only in men. This result may suggest a potential of gender-specific difference in the association between serum CRP level and the prevalence of carotid artery plaque formation. Further investigations are required to confirm our results and to clarify the underlying mechanism.

[33] *Sellegounder D, Zafari P, Rajabinejad M et al.* **Advanced glycation end products (AGEs) and its receptor, RAGE, modulate age-dependent COVID-19 morbidity and mortality. A review and hypothesis**. Int Immunopharmacol 2021; 98:107806.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34352471
ABSTRACT
Coronavirus Disease 2019 (COVID-19), caused by the novel virus SARS-CoV-2, is often more severe in older adults. Besides age, other underlying conditions such as obesity, diabetes, high blood pressure, and malignancies, which are also associated with aging, have been considered risk factors for COVID-19 mortality. A rapidly expanding body of evidence has brought up various scenarios for these observations and hyperinflammatory reactions associated with COVID-19 pathogenesis. Advanced glycation end products (AGEs) generated upon glycation of proteins, DNA, or lipids play a crucial role in the pathogenesis of age-related diseases and all of the above-mentioned COVID-19 risk factors. Interestingly, the receptor for AGEs (RAGE) is mainly expressed by type 2 epithelial cells in the alveolar sac, which has a critical role in SARS-CoV-2-associated hyper inflammation and lung injury. Here we discuss our hypothesis that AGEs, through their interaction with RAGE amongst other molecules, modulates COVID-19 pathogenesis and related comorbidities, especially in the elderly.

[34] *Na X, Chen Y, Ma X et al.* **Relations of Lifestyle Behavior Clusters to Dyslipidemia in China: A Compositional Data Analysis**. International journal of environmental research and public health 2021; 18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34360055
ABSTRACT
Dyslipidemia is associated with lifestyle behaviors, while several lifestyle behaviors exist collectively among some populaitons. This study aims to identify lifestyle behavior clusters and their relations to dyslipidemia. This cross-sectional study was conducted in Wuhai City, China. Cluster analysis combined with compositional data analysis was conducted, with 24-h time-use on daily activities and dietary patterns as input variables. Multiple logistic regression was conducted to compare dyslipidemia among clusters. A total of 4306 participants were included. A higher prevalence of newly diagnosed dyslipidemia was found among participants in cluster 1 (long sedentary behavior (SB) and the shortest sleep, high-salt and oil diet) /cluster 5 (the longest SB and short sleep), relative to the other clusters in both age groups (<50 years and ≥50 years). In conclusion, unhealthy lifestyle behaviors may exist together among some of the population, suggesting that these people are potential subjects of health education and behavior interventions. Future research should be conducted to investigate the relative significance of specific lifestyle behaviors in relation to dyslipidemia.

[35] *Zapata BR, Müller JM, Vásquez JE et al.* **Omega-3 Index and Clinical Outcomes of Severe COVID-19: Preliminary Results of a Cross-Sectional Study**. International journal of environmental research and public health 2021; 18.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34360016

ABSTRACT

The potentially detrimental effects of the worldwide deficiency of Omega-3 fatty acids on the COVID-19 pandemic have been underestimated. The Omega-3 Index (O3I), clinical variables, biometric indices, and nutritional information were directly determined for 74 patients with severe COVID-19 and 10 healthy quality-control subjects. The relationships between the OI3 and mechanical ventilation (MV) and death were analyzed. Results: Patients with COVID-19 exhibited low O3I (mean: 4.15%; range: 3.06-6.14%)-consistent with insufficient fish and Omega-3 supplement consumption, and markedly lower than the healthy control subjects (mean: 7.84%; range: 4.65-10.71%). Inverse associations were observed between O3I and MV (OR = 0.459; C.I.: 0.211-0.997) and death (OR = 0.28; C.I.: 0.08-0.985) in severe COVID-19, even after adjusting for sex, age, and well-known risk factors. Conclusion: We present preliminary evidence to support the hypothesis that the risk of severe COVID-19 can be stratified by the O3I quartile. Further investigations are needed to assess the value of the O3I as a blood marker for COVID-19.

[36] *Kon V, Yang HC, Smith LE et al.* **High-Density Lipoproteins in Kidney Disease**. International journal of molecular sciences 2021; 22.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34360965

ABSTRACT

Decades of epidemiological studies have established the strong inverse relationship between high-density lipoprotein (HDL)-cholesterol concentration and cardiovascular disease. Recent evidence suggests that HDL particle functions, including anti-inflammatory and antioxidant functions, and cholesterol efflux capacity may be more strongly associated with cardiovascular disease protection than HDL cholesterol concentration. These HDL functions are also relevant in non-cardiovascular diseases, including acute and chronic kidney disease. This review examines our current understanding of the kidneys' role in HDL metabolism and homeostasis, and the effect of kidney disease on HDL composition and functionality. Additionally, the roles of HDL particles, proteins, and small RNA cargo on kidney cell function and on the development and progression of both acute and chronic kidney disease are examined. The effect of HDL protein modification by reactive dicarbonyls, including malondialdehyde and isolevuglandin, which form adducts with apolipoprotein A-I and impair proper HDL function in kidney disease, is also explored. Finally, the potential to develop targeted therapies that increase HDL concentration or functionality to improve acute or chronic kidney disease outcomes is discussed.

[37] *Chun KH, Park JM, Lee CJ et al.* **Statin Therapy in HIGH-Risk Individuals with NORMal Coronary Arteries: The HIGH-NORM Study**. Journal of atherosclerosis and thrombosis 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34334544

ABSTRACT

AIMS: Mismatches between the risk status of a patient and coronary imaging data can lead to conflicting strategies to prevent a cardiovascular event. We evaluated whether statin use was associated with cardiovascular benefit in high-risk individuals whose coronary computed tomography angiography (CCTA) results showed normal coronary arteries. METHODS: Among asymptomatic individuals whose CCTA showed normal or near normal coronary arteries, 3,389 persons with high- or very-high-risk status were included in this retrospective study. After 1:2 propensity score matching,

906 individuals (302 new statin users and 604 controls; mean age 61 years; male 58%) were analysed. The primary outcome variable was major adverse cardiovascular and cerebrovascular events (MACCEs) that consisted of cardiovascular death, nonfatal myocardial infarction, coronary revascularisation, and nonfatal ischemic stroke. RESULTS: At a median follow-up of 5.8 years, 20 statin users and 17 controls (7.4 and 5.6 events/1,000 person-year, respectively; hazard ratio [HR) 1.04; p=0.92) experienced MACCE. Kaplan-Meier curves showed similar MACCE rates in both groups (p=0.91). In separate analyses for persons with normal (p=0.29) or near normal coronary arteries (p=0.67), MACCE rates did not differ between the groups. Age (HR 1.04; p=0.044), male sex (HR 3.06, p=0.018), and smoking (HR 2.87, p=0.019) were independently associated with MACCEs. In subgroup analyses, no significant factors affected the relationship between statin use and MACCEs. CONCLUSIONS: Statin use was not associated with cardiovascular risk reduction in high-risk persons with normal or near normal coronary arteries. More individualised lipid-lowering therapy may benefit this population.

[38] *Wang F, Huang L, Zhang J et al.* **Dyslipidemia in Chinese Pancreatic Cancer Patients: A Two-Center Retrospective Study**. Journal of Cancer 2021; 12:5338-5344.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34335950
ABSTRACT
Background: Pancreatic cancer (PC) is one of the most aggressive and lethal malignancies in the world. High cholesterol intake may have a certain association with an elevated risk of PC, though dyslipidemia in PC patients has rarely been reported. In this study, we compared serum lipids levels between PC and non-PC tumor patients and assessed their prognostic value in PC. Methods: 271 patients treated at Wuhan Union Hospital from January 2012 to December 2016 and 204 individuals at Shanghai General Hospital from January 2018 to December 2019 were recruited. Their demographic parameters, laboratory data, pathological information, and clinical outcomes were extracted and analyzed. The mRNA expressions of related lipoprotein, low density lipoprotein receptor (LDLR) and high density lipoprotein binding protein (HDLBP), in PC tissues and paired noncancerous tissues and follow-up information were assessed based on the GEO database (GSE15471 and GSE62165) and TCGA database. Results: A total of 172 non-PC tumor patients and 260 PC patients were finally eligible for our analysis. PC patients exhibited higher levels of serum triglyceride, cholesterol, and low-density lipoprotein (LDL) and a lower serum high-density lipoprotein (HDL) level on admission versus the non-PC tumor group. In PC patients, LDLR mRNA expression was upregulated, and HDLBP mRNA expression was downregulated in cancerous tissues compared to these levels in paired noncancerous tissues. The survival analysis revealed that dyslipidemia had a non-significant association with a poor prognosis, but PC patients with a high LDLR level were at risk of poor survival. Conclusion: Dyslipidemia is detected in PC patients but has a non-significant relation to PC prognosis. However, LDLR may be a potential predictive marker for PC prognosis.

[39] *Astaneh B, Makhdami N, Astaneh V, Guyatt G*. **The Effect of Mipomersen in the Management of Patients with Familial Hypercholesterolemia: A Systematic Review and Meta-Analysis of Clinical Trials**. Journal of cardiovascular development and disease 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34357325
ABSTRACT

Background: Familial hypercholesterolemia (FH) lead to significant adverse effects in coronary arteries. Mipomersen is a second-generation antisense oligonucleotide that inhibits the synthesis of apolipoprotein B-100, an essential component of low density lipoprotein (LDL), and thus decreases the production of LDL. We aimed to determine the effect of mipomersen in patients with FH. Methods: We searched Ovid Medline, Ovid EMBASE, WHO ICTRP search portal, ISI database, the reference lists of relevant articles, and also Google Scholar to retrieve articles. All randomized controlled trials (RCTs) comparing patients with FH receiving mipomersen as an add-on and a parallel group receiving a placebo or no intervention were selected. Results: Five studies with more than 500 patients were included. All had low risk of bias. Pooling data showed that mipomersen probably reduces LDL compared with placebo [mean difference: -24.79, 95% CI (-30.15, -19.43)] but with a moderate level of certainty. There was a high level of evidence for injection site reactions [RR = 2.56, CI (1.47-4.44)] and a low level for increased serum alanine transaminase (ALT) > 3 times upper limit of normal (ULN) [RR = 5.19, CI (1.01-26.69)]. Conclusion: A moderate level of evidence in decreasing serum LDL indicates that we are uncertain if this drug provides benefit in any outcome important to patients. Although a low level of evidence for an increase in serum ALT leaves uncertainty about this adverse effect, injection site reactions in 10% or more of patients can be an important concern.

[40] *Mateos N, Gómez M, Homar A et al.* **Plasmatic PCSK9 Levels Are Associated with Very Fast Progression of Asymptomatic Degenerative Aortic Stenosis**. Journal of cardiovascular translational research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34341879
ABSTRACT
The aim of this work was to study the association of potential biomarkers with fast aortic stenosis (AS) progression. Patients with moderate-to-severe AS were classified as very fast progressors (VFP) if exhibited an annualized change in peak velocity (aΔVmax) ≥0.45m/s/year and/or in aortic valve area (aΔAVA) ≥-0.2cm2/year. Respective cut-off values of ≥0.3m/s/year and ≥-0.1cm(2)/year defined fast progressors (FP), whereas the remaining patients were non-fast progressors (non-FP). Baseline markers of lipid metabolism, inflammation, and cardiac overload were determined. Two hundred and nine patients (97 non-FP, 38 FP, and 74 VFP) were included. PCSK9 levels were significantly associated with VFP (OR 1.014 [95%CI 1.005-1.024], for every 10 ng/mL), as were active smoking (OR 3.48) and body mass index (BMI, OR 1.09), with an AUC of 0.704 for the model. PCSK9 levels, active smoking, and BMI were associated with very fast AS progression in our series, suggesting that inflammation and calcification participate in disease progression.

[41] *Ashraf AP, Sunil B, Bamba V et al.* **Case Studies in Pediatric Lipid Disorders and Their Management**. The Journal of clinical endocrinology and metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34363474
ABSTRACT
CONTEXT: Identification of modifiable risk factors, including genetic and acquired disorders of lipid and lipoprotein metabolism is increasingly recognized as an opportunity to prevent premature cardiovascular disease (CVD) in at-risk youth. Pediatric endocrinologists are at the forefront of this emerging public health concern and can be instrumental in beginning early interventions to prevent premature CVD-related events during adulthood. AIM: In this article, we use informative case presentations to provide practical approaches to the management of pediatric dyslipidemia. CASES:

We present three scenarios which are commonly encountered in clinical practice: isolated elevation of low-density lipoprotein cholesterol (LDL-C), combined dyslipidemia, and severe hypertriglyceridemia. Treatment with statin is indicated when the LDL-C is ≥190 mg/dL (4.9 mmol/L) in children ≥10 years of age. For LDL-C levels between 130-189 mg/dL (3.4 - 4.89 mmol/L) despite dietary and lifestyle changes, the presence of additional risk factors and comorbid conditions would favor statin therapy. In the case of combined dyslipidemia, the primary treatment target is LDL-C ≤130 mg/dL (3.4 mmol/L) and the secondary target non-HDL-C <145 mg/dL(3.7 mmol/L). If the triglyceride is ≥400 mg/dL (4.5 mmol/L), prescription omega-3 fatty acids and fibrates are considered. In the case of triglyceride >1000 mg/dL (11.3mmol/L), dietary fat restriction remains the corner stone of therapy, even though the landscape of medications is changing. CONCLUSION: Gene variants, acquired conditions or both are responsible for dyslipidemia during childhood. Extreme elevations of triglycerides can lead to pancreatitis. Early identification and management of dyslipidemia and cardiovascular risk factors is extremely important.

[42] *Gao B, Luo Y, He Y et al.* **Carotid sheath xanthoma: A rare manifestation of lipid disorders**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34344629
ABSTRACT
Xanthomas are visibly deformed cholesterol deposits that are commonly associated with lipid disorders, such as familial hypercholesterolemia (FH) or rare sitosterolemia. We present the first report of two cases of carotid sheath xanthomas in patients with lipid disorders. Case 1 involved a 26-year-old woman presenting with two heterogeneous mutations on the ABCG5 gene-as noted on genetic testing-who was finally diagnosed with sitosterolemia. Ultrasonography (US) revealed hypoechoic masses centered in the bilateral carotid sheath, which gradually reduced in size after diet control and the use of ezetimibe. Case 2 involved a 27-year-old man who was diagnosed with possible FH and had recurrent bilateral buttock xanthomas, as well as bilateral carotid sheath masses detected by US. Postoperative pathological examination of the resected right neck mass confirmed a xanthoma with proliferation of multinucleated giant cells and deposition of cholesterol clefts.

[43] *Jakubowski B, Shao Y, McNeal C et al.* **Monogenic and polygenic causes of low and extremely low LDL-C levels in patients referred to specialty lipid clinics: Genetics of low LDL-C**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34340953
ABSTRACT
BACKGROUND: In clinical setting, current standard-of-care does not include genetic testing for patients with low (<50 mg/dL) and extremely low (<20 mg/dL) levels of serum low-density lipoprotein-cholesterol (LDL-C). OBJECTIVE: We aimed identify the underlying molecular cause - both monogenic and polygenic - of low and extremely low LDL-C levels in a cohort of patients presenting to specialty lipid clinics. METHODS: Whole exome sequencing was done in patients with low or extremely low LDL-C not due to any secondary causes. RESULTS: Nine patients (4 women), ranging in age from 25 to 63 years old, with low or extremely low LDL-C levels were evaluated. Median LDL-C was 16 mg/dL (range undetectable - 43), total cholesterol 82 mg/dL (42 - 101), triglycerides 35 mg/dL (19-239), and high-density lipoprotein-cholesterol 45 mg/dL (24-81). Of nine patients, two carried known pathogenic variants in APOB (one stop-gain, one deletion; LDL-C range undetectable -

10 mg/dL); three patients had novel APOB heterozygous mutations (two frameshift deletions and one splice site; LDL-C range undectable-13 mg/dL); two had heterozygous APOB frameshift deletions previously reported as variants of unknown significance (LDL-C 18 mg/dL in both patients); one (LDL-C 43 mg/dL) had two heterozygous mutations in PCSK9, both previously reported to be benign; and one patient (LDL-C 16 mg/dL) had the APO E2/E2 genotype along with several variants of unknown significance in genes associated with triglycerides. No patients had an LDL-C polygenic risk score below the 5th percentile (range 26th percentile to 93rd percentile). CONCLUSION: We found APOB mutations to be the most common molecular defect in patients presenting to lipid clinics with low or extremely low LDL-C . Whether clinical genetic testing and LDL-C polygenic risk scores have any utility - other than diagnostic purposes - for such patients remains unclear. In addition, further efforts may be needed to better reclassify pathogenicity of variants of unknown significance.

[44] *Leiherer A, Mündlein A, Brandtner EM et al.* **Lipid profiles of patients with manifest coronary versus peripheral atherosclerosis - is there a difference?** Journal of internal medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34337800

ABSTRACT

AIM: Peripheral arterial disease (PAD) and coronary artery disease (CAD) are both caused by atherosclerosis. Serum lipids and lipoproteins are predictive of the development of atherosclerosis but it is not clear if they differ in the two manifestations PAD and CAD. We tested whether a more detailed characterization of the lipid and lipoprotein patterns of PAD and CAD allows a clear differentiation between the two atherosclerotic phenotypes. METHODS: A cohort of 274 statin-naïve patients with either newly diagnosed imaging proven PAD (n = 89) or stable CAD (n = 185) was characterized using nuclear magnetic resonance- and liquid chromatography-tandem mass spectrometry-based advanced lipid and lipoprotein analysis. An independent cohort of 1239 patients with PAD and CAD was used for validation. RESULTS: We found a significant difference in markers of inflammation as well as ceramide and phosphatidylcholine levels between PAD and CAD patients. In contrast, basic lipid markers including total cholesterol, LDL cholesterol, HDL cholesterol, lipoprotein(a) or detailed lipoprotein profiles did not differ significantly between PAD and CAD patients. Applying ratios and scores derived from ceramides and phosphatidylcholines further improved the discrimination between PAD and CAD. These significant differences were independent of body composition, from the status of smoking or T2DM, and also from apolipoprotein C-III and other inflammatory parameters which were different between CAD and PAD. CONCLUSION: The present study clearly suggests that PAD and CAD differ in terms of their ceramide- and phosphatidylcholine-based lipid patterns but not in lipoprotein characteristics.

[45] *Nagarathna R, Kumar S, Anand A et al.* **Effectiveness of Yoga Lifestyle on Lipid Metabolism in a Vulnerable Population-A Community Based Multicenter Randomized Controlled Trial**. Medicines (Basel) 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34357153

ABSTRACT

Background: Dyslipidemia poses a high risk for cardiovascular disease and stroke in Type 2 diabetes (T2DM). There are no studies on the impact of a validated integrated yoga lifestyle protocol on lipid profiles in a high-risk diabetes population. Methods: Here, we report the results of lipid profile values of 11,254 (yoga 5932 and control 5322) adults (20-70 years) of both genders with high risk (≥60 on

Indian diabetes risk score) for diabetes from a nationwide rural and urban community-based two group (yoga and conventional management) cluster randomized controlled trial. The yoga group practiced a validated integrated yoga lifestyle protocol (DYP) in nine day camps followed by daily one-hour practice. Biochemical profiling included glycated hemoglobin and lipid profiles before and after three months. Results: There was a significant difference between groups ($p < 0.001$ ANCOVA) with improved serum total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein in the yoga group compared to the control group. Further, the regulatory effect of yoga was noted with a significant decrease or increase in those with high or low values of lipids, respectively, with marginal or no change in those within the normal range. Conclusion: Yoga lifestyle improves and regulates (lowered if high, increased if low) the blood lipid levels in both genders of prediabetic and diabetic individuals in both rural and urban Indian communities.

[46] *Aparisi Á, Iglesias-Echeverría C, Ybarra-Falcón C et al.* **Low-density lipoprotein cholesterol levels are associated with poor clinical outcomes in COVID-19**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021; 31:2619-2627.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34353699
ABSTRACT
BACKGROUND AND AIMS: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the sole causative agent of coronavirus infectious disease-19 (COVID-19). METHODS AND RESULTS: We performed a retrospective single-center study of consecutively admitted patients between March 1st and May 15th(,) 2020, with a definitive diagnosis of SARS-CoV-2 infection. The primary end-point was to evaluate the association of lipid markers with 30-days all-cause mortality in COVID-19. A total of 654 patients were enrolled, with an estimated 30-day mortality of 22.8% (149 patients). Non-survivors had lower total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) levels during the entire course of the disease. Both showed a significant inverse correlation with inflammatory markers and a positive correlation with lymphocyte count. In a multivariate analysis, LDL-c ≤ 69 mg/dl (hazard ratio [HR] 1.94; 95% confidence interval [CI] 1.14-3.31), C-reactive protein >88 mg/dl (HR 2.44; 95% CI, 1.41-4.23) and lymphopenia <1000 (HR 2.68; 95% CI, 1.91-3.78) at admission were independently associated with 30-day mortality. This association was maintained 7 days after admission. Survivors presented with complete normalization of their lipid profiles on short-term follow-up. CONCLUSION: Hypolipidemia in SARS-CoV-2 infection may be secondary to an immune-inflammatory response, with complete recovery in survivors. Low LDL-c serum levels are independently associated with higher 30-day mortality in COVID-19 patients.

[47] *Wang A, Tian X, Zuo Y et al.* **Association between the triglyceride-glucose index and carotid plaque stability in nondiabetic adults**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021; 31:2921-2928.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34353702
ABSTRACT
BACKGROUND AND AIMS: The rupture of an unstable atherosclerotic plaque is one of the major causes of thrombosis. However, there was limited evidence on the relationship of triglyceride-glucose (TyG) index, a simple surrogate marker of insulin resistance, with the carotid plaque stability. This study aimed to investigate the association between the TyG index and carotid plaque stability in nondiabetic adults. METHODS AND RESULTS: The study included 4748 nondiabetic participants

from the Asymptomatic Polyvascular Abnormalities Community study. Carotid plaque stability was assessed using ultrasonography. The TyG index was calculated as ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2]. Logistic regression was used to evaluate the association of the TyG index with carotid plaque stability by calculating odds ratio (OR) and 95% confidence interval (CI). Of the 4748 participants, 1192 (25.11%) participants had stable carotid plaque, and 1247 (26.26%) had unstable carotid plaque. The prevalence of unstable carotid plaque substantially increased with increasing TyG index tertile (P for trend <0.0001). In the fully adjusted model, the OR comparing participants in the highest versus the lowest tertile of the TyG index was 1.31 (95% CI, 1.09-1.57). The optimal cutoff point for the TyG index in case of unstable carotid plaque was 8.56. However, we did not observe a statistically significant association between the TyG index and stable carotid plaque. CONCLUSIONS: Elevated the TyG index was significantly associated with the prevalence of unstable carotid plaque in nondiabetic adults.

[48] *Lacaze P, Riaz M, Sebra R et al.* **Protective lipid-lowering variants in healthy older individuals without coronary heart disease**. Open heart 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34341098
ABSTRACT
OBJECTIVE: Genetic variants that disrupt the function of the PCSK9 (proprotein convertase subtilisin kexin type 9) and APOB (apolipoprotein B)genes result in lower serum low-density lipoprotein cholesterol (LDL-C) levels and subsequently confer protection against coronary heart disease (CHD). The objective of this study was to measure the prevalence and selective advantage of such variants among healthy older individuals without a history of CHD. METHODS: We performed targeted sequencing of the PCSK9 and APOB genes in 13 131 healthy individuals without CHD aged 70 years or older enrolled into the ASPirin in Reducing Events in the Elderly trial. We detected variants in the PCSK9 and APOB genes with predicted loss-of-function. We associated variant carrier status with serum LDL-C and total cholesterol (TC) levels at the time of study enrolment, adjusting for statin use. RESULTS: We detected 22 different rare PCSK9/APOB candidate variants with putative lipid-lowering effect, carried by 104 participants (carrier rate 1 in 126). Serum LDL-C and TC concentrations for rare PCSK9/APOB variant carriers were consistently lower than non-carriers. Rare variant carrier status was associated with 19.4 mg/dL (14.6%) lower LDL-C, compared with non-carriers ($p \leq 0.001$, adjusted for statin use). Statin prescriptions were less prevalent in rare variant carriers (16%) than non-carriers (35%). The more common PCSK9 R46L variant (rs11591147-T) was associated with 15.5 mg/dL (11.8%) lower LDL-C in heterozygotes, and 25.2 mg/dL (19.2%) lower LDL-C in homozygotes (both $p \leq 0.001$). CONCLUSIONS: Lipid-lowering genetic variants are carried by healthy older individuals and contribute to CHD-free survival. TRIAL REGISTRATION NUMBER: NCT01038583.

[49] *Alfaifi AA, Lai L, Althemery AU*. **Barriers in utilizing lipid-lowering agents in non-institutionalized population in the U.S.: Application of a theoretical framework**. PloS one 2021; 16:e0255729.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34352007
ABSTRACT
Cardiovascular diseases are a major cause of death globally. Epidemiological evidence has linked elevated levels of blood cholesterol with the risk of coronary heart disease. However, lipid-lowering

agents, despite their importance for primary prevention, are significantly underused in the United States. The objective of this study was to explore associations among socioeconomic factors and the use of antihyperlipidemic agents in 2018 in U.S. patients with hyperlipidemia by applying a theoretical framework. Data from the 2018 Medical Expenditure Panel Survey were used to identify the population of non-institutionalized U.S. civilians diagnosed with hyperlipidemia. This cross sectional study applied the Andersen Behavioral Model to identify patients' predisposing, enabling, and need factors. Approximately 43 million non-institutionalized adults were diagnosed with hyperlipidemia. With the exception of gender and race, predisposing factors indicated significant differences between patients who used antihyperlipidemic agents and those who did not. The relation between income level and use of antihyperlipidemic agents was significant: X2 (4, N = 3,781) = 7.09, p <.001. Hispanic patients were found to be less likely to receive treatment (OR: 0.62; 95% CI: 0.43-0.88), as observed using a logistic model, with controls for predisposing, enabling, and need factors. Patients without health insurance were less likely to use lipid-lowering agents (OR: 0.33; 95% CI: 0.14-0.77). The present study offers essential data for prioritizing interventions by health policy makers by identifying barriers in utilizing hyperlipidemia therapy. Non-adherence to treatment may lead to severe consequences and increase the frequency of fatal cardiac events in the near future.

[50] *Ferrières J, Banks V, Pillas D et al.* **Screening and treatment of familial hypercholesterolemia in a French sample of ambulatory care patients: A retrospective longitudinal cohort study**. PloS one 2021; 16:e0255345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34339471

ABSTRACT

BACKGROUND AND AIMS: Untreated Familial Hypercholesterolemia (FH) leads to premature morbidity and mortality. In France, its epidemiology and management are understudied in ambulatory care. We described the clinical profile, pharmacological management, and clinical outcomes in a French sample of FH patients. METHODS: This was a retrospective longitudinal study on patients from The Health Improvement Network (THIN®) database in France, between October 2016-June 2019. Patients ≥18 years, with probable/definite FH based on the Dutch Lipid Clinic Network (DLCN) criteria were included. Baseline characteristics, lipid profile, lipid-lowering therapy (LLT), low-density lipoprotein-cholesterol (LDL-C) goal achievement; and disease management at 6-month of follow-up were analyzed. RESULTS: 116 patients with probable (n = 70)/definite (n = 46) FH were included (mean age:57.8±14.0 years; 56.0% women; 9.5% with personal history of cardiovascular events); 90 patients had data available at follow-up. At baseline, 77.6% of patients had LDL-C>190 mg/dL, 27.6% were not receiving LLTs, 37.9% received statins alone, 20.7% statins with other LLTs, and 7.7% other LLTs. High-intensity statins were prescribed to 11.2% of patients, 30.2% received moderate-intensity statins, and 8.6% low-intensity statins. Only 6.0% of patients achieved LDL-C goal. At 6-month of follow-up, statins discontinuation and switching were 22.7% and 2.3%, respectively. None of the patients received proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors at baseline nor follow-up. CONCLUSIONS: Despite the existence of effective LLTs, FH patients are suboptimally-treated, do not achieve LDL-C goal, and exhibit worsened pharmacological management over time. Future studies with longer follow-up periods and assessment of factors affecting LDL-C management, including lifestyle and diet, are needed.

[51] *Ludwig CA, Vail D, Rajeshuni NA et al.* **Statins and the progression of age-related macular degeneration in the United States**. PloS one 2021; 16:e0252878.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34347799
ABSTRACT
PURPOSE: To study the effect of statin exposure on the progression from non-exudative to exudative age-related macular degeneration (AMD). METHODS: Retrospective cohort study of commercially insured patients diagnosed with non-exudative AMD (n = 231,888) from 2007 to 2015. Time-to-event analysis of the association between exposure to lipid-lowering medications and time from non-exudative AMD to exudative AMD diagnosis was conducted. Outcome measures included progression to exudative AMD, indicated by diagnosis codes for exudative AMD or procedural codes for intravitreal injections. RESULTS: In the year before and after first AMD diagnosis, 11,330 patients were continuously prescribed lipid-lowering medications and 31,627 patients did not take any lipid-lowering medication. Of those taking statins, 21 (1.6%) patients were on very-high-dose lipophilic statins, 644 (47.6%) on high-dose lipophilic statins, and 689 (50.9%) on low-dose lipophilic statins. We found no statistically significant relationship between exposure to low (HR 0.89, 95% CI 0.83 to 1.38) or high-dose lipophilic statins (HR 1.12, 95% CI 0.86 to 1.45) and progression to exudative AMD. No patients taking very-high-dose lipophilic statins converted from non-exudative to exudative AMD, though this difference was not statistically significant due to the subgroup size (p = .23, log-rank test). CONCLUSIONS: No statistically significant relationship was found between statin exposure and risk of AMD progression. Interestingly, no patients taking very-high-dose lipophilic statins progressed to exudative AMD, a finding that warrants further exploration.

[52] *Zainab R, Kaleem A, Ponczek MB et al.* **Finding inhibitors for PCSK9 using computational methods**. PloS one 2021; 16:e0255523.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34351937
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) is one of the key targets for atherosclerosis drug development as its binding with low-density lipoprotein receptor leads to atherosclerosis. The protein-ligand interaction helps to understand the actual mechanism for the pharmacological action. This research aims to discover the best inhibitory candidates targeting PCSK9. To start with, reported ACE inhibitors were incorporated into pharmacophore designing using PharmaGist to produce pharmacophore models. Selected models were later screened against the ZINC database using ZINCPHARMER to define potential drug candidates that were docked with the target protein to understand their interactions. Molecular docking revealed the top 10 drug candidates against PCSK9, with binding energies ranging from -9.8 kcal·mol-1 to -8.2 kcal·mol-1, which were analyzed for their pharmacokinetic properties and oral bioavailability. Some compounds were identified as plant-derived compounds like (S)-canadine, hesperetin or labetalol (an antihypertensive drug). Molecular dynamics results showed that these substances formed stable protein-ligand complexes. (S)-canadine-PCSK9 complex was the most stable with the lowest RMSD. It was concluded that (S)-canadine may act as a potential inhibitor against atherosclerosis for the development of new PCSK9 inhibitory drugs in future in vitro research.

[53] *Drakos S, Chatzantonis G, Bietenbeck M et al.* **A cardiovascular magnetic resonance imaging-based pilot study to assess coronary microvascular disease in COVID-19 patients**. Scientific reports 2021; 11:15667.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34341436

ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and is primarily characterised by a respiratory disease. However, SARS-CoV-2 can directly infect vascular endothelium and subsequently cause vascular inflammation, atherosclerotic plaque instability and thereby result in both endothelial dysfunction and myocardial inflammation/infarction. Interestingly, up to 50% of patients suffer from persistent exercise dyspnoea and a post-viral fatigue syndrome (PVFS) after having overcome an acute COVID-19 infection. In the present study, we assessed the presence of coronary microvascular disease (CMD) by cardiovascular magnetic resonance (CMR) in post-COVID-19 patients still suffering from exercise dyspnoea and PVFS. N = 22 patients who recently recovered from COVID-19, N = 16 patients with classic hypertrophic cardiomyopathy (HCM) and N = 17 healthy control patients without relevant cardiac disease underwent dedicated vasodilator-stress CMR studies on a 1.5-T MR scanner. The CMR protocol comprised cine and late-gadolinium-enhancement (LGE) imaging as well as velocity-encoded (VENC) phase-contrast imaging of the coronary sinus flow (CSF) at rest and during pharmacological stress (maximal vasodilation induced by 400 μg IV regadenoson). Using CSF measurements at rest and during stress, global myocardial perfusion reserve (MPR) was calculated. There was no difference in left ventricular ejection-fraction (LV-EF) between COVID-19 patients and controls (60% [57-63%] vs. 63% [60-66%], p = NS). There were only N = 4 COVID-19 patients (18%) showing a non-ischemic pattern of LGE. VENC-based flow measurements showed that CSF at rest was higher in COVID-19 patients compared to controls (1.78 ml/min [1.19-2.23 ml/min] vs. 1.14 ml/min [0.91-1.32 ml/min], p = 0.048). In contrast, CSF during stress was lower in COVID-19 patients compared to controls (3.33 ml/min [2.76-4.20 ml/min] vs. 5.32 ml/min [3.66-5.52 ml/min], p = 0.05). A significantly reduced MPR was calculated in COVID-19 patients compared to healthy controls (2.73 [2.10-4.15-11] vs. 4.82 [3.70-6.68], p = 0.005). No significant differences regarding MPR were detected between COVID-19 patients and HCM patients. In post-COVID-19 patients with persistent exertional dyspnoea and PVFS, a significantly reduced MPR suggestive of CMD-similar to HCM patients-was observed in the present study. A reduction in MPR can be caused by preceding SARS-CoV-2-associated direct as well as secondary triggered mechanisms leading to diffuse CMD, and may explain ongoing symptoms of exercise dyspnoea and PVFS in some patients after COVID-19 infection.

[54] *Klassen A, Faccio AT, Picossi CRC et al.* **Evaluation of two highly effective lipid-lowering therapies in subjects with acute myocardial infarction**. Scientific reports 2021; 11:15973.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34354179

ABSTRACT

For cardiovascular disease prevention, statins alone or combined with ezetimibe have been recommended to achieve low-density lipoprotein cholesterol targets, but their effects on other lipids are less reported. This study was designed to examine lipid changes in subjects with ST-segment elevation myocardial infarction (STEMI) after two highly effective lipid-lowering therapies. Twenty patients with STEMI were randomized to be treated with rosuvastatin 20 mg QD or simvastatin 40 mg

combined with ezetimibe 10 mg QD for 30 days. Fasting blood samples were collected on the first day (D1) and after 30 days (D30). Lipidomic analysis was performed using the Lipidyzer platform. Similar classic lipid profile was obtained in both groups of lipid-lowering therapies. However, differences with the lipidomic analysis were observed between D30 and D1 for most of the analyzed classes. Differences were noted with lipid-lowering therapies for lipids such as FA, LPC, PC, PE, CE, Cer, and SM, notably in patients treated with rosuvastatin. Correlation studies between classic lipid profiles and lipidomic results showed different information. These findings seem relevant, due to the involvement of these lipid classes in crucial mechanisms of atherosclerosis, and may account for residual cardiovascular risk.Randomized clinical trial: ClinicalTrials.gov, NCT02428374, registered on 28/09/2014.

[55] *Momtazi-Borojeni AA, Jaafari MR, Banach M et al.* **Pre-Clinical Evaluation of the Nanoliposomal antiPCSK9 Vaccine in Healthy Non-Human Primates**. Vaccines (Basel) 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34358164

ABSTRACT

BACKGROUND: Our previous studies showed the safe preventive and therapeutic effects of immunization using the nanoliposomal antiPCSK9 vaccine called "Liposomal Immunogenic Fused PCSK9-Tetanus plus Alum adjuvant" (L-IFPTA), in mouse models of atherosclerosis. Here we aimed to ascertain the immunogenicity and safety of the L-IFPTA vaccine in a pre-clinical study in healthy non-human primates. METHODS: Five male rhesus macaque monkeys were subcutaneously immunized with the L-IFPTA vaccine, four times with bi-weekly intervals. To evaluate immunogenicity, the plasma antiPCSK9 antibody in immunized monkeys was detected and quantified using the ELISA method. The functionality of the induced antiPCSK9 antibodies was determined by the PCSK9/LDLR in vitro binding assay kit. The safety of the vaccine was tested using the evaluation of several major circulating indicators including plasma lipid alterations, inflammatory biomarkers and organ injury biomarkers. RESULTS: The resultant data indicated that the L-IFPTA vaccine significantly and highly induced the generation of functional and safe antiPCSK9 antibodies in immunized monkeys. Plasma levels of specific biomarkers indicating organ performance including creatinine, urea, uric acid, bilirubin, ALP, AS, ALT and TSH were not significantly altered. After immunization in healthy monkeys, non-prespecified endpoints (plasma levels of TC, LDL-C, VLDL-C and TG) were non-significantly reduced by 11.6 ± 36%; 16 ± 28%; 22 ± 53% and 24 ± 51%, respectively, while HDL-C was slightly increased by 2 ± 64%. There were also no significant changes in plasma levels of pro- and anti-inflammatory biomarkers. CONCLUSION: The L-IFPTA vaccine could efficiently stimulate the host humoral immune response to produce active antibodies that inhibit plasma PCSK9 while not provoking systemic inflammation and not adversely affecting organ performance.

[56] *Lupilov A, Krause D, Klaassen-Mielke R et al.* **Effects of Three Different Methods Defining Onset of Peripheral Artery Disease on the Assessments of Incidence and Important Predictors - Results from the German Epidemiological Trial on Ankle Brachial Index (getABI)**. Vascular health and risk management 2021; 17:421-429.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34335027

ABSTRACT

PURPOSE: The common definition of asymptomatic peripheral artery disease (PAD) by a single determination of the ankle brachial index (ABI) has some uncertainty due to measurement errors.

This may impact estimates of PAD incidence and assessment of PAD risk factors. To investigate this issue, we used three methods to define asymptomatic PAD and made use of data from the German Epidemiological Trial on Ankle Brachial Index (getABI). PATIENTS AND METHODS: A total of 6,880 unselected subjects aged ≥65 years, enrolled by 344 trained general practitioners, had ABI assessments at baseline and four visits during follow-up. The first approach defined asymptomatic PAD onset as soon as a single ABI value was below 0.9 (single ABI). The second approach employed a regression method using all available ABI values (regression A), while for the third approach (regression B), an extended regression beyond the last valid ABI value for the observation time of the study was allowed. For each approach, we calculated PAD incidence rates and assessed the effect of important PAD predictors using multivariable Cox proportional hazards regression. RESULTS: The regression method A showed the lowest (25.0 events per 1,000 person years) and the single ABI method the highest incidence rate (41.2). The regression methods assigned greater impact to several risk factors of incident PAD. Using regression A, the hazard ratios (HR) of active smoking (2.36; 95% CI 1.92 to 2.90) and of diabetes (1.33; 95% CI 1.13 to 1.56), using regression B the HR of older age (1.72; 95% CI 1.50 to 1.97) were about twice as high as the corresponding HR of the single ABI approach. CONCLUSION: Use of the single ABI method leads to higher PAD incidence rates and to lower impact of important PAD predictors compared to regression methods. For an alert risk factor management, multiple ABI determination may be useful.

[57] *Bellos I, Pergialiotis V, Perrea DN*. **Comparative efficacy of fixed-dose statin and antihypertensive agent combinations: A network meta-analysis of randomized controlled trials**. Vascular pharmacology 2021:106900.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34343694

ABSTRACT

BACKGROUND: The concurrent administration of statins and antihypertensive agents has been associated with improved cardiovascular outcomes, although the optimal fixed-dose combination remains unclear. This meta-analysis aims to compare the blood pressure and lipid-lowering effects of various statin and antihypertensive drug combinations. METHODS: PubMed, Scopus, Web of Science, CENTRAL and Clinicaltrials.gov were systematically searched from inception to 20 March 2021. Randomized controlled trials evaluating the effects of statin-antihypertensive agent combinations on systolic blood pressure or serum lipids were held eligible. A random-effects frequentist model was applied to provide estimates of mean difference of percentage change. RESULTS: Overall, 18 studies were included, comprising 4450 patients. Compared to statin monotherapy no significant difference in the percentage change of low-density lipoprotein cholesterol was achieved by adding any antihypertensive agent. Compared to amlodipine monotherapy, the addition of moderate-intensity statin resulted in a significantly greater percentage reduction of systolic blood pressure (-2.22%, 95% confidence intervals: [-3.82 to -0.62]). Combined high-intensity statin and amlodipine lead to significant increase of high-density lipoprotein cholesterol (8.34%, 95% confidence intervals: [0.73 to 15.95]), while effective triglyceride reduction was achieved by adding amlodipine and telmisartan to high-intensity statin (-14.68%, 95% confidence intervals: [-28.48 to -0.89]). No significant difference of adverse effects was observed. CONCLUSION: The present network meta-analysis suggests that the administration of fixed-dose combinations of statins and antihypertensive agents is safe and effective in reducing blood pressure and serum lipids. The optimal dosing strategy to prevent cardiovascular events remains to be determined.

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