[1] *Gatzke LC*. **Heterozygous Familial Hyperlipidemia in a Fighter Pilot**. Aerosp Med Hum Perform 2021; 92:835-837.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34642005

ABSTRACT

BACKGROUND: Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant disease characterized by elevated low-density lipoprotein cholesterol (LDL-C) that increases risk for clinically significant atherosclerotic cardiovascular disease (ASCVD). This common (1:220) disease is present within the fighter pilot community and hesitation to treat this condition at younger ages results in a higher risk for coronary artery disease (CAD), the presence of which can be catastrophic for flying safety. CASE REPORT: A 40-yr-old asymptomatic F-15 pilot presented with persistently elevated LDL-C levels > 190 mg dL(1) and a significant family history of CAD. Coronary artery calcium, CT angiography, and finally, invasive angiography were used to further stratify him as having mild CAD. Initiation of statin therapy significantly lowered his LDL and subsequent risk for disease progression, allowing him to return to flying. DISCUSSION: Early recognition and treatment of HeFH is imperative for lowering the risk of ASCVD. Often the medical community supporting flyers is hesitant to diagnose or treat this condition, due to nonrecognition, the young age of presentation, or reluctance to potentially ground a flyer. By intervening earlier, rather than waiting, aviators can remain on flying status longer with lower risk to themselves and their aircrew. Gatzke LC. Heterozygous familial hyperlipidemia in a fighter pilot. Aerosp Med Hum Perform. 2021; 92(10):835837.

[2] *Pereira B, Mazzitelli M, Milinkovic A et al.* **Predictive value of HIV-related versus traditional risk factors for coronary atherosclerosis in people aging with HIV**. AIDS research and human retroviruses 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34652963

ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is an important cause of morbidity in people living with HIV (PLWH). We compared the predictive value of HIV-related and traditional CVD risk factors to assess which factors best predict the presence of subclinical coronary atherosclerosis in PLWH. METHODS: Cross-sectional study in PLWH over 50 years of age who performed CT coronary artery calcium (CAC) scoring between 2009-2019 at Chelsea and Westminster Hospital. The following outcomes were analyzed: CAC=0 (no calcification), CAC >0 (any calcification), CAC >100 (moderate calcification) and CAC >400 (severe calcification). Univariate and multivariate logistic regression analyses were performed to assess predictors of coronary calcification. RESULTS: A total of 744 patients were included (mean age 56 ± 5.7 years, 94.8% male, 84% white). A CAC >0 was found in 392 (52.7%), CAC >100 in 90 (12.1%) and CAC >400 in 42 (5.6%) subjects. CAC >100 was strongly associated with hypertension [odds ratio OR: 2.91, (95% confidence interval CI: 1.93-4.36), P < 0.001], dyslipidemia [2.71 (1.81-4.06), P < 0.001] and diabetes [2.53 (1.29-4.96), P = 0.01]. Regarding HIV-specific factors, a significant association was found with exposure (> 6 years) to protease inhibitors [1.67 (1.06-2.61), P =0.05] whereas exposure to tenofovir (> 8 years) was negatively associated with CAC >100 [0.54 (0.30-0.98), P =0.05]. Despite the high prevalence of hypertension (45.4%), only 21.5% were on anti-hypertensives whereas only 29.2% of eligible candidates were receiving lipid lowering drugs for primary prevention of CVD. CONCLUSIONS: Traditional cardio-metabolic risk factors remain the strongest predictors of coronary atherosclerosis in

PLWH as in the general population. These results underscore the importance of optimizing treatment of hypertension and promoting primary prevention strategies that may be underused in PLWH.

[3] *Yu P, He X, Chang J*. **Effects of targeted community healthcare on the prevention of thrombotic adverse events in patients with coronary heart disease under the guidance of behavior change theory**. American journal of translational research 2021; 13:10703-10711.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34650745

ABSTRACT

OBJECTIVE: To explore the effects of targeted community healthcare on the prevention of thrombotic adverse events in patients with coronary heart disease under the guidance of behavior change theory. METHODS: A total of 89 patients with coronary heart disease who were admitted to our hospital were selected prospectively as subjects and divided into a research group (n=45, receiving targeted community healthcare under the guidance of behavior change theory) and a control group (n=44, receiving regular community healthcare) using a random number table method. The treatment period was 6 months. Then, patient's knowledge and attitude towards coronary heart disease as well as their personal habits, glucose and lipid metabolism indicators, compliance behaviors, quality of life and the incidence of thrombotic adverse events after 1-year of follow-up were compared between the two groups. RESULTS: The scores of patient's knowledge, attitude and personal habits, compliance behaviors and quality of life were all higher in the research group than those in the control group after intervention (all P<0.05); and the glucose and lipid metabolism indicators including fasting insulin (INS), insulin resistance index (HOMA-IR), total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in the research group were significantly better than those in the control group after intervention (all P<0.05); after follow-up for 1 year, the total incidence of cerebral infarction, systemic embolism and myocardial infarction was significantly lower in the research group (6.67%) than that in the control group (25.00%) (P<0.05). CONCLUSION: Targeted community healthcare under the guidance of the behavior change theory can effectively improve patient's compliance behaviors, change their knowledge, attitudes as well as their personal habits, keep their glucose and lipid metabolism indicators under control and reduce the risks of cardiovascular disease. Therefore, it is worth being applied in clinical settings.

[4] *Grieger JA, Leemaqz SY, Knight EJ et al.* **Relative importance of metabolic syndrome components for developing gestational diabetes**. Arch Gynecol Obstet 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34655325

ABSTRACT

PURPOSE: To assess the independent and joint contribution of the individual components of metabolic syndrome, and known risk factors for gestational diabetes (GDM), on risk of GDM. METHODS: Two thousand nine hundred and fifteen women from Australia and New Zealand, who participated in The Screening for Pregnancy Endpoints Study (SCOPE), were included. Using the SCOPE clinical data set and biomarkers obtained at 14-16 weeks' gestation, a logistic regression model was fitted to the binary outcome GDM, with individual metabolic syndrome components (waist circumference, blood pressure, glucose, HDL-C, triglycerides), recruitment site, and other established factors associated with GDM. Hierarchical partitioning was used to assess the relative contribution of each variable. RESULTS: Of the 2915 women, 103 women (3.5%) developed GDM. The deviance explained by the logistic regression model containing all variables was 18.65% and the AUC was

0.809. Seventy percent of the independent effect was accounted for by metabolic syndrome components. The highest independent relative contribution to GDM was circulating triglycerides (17±3%), followed by waist circumference (13±3%). Glucose and maternal BMI contributed 12±2% and 12±3%, respectively. The remaining factors had an independent relative contribution of<10%. CONCLUSION: Triglyceride concentrations had the highest independent relative importance for risk of GDM. Increased focus for lowering triglycerides as an important risk factor for GDM is warranted.

[5] *Biessen EAL, Van Berkel TJC*. **N-Acetyl Galactosamine Targeting: Paving the Way for Clinical Application of Nucleotide Medicines in Cardiovascular Diseases**. Arteriosclerosis, thrombosis, and vascular biology 2021; 41:2855-2865.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34645280
ABSTRACT
While the promise of oligonucleotide therapeutics, such as (chemically modified) ASO (antisense oligonucleotides) and short interfering RNAs, is undisputed from their introduction onwards, their unfavorable pharmacokinetics and intrinsic capacity to mobilize innate immune responses, were limiting widespread clinical use. However, these major setbacks have been tackled by breakthroughs in chemistry, stability and delivery. When aiming an intervention hepatic targets, such as lipid and sugar metabolism, coagulation, not to mention cancer and virus infection, introduction of N-acetylgalactosamine aided targeting technology has advanced the field profoundly and by now a dozen of N-acetylgalactosamine therapeutics for these indications have been approved for clinical use or have progressed to clinical trial stage 2 to 3 testing. This technology, in combination with major advances in oligonucleotide stability allows safe and durable intervention in targets that were previously deemed undruggable, such as Lp(a) and PCSK9 (proprotein convertase subtilisin/kexin type 9), at high efficacy and specificity, often with as little as 2 doses per year. Their successful use even the most visionary would not have predicted 2 decades ago. Here, we will review the evolution of N-acetylgalactosamine technology. We shall outline their fundamental design principles and merits, and their application for the delivery of oligonucleotide therapeutics to the liver. Finally, we will discuss the perspectives of N-acetylgalactosamine technology and propose directions for future research in receptor targeted delivery of these gene medicines.

[6] *Shurshalova GS, Scheidt HA, Fischer M et al.* **Interaction of the pitavastatin with model membranes**. Biochemistry and biophysics reports 2021; 28:101143.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34632116
ABSTRACT
Pitavastatin is a statin drug that, by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, can lower serum cholesterol levels of low-density lipoprotein (LDL) accompanied by side effects due to pleiotropic effects leading to statin intolerance. These effects can be explained by the lipophilicity of statins, which creates membrane affinity and causes statin localization in cellular membranes. In the current report, the interaction of pitavastatin with POPC model membranes and its influence on the membrane structure were investigated using H, H and P solid-state NMR spectroscopy. Our experiments show the average localization of pitavastatin at the lipid/water interface of the membrane, which is biased towards the hydrocarbon core in comparison to other statin molecules. The membrane binding of pitavastatin also introduced an isotropic component into

the (31)P NMR powder spectra, suggesting that some of the lamellar POPC molecules are converted into highly curved structures.

[7] *Kjeldsen EW, Thomassen JQ, Frikke-Schmidt R*. **HDL cholesterol concentrations and risk of atherosclerotic cardiovascular disease - Insights from randomized clinical trials and human genetics**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2022; 1867:159063.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34637926

ABSTRACT

Through seven decades the inverse association between HDL cholesterol concentrations and risk of atherosclerotic cardiovascular disease (ASCVD) has been observed in case-control and prospective cohort studies. This robust inverse association fuelled the enthusiasm towards development of HDL cholesterol increasing drugs, exemplified by the cholesteryl ester transfer protein (CETP) inhibitor trials and the extended-release niacin HPS2-THRIVE trial. These HDL cholesterol increasing trials were launched without conclusive evidence from human genetics, and despite discrepant species dependent evidence from animal studies. Evidence from human genetics and from randomized clinical trials over the last 13 years now point in the direction that concentrations of HDL cholesterol, do not appear to be a viable future path to target therapeutically for prevention of ASCVD. A likely explanation for the strong observational association between low HDL cholesterol and high ASCVD risk is the concomitant inverse association between HDL cholesterol and atherogenic triglyceride-rich lipoproteins. The purpose of the present review is to bring HDL cholesterol increasing trials into a human genetics context exemplified by candidate gene studies of key players in HDL biogenesis as well as by HDL cholesterol related genome-wide association studies.

[8] *Nyambuya TM, Dludla PV, Mxinwa V, Nkambule BB*. **The pleotropic effects of fluvastatin on complement-mediated T-cell activation in hypercholesterolemia**. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021; 143:112224.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34649351

ABSTRACT

T-cells orchestrate the inflammatory responses in atherosclerosis, and their function is modified by the lipoprotein milieu and complement activity. We investigated the effects of fluvastatin on the expression of complement decay-accelerating factor (DAF/CD55) antigen, and the levels of transcription factors in circulating T-cells in hypercholesterolemia. The hypercholesterolemic state was associated with the upregulation of DAF expression on circulating T-cells and increased levels nuclear factor kappa B (NF-kB) and interferon regulatory factor 4 (IRF4). Notably, the elevated levels of DAF and NF-kB expression persisted following treatment with fluvastatin. Therefore, the pleiotropic effects of fluvastatin are partially ascribed to its ability to mediate T-cell activation and regulate complement activity. Consequently, enhanced therapeutic interventions that targets complement-induced T-cell activation may be important in mitigating the development of atherosclerosis and major cardiovascular events in individuals with hypercholesterolemia.

[9] *Byrne P, Demasi M, Smith SM*. **NICE guidance on inclisiran should be reconsidered**. Bmj 2021; 375:n2462.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34642203

ABSTRACT

[10] *Naghshi S, Aune D, Beyene J et al.* **Dietary intake and biomarkers of alpha linolenic acid and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of cohort studies**. Bmj 2021; 375:n2213.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34645650
ABSTRACT
OBJECTIVE: To examine the associations between dietary intake and tissue biomarkers of alpha linolenic acid (ALA) and risk of mortality from all causes, cardiovascular disease (CVD), and cancer. DESIGN: Systematic review and meta-analysis of prospective cohort studies. DATA SOURCES: PubMed, Scopus, ISI Web of Science, and Google Scholar to 30 April 2021. STUDY SELECTION: Prospective cohort studies that reported the risk estimates for death from all causes, CVD, and cancer. DATA SYNTHESIS: Summary relative risks and 95% confidence intervals were calculated for the highest versus lowest categories of ALA intake using random effects and fixed effects models. Linear and non-linear dose-response analyses were conducted to assess the dose-response associations between ALA intake and mortality. RESULTS: 41 articles from prospective cohort studies were included in this systematic review and meta-analysis, totalling 1 197 564 participants. During follow-up ranging from two to 32 years, 198 113 deaths from all causes, 62 773 from CVD, and 65 954 from cancer were recorded. High intake of ALA compared with low intake was significantly associated with a lower risk of deaths from all causes (pooled relative risk 0.90, 95% confidence interval 0.83 to 0.97, I(2)=77.8%, 15 studies), CVD (0.92, 0.86 to 0.99, I(2)=48.2%, n=16), and coronary heart disease (CHD) (0.89, 0.81 to 0.97, I(2)=5.6%, n=9), and a slightly higher risk of cancer mortality (1.06, 1.02 to 1.11, I(2)=3.8%, n=10). In the dose-response analysis, a 1 g/day increase in ALA intake (equivalent to one tablespoon of canola oil or 0.5 ounces of walnut) was associated with a 5% lower risk of all cause (0.95, 0.91 to 0.99, I(2)=76.2%, n=12) and CVD mortality (0.95, 0.91 to 0.98, I(2)=30.7%, n=14). The pooled relative risks for the highest compared with lowest tissue levels of ALA indicated a significant inverse association with all cause mortality (0.95, 0.90 to 0.99, I(2)=8.2%, n=26). Also, based on the dose-response analysis, each 1 standard deviation increment in blood concentrations of ALA was associated with a lower risk of CHD mortality (0.92, 0.86 to 0.98, I(2)=37.1%, n=14). CONCLUSIONS: The findings show that dietary ALA intake is associated with a reduced risk of mortality from all causes, CVD, and CHD, and a slightly higher risk of cancer mortality, whereas higher blood levels of ALA are associated with a reduced risk of all cause and CHD mortality only. SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42021229487.

[11] *Lv L, Wu S, Yang Y, Yue X*. **Modified effect of active or passive smoking on the association between age and abdominal aortic calcification: a nationally representative cross-sectional study**. BMJ open 2021; 11:e047645.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34642189
ABSTRACT
OBJECTIVE: The deleterious effects of smoking on atherosclerosis were well known; however, the interaction among ageing, smoking and atherosclerosis remains unclear. This study tested the hypothesis that the association between age and vascular calcification, a critical mark of atherosclerosis, was modified by smoking. DESIGN: Cross-sectional study. SETTING: A nationally representative sample, the National Health and Nutrition Examination Surveys 2013-2014. PARTICIPANTS: This study included 3140 adults aged 40-80 years with eligible data for abdominal

aortic calcification (AAC). Active and passive smoking exposure was identified through self-reports and tobacco metabolites (serum cotinine and urinary 4-methylnitrosamino-3-pyridyl-1-butanol). PRIMARY OUTCOME MEASURES: AAC score was determined using dual-energy X-ray absorptiometry (DXA) scans. OR was estimated using the logistic regression method to assess the association between age and the presence of severe or subclinical AAC stratified by smoking exposure. The survey-weighted Wald test was used to evaluate potential interactions. RESULTS: AAC was positively associated with age in the general population. After adjustment for age, sex, race/ethnicity and other cardiovascular risk factors, age was significantly associated with the odds of severe AAC (OR for each 5-year increase in age: 1.66, 95% CI 1.48 to 1.87, p<0.001). As expected, the association between age and vascular calcification was especially stronger in smokers than in never smokers (p value for interaction ≤0.014). According to spline fitting, the progression of vascular calcification was significantly increased after 45 years in smokers compared with that after 60 years in never smokers. Quitting smoking may compromise the deleteriousness of the vascellum especially in younger adults. However, the difference in age-related calcification among never smokers with or without secondhand smoke exposure was minor, regardless of the definition by self-report, serum cotinine, or urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. CONCLUSIONS: Smoking significantly accelerated the progression of age-related subclinical atherosclerosis. Early smoking cessation should be encouraged among young smokers. The effect of passive smoking exposure on arteriosclerosis should be assessed further.

[12] *Carr MJ, Wright AK, Leelarathna L et al.* **Impact of COVID-19 restrictions on diabetes health checks and prescribing for people with type 2 diabetes: a UK-wide cohort study involving 618 161 people in primary care**. BMJ Qual Saf 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34642228
ABSTRACT
OBJECTIVE: To compare rates of performing National Institute for Health and Care Excellence-recommended health checks and prescribing in people with type 2 diabetes (T2D), before and after the first COVID-19 peak in March 2020, and to assess whether trends varied by age, sex, ethnicity and deprivation. METHODS: We studied 618 161 people with T2D followed between March and December 2020 from 1744 UK general practices registered with the Clinical Practice Research Datalink. We focused on six health checks: haemoglobin A1c, serum creatinine, cholesterol, urinary albumin excretion, blood pressure and body mass index assessment. Regression models compared observed rates in April 2020 and between March and December 2020 with trend-adjusted expected rates derived from 10-year historical data. RESULTS: In April 2020, in English practices, rates of performing health checks were reduced by 76%-88% when compared with 10-year historical trends, with older people from deprived areas experiencing the greatest reductions. Between May and December 2020, the reduced rates recovered gradually but overall remained 28%-47% lower, with similar findings in other UK nations. Extrapolated to the UK population, there were ~7.4 million fewer care processes undertaken March-December 2020. In England, rates for new medication fell during April with reductions varying from 10% (95% CI: 4% to 16%) for antiplatelet agents to 60% (95% CI: 58% to 62%) for antidiabetic medications. Overall, between March and December 2020, the rate of prescribing new diabetes medications fell by 19% (95% CI: 15% to 22%) and new antihypertensive medication prescribing fell by 22% (95% CI: 18% to 26%), but prescribing of new lipid-lowering or antiplatelet therapy was unchanged. Similar trends were observed across the UK, except for a

reduction in new lipid-lowering therapy prescribing in the other UK nations (reduction: 16% (95% CI: 10% to 21%)). Extrapolated to the UK population, between March and December 2020, there were ~31 800 fewer people with T2D prescribed a new type of diabetes medication and ~14 600 fewer prescribed a new type of antihypertensive medication. CONCLUSIONS: Over the coming months, healthcare services will need to manage this backlog of testing and prescribing. We recommend effective communications to ensure patient engagement with diabetes services, monitoring and opportunities for prescribing, and when appropriate use of home monitoring, remote consultations and other innovations in care.

[13] *Higgins V, Leiter LA, Delaney SR, Beriault DR*. **Validating the NIH LDL-C equation in a specialized lipid cohort: Does it add up?** Clinical biochemistry 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34656564
ABSTRACT
BACKGROUND: Guideline recommendations for the management of lipids in patients at risk for cardiovascular disease is largely based on low-density lipoprotein cholesterol (LDL-C) concentration. LDL-C is commonly calculated by the Friedewald equation, which has many limitations. The National Institutes of Health (NIH) equation better estimates LDL-C, particularly in patients with hypertriglyceridemia and/or low LDL-C. We validated the NIH LDL-C equation at the first Canadian clinical laboratory to implement this equation. METHODS: A total of 3161 lipid ultracentrifugation results from a specialized lipid cohort of 2836 patients were included. LDL-C was calculated using the NIH and Friedewald equations and compared to LDL-C measured by ultracentrifugation. We determined the accuracy of these equations at treatment thresholds and developed NIH equation restriction criteria to ensure only accurate results are reported. RESULTS: Ultracentrifugation LDL-C more strongly correlated with NIH-calculated LDL-C ($r(2) = 0.889$) than Friedewald-calculated LDL-C ($r(2) = 0.807$) and resulted in fewer non-sensical negative LDL-C values. The correlation for NIH-calculated LDL-C improved to $r(2) = 0.975$ after applying our restriction criteria. The NIH equation showed equivalent or superior concordance with ultracentrifugation at treatment thresholds. The LDL-C mean absolute difference increased with increasing TG and decreasing LDL-C concentrations, although the NIH equation was more robust under both conditions. CONCLUSIONS: We validated the NIH equation against ultracentrifugation in a cohort with a wide lipid concentration range, which supported its superiority over the Friedewald equation. We recommend clinical implementing the NIH equation for all patients except those with type III hyperlipoproteinemia or TG > 9.04 mmol/L, with an LDL-C lower reporting limit of <0.50 mmol/L.

[14] *Gong Y, Li X, Ma X et al.* **Lipid goal attainment in post-acute coronary syndrome patients in China: Results from the 6-month real-world dyslipidemia international study II**. Clinical cardiology 2021; 44:1575-1585.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34651329
ABSTRACT
BACKGROUND: Dyslipidemia International Study II (DYSIS II)-China was conducted to determine the low-density lipoprotein cholesterol (LDL-C) goal (<1.8 mmol/L) attainment rate in patients with post-acute coronary syndrome (ACS). HYPOTHESIS: Compliance with treatment guideline recommendations improves the LDL-C goal attainment rate in post-ACS patients. METHODS: This multicenter prospective observational study conducted at 28 tertiary hospitals determined the LDL-C

goal attainment rates at admission and 6-month follow-up in patients on lipid-lowering treatment (LLT) for ≥3 months and those not on LLT (LLT-naive or off LLT for ≥3 months) at admission. Predictors of goal attainment at 6 months were identified using multivariate logistic regression. RESULTS: The LDL-C goal attainment rate at admission in 1102/1103 enrolled patients was 17.1%; it was 41.2% among 752 patients with available lipid results at 6 months. The distance to goal was 0.7 mmol/L at 6 months. Statin monotherapy was the most prescribed LLT. Only 7.7% of patients were receiving statin + ezetimibe and 8.4% of patients were receiving an atorvastatin-equivalent dose of ≥40 mg/day at 6 months. Being male (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.1-2.6) and undergoing percutaneous coronary intervention during index hospitalization (OR 1.5, 95% CI 1.1 to 2.1) were the independent predictors for LDL-C goal attainment. CONCLUSIONS: This real-world DYSIS II study in China reports a low LDL-C goal attainment rate in post-ACS patients even after 6 months of LLT. Lack of intensification of statin therapy and underutilization of combinations suggest gaps between real-world treatment practices and guideline recommendations.

[15] *Guijarro C, Civeira F, López-Miranda J et al.* **Situation in 2020 of the requirements for the use of PCSK9 inhibitors in Spain: Results of a national survey**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34656373

ABSTRACT

AIMS: During 2019 and 2020 a series of meetings over the country were carried out, with the aim of explaining the methodology and criteria for the ellaboration of the recommendations on the use of iPCSK9, published by the Spanish Society of Atherosclerosis (SEA in Spanish). At the end of the meetings, a survey was conducted among the participants, in order to describe the prescription requirements of these drugs in the Spanish regions. METHODOLOGY: Butterfly Project was developed by a scientific Committee of experts in lipids. After the ellaboration of the materials for the project, a train the trainers program was carried out, imparted by 17 experts who were the Project coordinators. Later, 16 regional workshops were performed, with the attendance of 169 medical doctors involved in the management of hipercolesterolemia. The attendants responded the survey, where they were asked different questions on the use of iPCSK9 on their clinical practice. RESULTS: A high heterogeneity among centers regarding the requirements and difficulties for iPCSK9 prescription was revealed. Twenty one per cent of responders indicated to have low difficulties to prescribe iPCSK9 in their hospitals, whereas 78% found moderate or high difficulties. The difficulties came from burocracy- administrative aspects (18%), restrictions in the indication (41%) and both (38%). In general, the obstacles did not depend on the hospital level, neither the speciality, or the presence of lipid units, although the existance of lipid units was associated with a higher number of patients treated with iPCSK9. The factors which were associated with higher difficulty in the prescription were: the presence of an approval committee in the hospitals, the frequency in the revision of the treatment by hospital pharmacy, the temporal cadence of the prescription, the profile of patients seen and the criteria followed by the specialists for the prescription. CONCLUSION: The results show important diferences in the treatment with iPCSK9 in the context of clinical practice in Spain. The analysis of these results will permit to make proposals regarding future actions addressed to reach the equity in the access to iPCSK9 in Spain, with the main aim of maximizing their potential benefit according to the patients profile.

[16] *Matta MG, Saenz B, Schreier L et al.* **Use and persistence of lipid-lowering therapy in patients with severe hypercholesterolemia: A prospective study**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33:308-313.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34656372

ABSTRACT

INTRODUCTION: Statins are the first line of treatment in patients with severe hypercholesterolemia (SH). However, despite the knowledge regarding its effectiveness and security for preventing cardiovascular diseases, treatment is a major challenge. MATERIAL AND METHODS: A prospective observational study was conducted by telephone survey to determine cardiovascular risk factors, annual monitoring, statins use and persistence and new-onset cardiovascular events (CVE) after 5 years in patients with SH including in a program for detection of familial hypercholesterolemia. RESULTS: 115 participants were analysed, the median age was 56 ±10 being 74% females. 63.4% of women and 43% of men had been correctly controlled in the last year. Patients on lipid lowering drugs stratified by sex was 38.8% in women and 26.7% in men, however, only 22 participants (31.8%) were persistence with statins since 2015.Overall, 48% of the patients presented a CVE and 3.4% died. Multivariate analysis did not reveal predictors for CVE. CONCLUSIONS: In our population with SH we found a high risk to present a CVE and a dramatic low use and persistence with the treatment.

[17] *Ma Y, Sun Y, Sun L et al.* **Effects of gut microbiota and fatty acid metabolism on dyslipidemia following weight-loss diets in women: Results from a randomized controlled trial**. Clinical nutrition (Edinburgh, Scotland) 2021; 40:5511-5520.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34656033

ABSTRACT

BACKGROUND & AIMS: In our early feeding trial among overweight and obese Chinese women, both low-carbohydrate (LC) and calorie-restricted (CR) diets reduced weight and fat mass, but only the LC diet significantly improved dyslipidemia. We aimed to investigate the impacts of altered gut microbiota, fatty acid (FAs), and acylcarnitines, markers of mitochondrial function on blood lipids. METHODS: Fecal and blood samples from 48 participants at baseline and the end of a 12-week trial were used to perform metagenomics and targeted-metabolomics including erythrocyte FAs and plasma acylcarnitines, respectively. RESULTS: The two diets altered microbial structure and co-abundance gene clusters (CAGs) at different magnitudes. After a 12-week intervention, the Bacteroidetes/Firmicutes ratio increased significantly in the LC diet (P = 0.015) but not in the CR diet, which only showed an increased trend (P = 0.28). At the microbial function level, the LC group showed lower branched-chain amino acid biosynthesis and higher serine biosynthesis than the CR group. Moreover, the LC diet reduced levels of 14:0 and 16:1n-7 FAs in the de novo lipogenesis pathway, but increased 20:5n-3 compared with the CR diet. Both groups had increased plasma acylcarnitines except that the LC group had larger elevated short-chain acylcarnitines. After backward stepwise selection, a cluster of changed CAGs, FAs and acylcarnitines were found to be associated with improved lipid profile. However, changed CAGs showed higher contribution rates in elevating HDL-cholesterol (81.6%) and reducing triglycerides (89.3%) than changed FAs and acylcarnitines. CONCLUSIONS: The two weight-loss diets induced different changes of gut microbiota, plasma acylcarnitines, and erythrocyte FAs. Changes in gut microbiota rather than FA or acylcarnitine profiles

showed greater contribution to improved lipid profile in these overweight and obese Chinese women. TRIAL REGISTRATION: The trial was registered at http://clinicaltrials.gov/show/NCT01358890.

[18] *Lee MT, Mahtta D, Dlouhy L et al.* **Highlights of Cardiovascular Disease Studies Presented at the 2021 European Society of Cardiology Congress**. Current atherosclerosis reports 2021; 23:76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34648072
ABSTRACT
PURPOSE OF REVIEW: This review highlights select studies presented at the virtual 2021 European Society of Cardiology (ESC) Congress. RECENT FINDINGS: Reviewed studies assess single photon emission computed tomography, positron emission tomography, magnetic resonance imaging in coronary artery disease (PACIFIC-II); empagliflozin in heart failure with preserved ejection fraction (EMPEROR-Preserved); dapagliflozin in chronic heart failure (DAPA-HF); proprotein convertase subtilisin/kexin type 9 inhibitor and its lipid lowering effects (NATURE-PCSK9); fixed-dose combination therapies with or without aspirin in primary prevention; overview of contrasting results between REDUCE-IT versus STRENGTH trials; Quadruple UltrA-low-dose tReaTment for hypertension (QUARTET); evolocumab and changes in plaque composition on optical coherence tomography (HUYGENS); and low-dose rivaroxaban during the acute phase of acute coronary syndrome (H-REPLACE). Research presented at the 2021 ESC Congress shows promise in reducing burden of cardiovascular disease and reinforces the value of cardiovascular disease prevention.

[19] *Parhofer KG*. **Oral Lipid-Lowering Treatments Beyond Statins: Too Old and Outdated or Still Useful?** Current atherosclerosis reports 2021; 23:74.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34648074
ABSTRACT
PURPOSE OF REVIEW: For many years, the lipid-lowering armamentarium consisted of statins and/or ezetimibe and/or bile acid sequestrants and/or fibrates. Now, with the availability of new drugs mostly injectables, the field has changed and the role of oral non-statin drugs (including bempedoic acid) must be reevaluated. RECENT FINDINGS: Ezetimibe remains a very important combination partner for statins with continuously increasing treatment numbers. Bempedoic acid is another interesting combination partner for statin/ezetimibe or ezetimibe alone but lacks in contrast to ezetimibe evidence from outcome trials. The role of fibrates is less clear as they have shown disappointing results in outcome trials but may still be used in selected, high-risk patients with combined dyslipidemia. Bile acid sequestrants are now rarely used as there are stronger, better tolerable ways to lower LDL-cholesterol. With the introduction of new injectable lipid-lowering drugs, some oral drugs such as ezetimibe and bempedoic acid still have an important spot in our treatment algorithm others such as fibrates have a less clear role while again others are now rarely used.

[20] *McIntosh CS, Watts GF, Wilton SD, Aung-Htut MT*. **Splice correction therapies for familial hypercholesterolemic patients with low-density lipoprotein receptor mutations**. Current opinion in lipidology 2021; 32:355-362.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34653074
ABSTRACT

PURPOSE OF REVIEW: Antisense oligomers (ASOs) have been available for decades: however, only recently have these molecules been applied clinically. This review aims to discuss the possible development of antisense-mediated splice correction therapies as precision medicines for familial hypercholesterolemic patients carrying mutations that compromise normal splicing of the low-density lipoprotein receptor (LDLR) gene transcript. RECENT FINDINGS: Three antisense drugs are currently being assessed in ongoing clinical trials for dyslipidemias, aiming to lower the plasma concentrations of lipoproteins that lead to end-organ damage, principally coronary artery disease. Although a handful of drugs may be applicable to many patients with familial hypercholesterolemia (FH), mutation-specific personalised antisense drugs may be even more effective in selected patients. Currently, there is no therapy that effectively addresses mutations in the LDLR, the major cause of FH. Many mutations in the LDLR that disrupt normal pre-mRNA processing could be applicable to splice correction therapy to restore receptor activity. SUMMARY: Precision medicine could provide long-term economic and social benefits if they can be implemented effectively and sustainably. Many mutations found in the LDLR gene could be amendable to therapeutic splice correction and we should consider developing a therapeutic ASO platform for these mutations.

[21] *Ray KK, Reeskamp LF, Laufs U et al.* **Combination lipid-lowering therapy as first-line strategy in very high-risk patients**. European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34636884
ABSTRACT

[22] *Perna GP*. **Statins and age: is there a limit beyond which primary prevention is futile?** European heart journal supplements : journal of the European Society of Cardiology 2021; 23:E109-e111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34650367
ABSTRACT
Hypercholesterolaemic patients at an advanced age (>75 years) with and without known cardiovascular disease are at higher cardiovascular risk than younger subjects, and the frequency of vascular events in this group of the patient increases with increasing age. However, in clinical practice, these subjects are undertreated for various reasons: conservative cultural attitude, fear of side effects, doubts about efficacy, lack of specific trials. Two recent meta-analyses have shown that the use of lipid-lowering drugs is as safe and effective in this age group as in younger subjects. Subjects aged >75 years in primary prevention are poorly represented in trials but should be considered for treatment in daily clinical practice, because, in the risk assessment (SCORE algorithm), they are very often classified as intermediate or high risk but can also be reclassified at increased risk if an additional assessment step with clinical markers (diabetes and reduced glomerular filtrate) or cardiovascular imaging is used for the detection of subclinical atherosclerosis. Greater attention to treatment methods and monitoring of possible side effects is recommended, but the only limit to the treatment is its 'futility' in the fragile patient.

[23] *Louloudis G, Ambrosini S, Paneni F et al.* **Adeno-Associated Virus-Mediated Gain-of-Function mPCSK9 Expression in the Mouse Induces Hypercholesterolemia, Monocytosis, Neutrophilia, and a Hypercoagulative State**. Frontiers in cardiovascular medicine 2021; 8:718741.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34631822

ABSTRACT
Hypercholesterolemia has previously been induced in the mouse by a single intravenous injection of adeno-associated virus (AAV)-based vector harboring gain-of-function pro-protein convertase subtilisin/kexin type 9. Despite the recent emergence of the PCSK9-AAV model, the profile of hematological and coagulation parameters associated with it has yet to be characterized. We injected 1.0 × 10(11) viral particles of mPCSK9-AAV or control AAV into juvenile male C57BL/6N mice and fed them with either a Western-type high-fat diet (HFD) or standard diet over the course of 3 weeks. mPCSK9-AAV mice on HFD exhibited greater plasma PCSK9 concentration and lower low-density lipoprotein levels, concomitant with increased total cholesterol and non-high-density lipoprotein (non-HDL)-cholesterol concentrations, and lower HDL-cholesterol concentrations than control mice. Furthermore, mPCSK9-AAV-injected mice on HFD exhibited no signs of atherosclerosis at 3 weeks after the AAV injection. Hypercholesterolemia was associated with a thromboinflammatory phenotype, as neutrophil levels, monocyte levels, and neutrophil-to-lymphocyte ratios were higher and activated partial thromboplastin times (aPTTs) was lower in HFD-fed mPCSK9-AAV mice. Therefore, the mPCSK9-AAV is a suitable model of hypercholesterolemia to examine the role of thromboinflammatory processes in the pathogenesis of cardiovascular and cerebrovascular diseases.

[24] *Ning C, Su S, Li J et al.* **Evaluation of a Clinically Relevant Drug-Drug Interaction Between Rosuvastatin and Clopidogrel and the Risk of Hepatotoxicity**. Frontiers in pharmacology 2021; 12:715577.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34646133

ABSTRACT
Purpose: The combination therapy of rosuvastatin (RSV) and the platelet inhibitor clopidogrel (CP) is widely accepted in the management of cardiovascular diseases. The objective of the present study was to identify the mechanism of RSV-CP DDI and evaluate the risk of hepatotoxicity associated with the concomitant use of CP. Methods: We first studied the effect of CP and its major circulating metabolite, carboxylic acid metabolite (CPC), on RSV transport by overexpressing cells and membrane vesicles. Second, we investigated whether a rat model could replicate this DDI and then be used to conduct mechanistic studies and assess the risk of hepatotoxicity. Then, cytotoxicity assay in hepatocytes, biochemical examination, and histopathology were performed to measure the magnitude of liver injury in the presence and absence of DDI. Results: CP inhibited OATP1B1-mediated transport of RSV with an IC(50) value of 27.39 μM. CP and CPC inhibited BCRP-mediated RSV transport with IC(50) values of <0.001 and 5.96 μM, respectively. The CP cocktail (0.001 μM CP plus 2 μM CPC) significantly inhibited BCRP-mediated transport of RSV by 26.28%. Multiple p.o. doses of CP significantly increased intravenous RSV plasma AUC(0-infinity) by 76.29% and decreased intravenous RSV CL by 42.62%. Similarly, multiple p.o. doses of CP significantly increased p.o. RSV plasma AUC(0-infinity) by 87.48% and decreased p.o. RSV CL by 43.27%. CP had no effect on cell viability, while RSV exhibited dose-dependent cytotoxicity after 96 h incubation. Co-incubation of 100 μM CP and RSV for 96 h significantly increased intracellular concentrations and cell-to-medium concentration ratios of RSV and reduced hepatocyte viability. Histological evaluation of liver specimens showed patterns of drug-induced liver injury. Cholestasis was found in rats in the presence of DDI. Conclusion: CP is not a clinically relevant inhibitor for OATP1B1 and OATP1B3. The primary mechanism of RSV-CP DDI can be attributed to the inhibition of intestinal BCRP by CP

combined with the inhibition of hepatic BCRP by CPC. The latter is likely to be more clinically relevant and be a contributing factor for increased hepatotoxicity in the presence of DDI.

[25] *Watts GF, Raal FJ, Chan DC*. **Transcriptomic therapy for dyslipidemias utilizing nucleic acids targeted at ANGPTL3**. Future cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34651521
ABSTRACT
Angiopoietin-like protein 3 (ANGPTL3) is a key physiological regulator of plasma lipid and lipoprotein metabolism that involves the control of enzymes, lipoprotein and endothelial lipases. Inhibition of ANGPTL3 offers a new approach for correcting the health risks of dyslipidemia, including familial hypercholesterolemia, mixed hyperlipidemia, metabolic syndrome and/or severe hypertriglyceridemia. ANGPTL3 inhibition with nucleic acid-based antisense oligonucleotide and siRNA can correct dyslipidemia chiefly by reducing production and increasing catabolism of triglyceride-rich lipoprotein and LDL particles. Early clinical trials have demonstrated that these agents can safely and effectively lower plasma triglyceride and LDL-cholesterol levels by up to 70 and 50%, respectively. However, the long-term safety and cost-effectiveness of these agents await to be confirmed in an ongoing and future clinical trials.
Lay abstract Angiopoietin-like protein 3 (ANGPTL3) is a protein that is produced by the liver. ANGPTL3 plays an important role in controlling the blood levels of fats, such as cholesterol. Inhibition of ANGPTL3 is a new approach to improve the health in people with abnormal blood fat levels. Treatments that inhibits ANGPTL3, such as nucleic acids that reduce products of genes called RNA, can safely and significantly lower blood fat levels. The safety and value of this new treatment in preventing heart disease in people needs further research.
eng

[26] *Kluck GEG, Yoo JA, Sakarya EH, Trigatti BL*. **Good Cholesterol Gone Bad? HDL and COVID-19**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34638523
ABSTRACT
The transmissible respiratory disease COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of people worldwide since its first reported outbreak in December of 2019 in Wuhan, China. Since then, multiple studies have shown an inverse correlation between the levels of high-density lipoprotein (HDL) particles and the severity of COVID-19, with low HDL levels being associated with an increased risk of severe outcomes. Some studies revealed that HDL binds to SARS-CoV-2 particles via the virus's spike protein and, under certain conditions, such as low HDL particle concentrations, it facilitates SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) and infection of host cells. Other studies, however, reported that HDL suppressed SARS-CoV-2 infection. In both cases, the ability of HDL to enhance or suppress virus infection appears to be dependent on the expression of the HDL receptor, namely, the Scavenger Receptor Class B type 1 (SR-B1), in the target cells. SR-B1 and HDL represent crucial mediators of cholesterol metabolism. Herein, we review the complex role of HDL and SR-B1 in SARS-CoV-2-induced disease. We also review recent advances in our understanding of HDL structure, properties, and function during SARS-CoV-2 infection and the resulting COVID-19 disease.

[27] *Laudanski K*. **Persistence of Lipoproteins and Cholesterol Alterations after Sepsis: Implication for Atherosclerosis Progression**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34638860

ABSTRACT

Background: Sepsis is one of the most common critical care illnesses with increasing survivorship. The quality of life in sepsis survivors is adversely affected by several co-morbidities, including increased incidence of dementia, stroke, cardiac disease and at least temporary deterioration in cognitive dysfunction. One of the potential explanations for their progression is the persistence of lipid profile abnormalities induced during acute sepsis into recovery, resulting in acceleration of atherosclerosis. (2) Methods: This is a targeted review of the abnormalities in the long-term lipid profile abnormalities after sepsis; (3) Results: There is a well-established body of evidence demonstrating acute alteration in lipid profile (HDL-c ↓↓, LDL-C -c ↓↓). In contrast, a limited number of studies demonstrated depression of HDL-c levels with a concomitant increase in LDL-C -c in the wake of sepsis. VLDL-C -c and Lp(a) remained unaltered in few studies as well. Apolipoprotein A1 was altered in survivors suggesting abnormalities in lipoprotein metabolism concomitant to overall lipoprotein abnormalities. However, most of the studies were limited to a four-month follow-up and patient groups were relatively small. Only one study looked at the atherosclerosis progression in sepsis survivors using clinical correlates, demonstrating an acceleration of plaque formation in the aorta, and a large metanalysis suggested an increase in the risk of stroke or acute coronary event between 3% to 9% in sepsis survivors. (4) Conclusions: The limited evidence suggests an emergence and persistence of the proatherogenic lipid profile in sepsis survivors that potentially contributes, along with other factors, to the clinical sequel of atherosclerosis.

[28] *Smigoc Schweiger D, Battelino T, Groselj U*. **Sex-Related Differences in Cardiovascular Disease Risk Profile in Children and Adolescents with Type 1 Diabetes**. International journal of molecular sciences 2021; 22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34638531

ABSTRACT

Cardiovascular disease (CVD) is the primary cause of higher and earlier morbidity and mortality in people with type 1 diabetes (T1D) compared to people without diabetes. In addition, women with T1D are at an even higher relative risk for CVD than men. However, the underlying pathophysiology is not well understood. Atherosclerotic changes are known to progress early in life among people with T1D, yet it is less clear when excess CVD risk begins in females with T1D. This review explores the prevalence of classical CVD risk factors (such as glycemic control, hypertension, dyslipidemia, obesity, albuminuria, smoking, diet, physical inactivity), as well as of novel biomarkers (such as chronic inflammation), in children and adolescents with T1D with particular regard to sex-related differences in risk profile. We also summarize gaps where further research and clearer clinical guidance are needed to better address this issue. Considering that girls with T1D might have a more adverse CVD risk profile than boys, the early identification of and sex-specific intervention in T1D would have the potential to reduce later CVD morbidity and excess mortality in females with T1D. To conclude, based on an extensive review of the existing literature, we found a clear difference between boys and girls with T1D in the presence of individual CVD risk factors as well as in overall CVD risk profiles; the girls were on the whole more impacted.

[29] *Talasaz AH, Sadeghipour P, Aghakouchakzadeh M et al.* **Investigating Lipid-Modulating Agents for Prevention or Treatment of COVID-19: JACC State-of-the-Art Review**. Journal of the American College of Cardiology 2021; 78:1635-1654.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34649702

ABSTRACT

Coronavirus disease-2019 (COVID-19) is associated with systemic inflammation, endothelial activation, and multiorgan manifestations. Lipid-modulating agents may be useful in treating patients with COVID-19. These agents may inhibit viral entry by lipid raft disruption or ameliorate the inflammatory response and endothelial activation. In addition, dyslipidemia with lower high-density lipoprotein cholesterol and higher triglyceride levels portend worse outcomes in patients with COVID-19. Upon a systematic search, 40 randomized controlled trials (RCTs) with lipid-modulating agents were identified, including 17 statin trials, 14 omega-3 fatty acids RCTs, 3 fibrate RCTs, 5 niacin RCTs, and 1 dalcetrapib RCT for the management or prevention of COVID-19. From these 40 RCTs, only 2 have reported preliminary results, and most others are ongoing. This paper summarizes the ongoing or completed RCTs of lipid-modulating agents in COVID-19 and the implications of these trials for patient management.

[30] *Liu R, Jiang J, Fu Z et al.* **Effects of Omega-3 Fatty Acid Intake in Patients Undergoing Dialysis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Journal of the American College of Nutrition 2021:1-16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34635026

ABSTRACT

Objective: Fish oil supplementation has been shown to be beneficial for hemodialysis (HD) patients. The aim of this study was to evaluate the efficacy and safety of omega-3 fatty acid supplementation or dietary adjustment in dialysis patients.Methods: A systematic literature search was performed to identify relevant randomized controlled trials (RCTs) to study the effects of omega-3 supplementation on dialysis patients. The variables of interest included the levels of blood lipids, inflammatory indicators, proteins, parathyroid hormone (PTH), gastrointestinal adverse reactions, and all-cause mortality. The mean differences (MDs) and 95% confidence intervals (CIs) were calculated, and heterogeneity was assessed with the I(2) test. Subgroup and sensitivity analyses were performed to identify potential sources.Results: The systematic review included 49 RCTs and evaluated the efficacy and safety of omega-3 fatty acid supplementation in dialysis patients. Data synthesis showed that compared with the control group, the group receivingomega-3 supplementation exhibited significantly decreased serum triglyceride (TG) levels, decreased C-reactive protein (CRP) and TNF-alpha levels, increased hemoglobin levels, reduced serum phosphorus levels, increased PTH levels, and increased gastrointestinal adverse reactions to a certain extent. Furthermore, there was no effect on the blood total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), albumin or calcium levels and all-cause mortality.Conclusion: Omega-3 fatty acid supplementation is related to a reduction in serum TG, LDL and inflammation index levels and has few adverse reactions. Therefore, omega-3 fatty acid supplementation may be a useful nutrition therapy for dialysis patients.

[31] *Jacob L, Greiner RA, Luedde M, Kostev K*. **Prevalence of and factors associated with the prescription of fibrates among patients receiving lipid-lowering drugs in Germany**. Journal of cardiovascular pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34654787
ABSTRACT
Little recent data is available about the patterns of prescription for fibrates in patients followed in primary care practices. Therefore, the goal of the present study was to analyze the prevalence of and the factors associated with the use of fibrates among patients receiving lipid-lowering drugs in Germany. The study included patients aged ≥18 years with at least one visit to one of 1,070 general practices in Germany between January and December 2019. Lipid-lowering drugs included statins (without and with ezetimibe) and fibrates. The prevalence of the prescription of fibrates corresponded to the number of patients with at least one prescription for fibrates divided by the total number of patients receiving lipid-lowering drugs. A logistic regression model was used to assess the relationship between several demographic, clinical, and biological factors and the prescription of fibrates. A total of 111,329 patients were included in this study (mean [SD] age 68.8 [11.5] years; 56.0% of patients were men). The prevalence of the prescription of fibrates was 1.5%. Male sex, hypertension, diabetes mellitus, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and high triglyceride were positively associated with the use of fibrates. By contrast, there was a negative relationship between the odds of receiving fibrates and coronary heart disease, myocardial infarction, peripheral arterial disease, and stroke including transient ischemic attack. Overall, we found that fibrates were infrequently prescribed in general practices in Germany.

[32] *Zhang X, Chen X, Liang Z et al.* **Atorvastatin Promotes Macrocalcification, But Not Microcalcification in Atherosclerotic Rabbits: An 18F-NaF PET/CT Study**. Journal of cardiovascular pharmacology 2021; 78:544-550.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34651601
ABSTRACT
INTRODUCTION: Our study aimed to investigate the effect of atorvastatin on plaque calcification by matching the results obtained by 18F-sodium fluoride (18F-NaF) positron emission tomography (PET)/computed tomography (CT) with data from histologic sections. METHODS AND RESULTS: The rabbits were divided into 2 groups as follows: an atherosclerosis group (n = 10) and an atorvastatin group (n = 10). All rabbits underwent an abdominal aortic operation and were fed a high-fat diet to induce atherosclerosis. Plasma samples were used to analyze serum inflammation markers and blood lipid levels. 18F-NaF PET/CT scans were performed twice. The plaque area, macrophage number and calcification were measured, and the data from the pathological sections were matched with the 18F-NaF PET/CT scan results. The mean standardized uptake value (0.725 ± 0.126 vs. 0.603 ± 0.071, $P < 0.001$) and maximum standardized uptake value (1.024 ± 0.116 vs. 0.854 ± 0.091, $P < 0.001$) significantly increased in the atherosclerosis group, but only slightly increased in the atorvastatin group (0.616 ± 0.103 vs. 0.613 ± 0.094, $P = 0.384$; 0.853 ± 0.099 vs.0.837 ± 0.089, $P < 0.001$, respectively). The total calcium density was significantly increased in rabbits treated with atorvastatin compared with rabbits not treated with atorvastatin (1.64 ± 0.90 vs. 0.49 ± 0.35, $P < 0.001$), but the microcalcification level was significantly lower. There were more microcalcification deposits in the areas with increased radioactive uptake of 18F-NaF. CONCLUSIONS: Our study suggests that the anti-inflammatory activity of atorvastatin may promote macrocalcification but not

microcalcification within atherosclerotic plaques. 18F-NaF PET/CT can detect plaque microcalcifications.

[33] *Hamasaki M, Sakane N, Hara K, Kotani K*. **LDL-cholesterol and PCSK9 in patients with familial hypercholesterolemia: influence of PCSK9 variants under lipid-lowering therapy**. Journal of clinical laboratory analysis 2021; 35:e24056.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34652028
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH), an autosomal dominant genetic disease with the elevated levels of low-density lipoprotein (LDL) cholesterol (LDL-C), increases the risk of coronary artery disease (CAD). The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene is associated with FH. There is a positive relationship between circulating LDL-C and PCSK9 levels, a potential CAD condition, without lipid-lowering therapy (LLT); however, we do not know whether their correlation exists in FH patients under LLT. METHODS: This study compared the correlation of PCSK9 variants among patients with FH under LLT (n = 70; mean age, 53 years; male, 63%). LDLR, PCSK9 and APOB variants were analyzed using next-generation sequencing. RESULTS: The LDL-C and PCSK9 levels in patients with gain-of-function (GOF) variants of PCSK9 (n = 7) were mostly similar to those in patients with LDLR variants (n = 17) or variant-negative patients (n = 46). A significant positive correlation was observed between LDL-C and PCSK9 levels in patients with GOF variants of PCSK9 ($r = 0.79$, $p = 0.04$), but not in patients with LDLR variants or variant-negative patients. CONCLUSION: The LDL-C-PCSK9 correlation is suggested to be retained in FH patients with GOF variants of PCSK9 even under LLT, and these variants can be used as molecular markers for additional treatment with statins in FH patients.

[34] *Aldana-Bitar J, Moore J, Budoff MJ*. **LDL receptor and pathogen processes: Functions beyond normal lipids**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34645587
ABSTRACT
Although the role of the LDL receptor concerning lipids is well known, its role in various viral and parasitic infections, and in regulating the inflammatory response is poorly understood. Several infectious agents use the LDL receptor as a port of entry, and others depend on it for their cycle of infection. In this review, we focus on the discovery, structure, and normal function of the LDL receptor, as well as its role in a selection of infections. The LDL receptor plays an important role in certain infections and is a potential target for treatment deserving further research.

[35] *Bekele N, Agarwala A, Wang Z, Goldberg AC*. **Transcatheter aortic valve replacement in a patient with premature coronary artery disease and calcific aortic stenosis complicated by heterozygous familial hypercholesterolemia**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34645588
ABSTRACT
We describe a case of a 59-year-old man with severe heterozygous familial hypercholesterolemia (FH) and elevated lipoprotein(a) presenting with severe aortic stenosis, treated with transcatheter aortic valve replacement (TAVR). His history also includes premature coronary artery disease requiring coronary artery bypass surgery at age 48 and a stroke at age 55. His pre-treatment lipid

values include an LDL-Cholesterol (LDL-C) of 458 mg/dL, total cholesterol of 588 mg/dL, and lipoprotein (a) level of 351 nmol/L. Since his FH diagnosis, he has received several lipid-lowering agents including statins, bile acid sequestrants, nicotinic acid derivatives, and PCSK9 inhibitors. This case reflects the association of FH and elevated lipoprotein(a) with aortic stenosis and TAVR as a viable and effective treatment.

[36] *Maki KC, Dicklin MR, Kirkpatrick CF*. **Saturated fats and cardiovascular health: Current evidence and controversies**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34649831
ABSTRACT
A diet high in saturated fatty acids (SFA) is a suspected contributor to atherosclerotic cardiovascular disease (ASCVD) risk, in large part because of an effect to raise the low-density lipoprotein cholesterol (LDL-C) concentration. Most dietary guidance from health authorities advocates limiting intake of SFA, particularly for people with clinical ASCVD, dyslipidemia, or diabetes mellitus. However, recent reviews have highlighted controversies regarding SFA intake and cardiovascular health. This brief editorial commentary includes a discussion of the evidence regarding SFA intake and cardiovascular health, outlines gaps in the available evidence, and proposes tentative conclusions based on what is known today about SFA consumption and ASCVD risk. Results from observational studies demonstrate that dietary patterns with lower average intakes of SFA are associated with favorable cardiovascular outcomes. Additionally, although the number of randomized controlled trials testing the effects of reducing SFA intake on ASCVD outcomes is limited, the available evidence supports the view that replacing SFA with unsaturated fatty acids, particularly polyunsaturated fatty acids, may reduce ASCVD risk. Beyond raising LDL-C and atherogenic lipoprotein particle concentrations, higher intakes of SFA may influence pathways affecting inflammation, cardiac rhythm, hemostasis, apolipoprotein CIII production, and high-density lipoprotein function. However, the impacts of these effects on ASCVD risk remain uncertain. In the authors' view, the totality of the evidence supports the current recommendation to limit SFA intake to <10% of total daily energy for the general healthy population and further (e.g., to 5-6% of total daily energy) for patients with hypercholesterolemia.

[37] *Labuz-Roszak B, Banach M, Skrzypek M et al.* **Secondary Stroke Prevention in Polish Adults: Results from the LIPIDOGRAM2015 Study**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34640490
ABSTRACT
BACKGROUND: The purpose of the study was to evaluate secondary stroke prevention in Poland and its association with sociodemographic factors, place of residence, and concomitant cardiovascular risk factors. MATERIAL AND METHODS: From all patients in LIPIDOGRAM2015 Study (n = 13,724), 268 subjects had a history of ischaemic stroke and were included. RESULTS: 165 subjects (61.6%) used at least one preventive medication. Oral antiplatelet and anticoagulation agents were used by 116 (43.3%) and 70 (26.1%) patients, respectively. Only 157 (58.6%) participants used lipid-lowering drugs, and 205 (76.5%) were treated with antihypertensive drugs. Coronary heart disease (CHD) and dyslipidaemia were associated with antiplatelet treatment ($p = 0.047$ and $p = 0.012$, respectively). A history of atrial fibrillation, CHD, and previous myocardial infarction correlated with anticoagulant treatment ($p = 0.001$, $p = 0.011$, and $p < 0.0001$, respectively).

Age, gender, time from stroke onset, place of residence, and level of education were not associated with antiplatelet or anticoagulant treatment. Only 31.7% of patients were engaged in regular physical activity, 62% used appropriate diet, and 13.6% were current smokers. CONCLUSIONS: In Poland drugs and lifestyle modification for secondary stroke prevention are not commonly adhered to. Educational programmes for physicians and patients should be developed to improve application of effective secondary prevention of stroke.

[38] *Lewek J, Konopka A, Starostecka E et al.* **Clinical Features of Familial Hypercholesterolemia in Children and Adults in EAS-FHSC Regional Center for Rare Diseases in Poland**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34640319
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is a genetic autosomal co-dominant metabolic disorder leading to elevated circulating concentrations of low-density lipoprotein cholesterol (LDL-C). Early development of atherosclerotic cardiovascular disease (ASCVD) is common in affected patients. We aimed to evaluate the characteristics and differences in the diagnosis and therapy of FH children and adults. Methods: All consecutive patients who were diagnosed with FH, both phenotypically and with genetic tests, were included in this analysis. All patients are a part of the European Atherosclerosis Society FH-Study Collaboration (FHSC) regional center for rare diseases at the Polish Mother's Memorial Hospital Research Institute (PMMHRI) in Lodz, Poland. Results: Of 103 patients with FH, there were 16 children (15.5%) at mean age of 9 ± 3 years and 87 adults aged 41 ± 16; 59% were female. Children presented higher mean levels of total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C) measured at the baseline visit (TC 313 vs. 259 mg/dL (8.0 vs. 6.6 mmol/L), p = 0.04; LDL 247 vs. 192 mg/dL (6.3 vs. 4.9 mmol/L), p = 0.02, HDL 53 vs. 48 mg/dL (1.3 vs. 1.2 mmol/L), p = 0.009). Overall, 70% of adult patients and 56% of children were prescribed statins (rosuvastatin or atorvastatin) on admission. Combination therapy (dual or triple) was administered for 24% of adult patients. Furthermore, 13.6% of adult patients and 19% of children reported side effects of statin therapy; most of them complained of muscle pain. Only 50% of adult patients on combination therapy achieved their treatment goals. None of children achieved the treatment goal. CONCLUSIONS: Despite a younger age of FH diagnosis, children presented with higher mean levels of LDL-C than adults. There are still urgent unmet needs concerning effective lipid-lowering therapy in FH patients, especially the need for greater use of combination therapy, which may allow LDL-C targets to be met in most of the patients.

[39] *Scicali R, Piro S, Ferrara V et al.* **Direct and Indirect Effects of SARS-CoV-2 Pandemic in Subjects with Familial Hypercholesterolemia: A Single Lipid-Center Real-World Evaluation**. Journal of clinical medicine 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34640388
ABSTRACT
We evaluated the impact of direct and indirect effects of SARS-CoV-2 infection in subjects with familial hypercholesterolemia (FH). In this observational, retrospective study, 260 FH subjects participated in a telephone survey concerning lipid profile values, lipidologist and cardiologist consultations and vascular imaging evaluation during the 12 months before and after the Italian lockdown. The direct effect was defined as SARS-CoV-2 infection; the indirect effect was defined as

the difference in one of the parameters evaluated by the telephone survey before and after lockdown. Among FH subjects, the percentage of the lipid profile evaluation was lower after lockdown than before lockdown (56.5% vs. 100.0%, $p < 0.01$), HDL-C was significantly reduced (47.78 ± 10.12 vs. 53.2 ± 10.38 mg/dL, $p < 0.05$) and a significant increase in non-HDL-C was found (117.24 ± 18.83 vs. 133.09 ± 19.01 mg/dL, $p < 0.05$). The proportions of lipidologist and/or cardiologist consultations and/or vascular imaging were lower after lockdown than before lockdown (for lipidologist consultation 33.5% vs. 100.0%, $p < 0.001$; for cardiologist consultation 22.3% vs. 60.8%, $p < 0.01$; for vascular imaging 19.6% vs. 100.0%, $p < 0.001$); the main cause of missed lipid profile analysis and/or healthcare consultation was the fear of SARS-CoV-2 contagion. The percentage of FH subjects affected by SARS-CoV-2 was 7.3%. In conclusion, a lower percentage of FH subjects underwent a lipid profile analysis, lipidologist and cardiologist consultations and vascular imaging evaluation after SARS-CoV-2 Italian lockdown.

[40] *Chang YC, Lin CJ, Yeh TL et al.* **Lipid biomarkers and Cancer risk - a population-based prospective cohort study in Taiwan**. Lipids in health and disease 2021; 20:133.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34629064
ABSTRACT
BACKGROUND: Blood lipids are essential components for cellular growth. An inverse association between serum lipid levels and risk of cancer has led to a controversy among previous studies. The aim of this prospective cohort study was to investigate the association between blood lipids change and risk of cancer incidence. METHODS: A cohort of 4130 Taiwanese adults from the Taiwanese Survey on the Prevalence of Hypertension, Hyperglycemia, and Hyperlipidemia database underwent repeated examinations in 2002 and 2007. Six groups were established based on the combined baseline (lower/higher) and interval change (decreasing/stable/increasing) in plasma lipid levels. Multivariable Cox proportional hazard model was used to investigate the relationship between lipids change and all-cause cancer incidence. RESULTS: Two hundred and forty cancer events developed over a median follow-up of 13.4 years. Comparing these with individuals with decreasing lower-baseline lipid levels, cancer risk reduction was demonstrated in those with increasing lower-baseline total cholesterol (adjusted hazard ratio [aHR], 0.48; 95% confidence interval [CI], 0.27 to 0.85), low-density lipoprotein cholesterol (LDL-C; aHR, 0.56; 95% CI, 0.35 to 0.92), and non-high-density lipoprotein cholesterol (non-HDL-C) (aHR, 0.54; 95% CI, 0.31 to 0.92) levels. A decreased risk for cancer incidence also presented in participants with stable lower-baseline, decreasing and increasing higher-baseline LDL-C levels, and with decreasing and stable higher-baseline non-HDL-C levels. CONCLUSIONS: The interval decline in lower-baseline total cholesterol, LDL-C, and non-HDL-C levels was linked to a higher risk for all-cause cancer incidence. More attention to a potential cancer risk may be warranted for an unexplained fall in serum lipids.

[41] *Zink N.* **[Not Available]**. MMW Fortschritte der Medizin 2021; 163:10-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34652641
ABSTRACT

[42] *Talasaz AH, Ho AJ, Bhatty F et al.* **Meta-analysis of clinical outcomes of PCSK9 modulators in patients with established ASCVD**. Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34657313

ABSTRACT
The advent of monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) ushered in a new era of dyslipidemia pharmacotherapy. The first two antibodies targeting PCSK9 (evolocumab, alirocumab) approved by the United States Food and Drug Administration (FDA) provided significant and sustained reductions in atherogenic lipids and a reduced risk of atherosclerotic cardiovascular disease (ASCVD) events. More recently, phase 3 trials of inclisiran-a small interfering RNA-based agent targeting PCSK9-reported similar lipid-lowering effects and preliminary evidence of ASCVD risk reduction, although significant questions remain regarding the extent of benefits across cardiovascular outcomes. We conducted a systematic review and meta-analysis (random-effects model) of the available data on lipid lowering, incidence of atherosclerotic cardiovascular disease (ASCVD) events, and safety of pharmacologic agents targeting PCSK9. A significant and consistent reduction in low-density lipoprotein cholesterol (LDL-C) was observed across all agents (-51% [95% confidence interval {CI}: -61%, -41%]). Despite the impressive reduction in LDL-C, the individual effects on mortality, cardiovascular death, myocardial infarction (MI), and stroke remained nonsignificant. However, a consistent reduction was observed in the composite outcomes of MI, stroke, and cardiovascular death [relative risk {RR} (95% CI): 0.80 (0.73-0.87)] and MI, stroke, unstable angina (requiring revascularization), and cardiovascular death [RR (95% CI): 0.85 (0.74-0.97)]. In terms of safety outcomes, there was no significant difference in severe adverse events, new onset diabetes, neurocognitive disorders, or myalgia. Meanwhile, injection site reaction was more frequent in patients receiving these agents compared to placebo [RR 2.11 (95% CI): 1.26-3.54]. These findings suggest a class effect for favorable lipid changes and a low risk of serious adverse events among pharmacologic agents targeting PCSK9. Although there is compelling evidence that PCSK9-targeting agents reduce the risk of some cardiovascular outcomes, adequately powered studies with longer follow-up may be needed to fully characterize the magnitude of benefits across the cardiovascular spectrum.

[43] *Yonezawa Y, Sakuma M, Abe S et al.* **Repeated In-Stent Restenosis Despite Aggressive Lipid Loweringby PCSK-9 Inhibitor Treatment: A Case Report**. Tohoku J Exp Med 2021; 255:123-126.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34645737

ABSTRACT
A 76-year-old woman with unstable angina underwent coronary stent implantation. At the same time, rosuvastatin therapy was started. However, she experienced repeated in-stent restenosis (ISR). Treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor along with rosuvastatin (5 mg/day) reduced plasma low-density lipoprotein cholesterol to 10 mg/dL, but failed to prevent further ISR. Eventually, an increase in the rosuvastatin dose to the permitted maximum of 20 mg/day succeeded in preventing further in-stent restenosis. Rather than using PCSK9 inhibitors, intensive statin treatment, using the maximum dose of statins, should be prioritized for the secondary prevention of coronary artery disease.

[44] *Verberk SGS, Kuiper KL, Lauterbach MA et al.* **The multifaceted therapeutic value of targeting ATP-citrate lyase in atherosclerosis**. Trends in molecular medicine 2021; 27:1095-1105.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34635427

ABSTRACT

Literature update week 41 (2021)

ATP-citrate lyase (Acly) is the target of the new class low-density lipoprotein-cholesterol (LDL-C)-lowering drug bempedoic acid (BA). Acly is a key metabolic enzyme synthesizing acetyl-CoA as the building block of cholesterol and fatty acids. Treatment with BA lowers circulating lipid levels and reduces systemic inflammation, suggesting a dual benefit of this drug for atherosclerosis therapy. Recent studies have shown that targeting Acly in macrophages can attenuate inflammatory responses and decrease atherosclerotic plaque vulnerability. Therefore, it could be beneficial to extend the application of Acly inhibition from solely lipid-lowering by liver-specific inhibition to also targeting macrophages in atherosclerosis. Here, we outline the possibilities of targeting Acly and describe the future needs to translate these findings to the clinic.