

[1] *Byonanebye DM. Incidence of dyslipidemia in people with HIV who are treated with integrase inhibitors versus other antiretroviral agents. Aids 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33443370>

ABSTRACT

OBJECTIVE: To compare the incidence of dyslipidemia in people with HIV (PLWH) receiving integrase inhibitors (INSTI) versus boosted protease inhibitors (PI/b) and non-nucleoside reverse transcriptase inhibitors (NNRTI) within RESPOND consortium of prospective cohorts. METHODS: Participants were eligible if they were ≥ 18 years, without dyslipidemia and initiated or switched to a three-drug ART-regimen consisting of either INSTI, NNRTI or PI/b for the first time, between 01/01/2012 and 31/12/2018. Dyslipidemia was defined as random total cholesterol >240 mg/dL, high-density lipoprotein <35 mg/dL, triglyceride >200 mg/dL, or initiation of lipid-lowering therapy. Poisson regression was used to determine the adjusted incidence rate ratios (aIRR). Follow-up was censored after three years or upon ART-regimen discontinuation or last lipid measurement or 31/12/2019, whichever occurred first. RESULTS: Overall, 4577 PLWH were eligible (INSTI=66.9%, PI/b=12.5%, and NNRTI=20.6%), 1938 (42.3%) of whom were ART-naive. During 1.7 (interquartile range, 0.6-3.0) median years of follow-up, 1460 participants developed dyslipidemia (incidence rate: 191.6 per 1000 person-years, 95% confidence interval [CI] 182.0-201.7). Participants taking INSTI had a lower incidence of dyslipidemia compared to those on PI/b (aIRR 0.71; CI 0.59-0.85), but higher rate compared to those on NNRTI (1.35; CI 1.15-1.58). Compared to dolutegravir, the incidence of dyslipidemia was higher with elvitegravir/cobicistat (1.20; CI 1.00-1.43) and raltegravir (1.24; CI 1.02-1.51), but lower with rilpivirine (0.77; CI 0.63-0.94). CONCLUSION: In this large consortium of heterogeneous cohorts, dyslipidemia was less common with INSTI than with PI/b. Compared to dolutegravir, dyslipidemia was more common with elvitegravir/cobicistat and raltegravir, but less common with rilpivirine.

[2] *Bos D, van Dam-Nolen DHK, Gupta A et al. Advances in Multimodality Carotid Plaque Imaging: AJR Expert Panel Narrative Review. AJR Am J Roentgenol 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33438455>

ABSTRACT

Contemporary imaging methods provide detailed visualization of carotid atherosclerotic plaque, enabling a major evolution of in-vivo carotid plaque imaging evaluation. The degree of luminal stenosis in the carotid artery bifurcation, as assessed by ultrasound, has historically served as the primary imaging feature in determining ischemic stroke risk and the potential need for surgery. However, stroke risk may be more strongly driven by the presence of specific characteristics of vulnerable plaque, as visualized on CT and MRI, than by traditional ultrasound-based assessment of luminal narrowing. This review highlights six promising imaging-based plaque characteristics that harbour unique information regarding plaque vulnerability: maximum plaque thickness and volume, calcification, ulceration, intraplaque haemorrhage, lipid-rich necrotic core, and thin or ruptured fibrous cap. Increasing evidence supports the association of these plaque characteristics with risk of ischemic stroke, although these characteristics are of varying suitability for clinical implementation. Key aspects of CT and MRI protocols for carotid plaque imaging are also considered. Practical next steps and hurdles are explored for implementing routine imaging assessment of these plaque characteristics in addition to, or even as replacement for, traditional assessment of the degree of vascular stenosis on ultrasound, in identification of individuals at high risk of ischemic stroke.

[3] Wong ND, Zhao Y, Sung J, Browne A. **Relation of First and Total Recurrent Atherosclerotic Cardiovascular Disease Events to Increased Lipoprotein(a) Levels among Statin Treated Adults with Cardiovascular Disease.** The American journal of cardiology 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454339>

ABSTRACT

The relation between elevated lipoprotein(a) and total atherosclerotic cardiovascular disease (ASCVD) residual risk in persons with known cardiovascular disease on statin therapy is not well-established. We examined first and total recurrent ASCVD event risk in statin-treated adults with prior ASCVD. We studied 3,359 adults (mean age 63.6 years, 85.1% male) with prior ASCVD on statin therapy from the AIM-HIGH clinical trial cohort. The first and total ASCVD event rates were calculated by lipoprotein(a) [Lp(a)] categories. Cox regression and Prentice, Williams and Peterson (PWP) models provided hazard ratios (HRs) for ASCVD events over a mean follow-up of 3.3 years, adjusted for age, sex, trial treatment, LDL-C, and other risk factors. A total of 747 events occurred during follow-up, among which 544 were first events. First and total ASCVD event rates were greater with higher Lp(a) levels. Compared to Lp(a)<15 mg/dL, HRs (95% CIs) for subsequent total ASCVD events among Lp(a) levels of 15-<30, 30-<50, 50-<70 and ≥70 mg/dL were 1.04 (0.82-1.32), 1.15 (0.88-1.49), 1.27 (1.00-1.63) and 1.51 (1.25-1.84). Moreover, a continuous relation for total events was observed (HR=1.08 [1.04-1.12] per 20 mg/dL greater Lp(a)). Findings for first ASCVD events and in those with LDL-C ≥70 mg/dL versus <70 mg/dL and without diabetes were similar. The risk of first and total ASCVD events is increased with Lp(a) levels of ≥70 mg/dL and ≥50 mg/dL, respectively, among adults with known CVD on statin therapy.

[4] Zhang R, Xie J, Zhou J et al. **Supravalvular Aortic Stenosis and the Risk of Premature Death among Patients with Homozygous Familial Hypercholesterolemia.** The American journal of cardiology 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454344>

ABSTRACT

Patients with homozygous familial hypercholesterolemia (HoFH) have a high risk for premature death. Supravalvular aortic stenosis (SVAS) is a common and the feature lesion of the aortic root in HoFH. The relationship between SVAS and the risk of premature death among patients with HoFH has not been fully investigated. The current study analysis included 97 HoFH patients with mean age of 14.7 (years) from the Genetic and Imaging of Familial Hypercholesterolemia in Han Nationality Study. During the median (±SD) follow-up 4.0 (±4.0) years, 40 (41.2%) participants had SVAS and 17(17.5%) participants experienced death. The proportion of premature death in the non-SVAS and SVAS group was 7.0% and 32.5%, respectively. Compared with the non-SVAS group, SVAS group cumulative survival was lower in the HoFH (log-rank test, P<0.001). This result was further confirmed in the multivariable Cox regression models. After adjusting for age, sex, low density lipoprotein cholesterol(LDL_C)-year-score, lipid-lowering drugs, cardiovascular disease (CVD) and carotid artery plaque, SVAS was an independent risk factor of premature death in HoFH on the multivariate analysis(hazard ratio(HR) 4.45; 95% confidence interval(CI),1.10 to 18.12; P =0.037). In conclusion, a significantly increased risk of premature death was observed among HoFH patients with SVAS. Our study emphasized the importance of careful and aggressive management in these patients when appropriate.

[5] Guo D, Meng Z, He F et al. **Infection-Induced Rhabdomyolysis in an Elderly Patient on Stable Rosuvastatin Therapy: A Case Report and Review of the Literature.** *American journal of therapeutics* 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33443867>

ABSTRACT

[6] Tang H, Xue S, Zhao G et al. **CLOCK disruption aggravates carotid artery stenosis through endoplasmic reticulum stress-induced endothelial-mesenchymal transition.** *American journal of translational research* 2020; 12:7885-7898.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33437367>

ABSTRACT

Carotid artery stenosis is a leading cause of ischemic stroke, but the underlying mechanism remains unclear. We aimed to determine the molecular mechanisms of carotid plaque progression. We analyzed the molecular and morphometric characteristics of carotid plaque samples obtained from 30 patients who underwent carotid endarterectomy. Additionally, we established a mouse model of carotid atherosclerosis by partially ligating the left common carotid arteries of male Clock($\Delta 19/\Delta 19$) (Clk) and wild-type (WT) C57BL/6J mice fed a high-fat diet. Clk and WT primary mouse aortic endothelial cells (pMAECs) were exposed to disturbed flow (DF) or undisturbed flow (UF) with or without treatment with the IRE-1 α inhibitor STF-083010 or the PERK inhibitor GSK2606414. In human carotid artery plaques, CLOCK expression was lower in the lipid-rich necrotic core than in transitional regions, especially in the endothelium. Decreased CLOCK mRNA levels were associated with more extensive stenosis, intraplaque hemorrhage, and complex plaque in human carotid plaques. In mice, the Clock($\Delta 19/\Delta 19$) mutation significantly increased neointima formation and neovascularization but decreased collagen content and lumen area in partially ligated carotid arteries. In addition, Clock($\Delta 19/\Delta 19$) mutants exhibited significantly decreased Cdh5 expression and increased expression of endothelial-mesenchymal transition (EndMT) and endoplasmic reticulum (ER) stress markers in mice with partially ligated carotid arteries and pMAECs exposed to DF. Notably, inhibition of the IRE1 α -XBP1 axis abrogated the increased EndMT caused by Clock($\Delta 19/\Delta 19$) mutation and DF in pMAECs. In conclusion, the disruption of CLOCK function aggravates EndMT via the IRE1 α -XBP1 axis, contributing to carotid artery stenosis.

[7] Coutinho ER, Miname MH, Rocha VZ et al. **Familial hypercholesterolemia and cardiovascular disease in older individuals.** *Atherosclerosis* 2020; 318:32-37.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33450476>

ABSTRACT

BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is characterized by high LDL-cholesterol (LDL-C) and early atherosclerotic cardiovascular disease (ASCVD). With a lipid lowering therapy (LLT), most individuals with FH may have a longer ASCVD-free survival. However, there is scant data about older individuals with FH. METHODS: We compared characteristics of genetically defined FH older individuals with age-matched non-FH counterparts. RESULTS: From 4111 genotyped individuals, 462 older than 60 years were included (198 positive and 264 negative for FH variants). There were no differences regarding median age [%25; 75%] 66.0 (62.0; 71.0) and 66.0 (62.2; 71.0) years, $p = 0.68$ for FH and non-FH, respectively. In both groups, there was a higher

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frequency of females, however, there were more males in the FH group 37.4% vs. 24.2%, $p = 0.002$. No differences were seen between FH and non-FH in LLT use: 88.5% vs. 91.5%, $p = 0.29$. Despite a longer LLT duration in FH patients (with 11.0 (7.0; 20.0) vs. 7.0 (3.0; 13.0) years, $p < 0.001$), treatment was started late in both groups: at 54.0 (47.0; 61.0) and 59.0 (52.0; 64.0) years, $p < 0.001$, in FH and non-FH, respectively. FH had greater frequencies of previous and early ASCVD (40.9% vs. 27.3%, $p = 0.002$, and 22.2% vs. 9.0%, $p < 0.001$). In FH, male sex [HR (95%CI)] 2.67 (1.50-4.73), $p = 0.001$, and LLT onset age 0.96 (0.93-0.99), $p = 0.009$, were independently associated with ASCVD. CONCLUSIONS: Among hypercholesterolemic older individuals participating in a cascade screening program, the genetic diagnosis of FH was associated with higher ASCVD rates, emphasizing the relevance of a monogenic defect as the cause of long-lasting hypercholesterolemia and ASCVD risk, particularly in men.

[8] *Bonaterra-Pastra A, Fernández-de-Retana S, Rivas-Urbina A et al. Comparison of Plasma Lipoprotein Composition and Function in Cerebral Amyloid Angiopathy and Alzheimer's Disease. Biomedicines* 2021; 9.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33445800>

ABSTRACT

Cerebral amyloid angiopathy (CAA) refers to beta-amyloid ($A\beta$) deposition in brain vessels and is clinically the main cause of lobar intracerebral hemorrhage (ICH). $A\beta$ can also accumulate in brain parenchyma forming neuritic plaques in Alzheimer's disease (AD). Our study aimed to determine whether the peripheral lipid profile and lipoprotein composition are associated with cerebral beta-amyloidosis pathology and may reflect biological differences in AD and CAA. For this purpose, lipid and apolipoproteins levels were analyzed in plasma from 51 ICH-CAA patients (collected during the chronic phase of the disease), 60 AD patients, and 60 control subjects. Lipoproteins (VLDL, LDL, and HDL) were isolated and their composition and pro/antioxidant ability were determined. We observed that alterations in the lipid profile and lipoprotein composition were remarkable in the ICH-CAA group compared to control subjects, whereas the AD group presented no specific alterations compared with controls. ICH-CAA patients presented an atheroprotective profile, which consisted of lower total and LDL cholesterol levels. Plasma from chronic ICH-CAA patients also showed a redistribution of ApoC-III from HDL to VLDL and a higher ApoE/ApoC-III ratio in HDL. Whether these alterations reflect a protective response or have a causative effect on the pathology requires further investigation.

[9] *Kuo TT, Huang YB, Hsieh CJ. Consumption and market share of cholesterol-lowering drugs in high-risk patients before and after the release of the 2013 ACC/AHA cholesterol guidelines: a retrospective observational study. BMJ open* 2020; 10:e036769.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33444173>

ABSTRACT

OBJECTIVE: We examined the use of cholesterol-lowering drugs in Taiwan in high-risk patients before and after the release of the 2013 American College of Cardiology and the American Heart Association (ACC/AHA) cholesterol guidelines. DESIGN: Retrospective observational study. SETTING: Kaohsiung Chang Gung Memorial Hospital database, Kaohsiung City, Taiwan. PARTICIPANTS: Outpatients aged ≥ 20 years with atherosclerosis cardiovascular disease, familial hypercholesterolaemia and diabetes. PRIMARY AND SECONDARY OUTCOME MEASURES: Data on brand and generic names, use and dosage of cholesterol-lowering drugs in 2012 and 2015 were

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compiled and the total amount used was calculated. Differences in usage and market share were compared. Usage rates of single and fixed-dose combination (FDC) products were compared. RESULTS: The number of patients receiving ambulatory care increased from 36 367 in 2012 to 41 807 in 2015. Single (3 679 979-4 568 086 tablets) and FDC (540 522-572 954 tablets) product use increased from 2012 to 2015, respectively. Statins were the most commonly prescribed medications in 2012 (71.14%) and 2015 (72.91%). The average monthly consumption of statin among high-risk patients in 2012 was 269 948.8 tablets, and it increased significantly to 343 975.3 tablets in 2015. The average monthly consumption of pitavastatin was 34 113.4 tablets in 2015, which was significantly higher than 0 in 2012. Conversely, the highest decline was observed for fluvastatin use, with the average monthly consumption being 38 754.3 tablets in 2015, which was significantly lower than 45 929.8 tablets consumed in 2012. Regarding FDC therapy for cholesterol-lowering drugs, Vytorin (ezetimibe 10 mg + simvastatin 20 mg) use was the highest among all FDCs in 2015. CONCLUSIONS: The 2013 ACC/AHA cholesterol guidelines likely promoted the use of fixed-dose, high-intensity and moderate-intensity monotherapy and FDC therapy statins in high-risk groups, and this was consistent with the use of high-intensity or moderate-intensity statins in the present study. Furthermore, these changes were associated with increased effectiveness and reduced adverse effects.

[10] Kura B, Kalocayova B, Szeiffova Bacova B et al. **The effect of selected drugs on the mitigation of myocardial injury caused by gamma radiation.** Canadian journal of physiology and pharmacology 2021:1-9.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33438486>

ABSTRACT

Radiation damage of healthy tissues represents one of the complications of radiotherapy effectiveness. This study is focused on the screening of potentially effective drugs routinely used in medical practice and involved in the mechanism of radiation injury, namely for radiation-induced production of free radicals in the body. Experiments in rats revealed significant reduction of oxidative stress (malondialdehyde) and inflammatory marker (tumor necrosis factor α) in 10 Gy irradiated groups after administration of atorvastatin and a slight decrease after tadalafil administration, which indicates that one of the possible mechanisms for mitigation of radiation-induced cardiac damage could be the modulation of nitric oxide (NO) in endothelium and phosphodiesterase 5. In addition, miRNAs were analyzed as potential markers and therapeutically effective molecules. Expression of miRNA-21 and miRNA-15b showed the most significant changes after irradiation. Atorvastatin and tadalafil normalized changes of miRNA (miRNA-1, miRNA-15b, miRNA-21) expression levels in irradiated hearts. This screening study concludes that administration of specific drugs could mitigate the negative impact of radiation on the heart, but more detailed experiments oriented to other aspects of drug effectiveness and their exact mechanisms are still needed.

[11] Malaeb S, Spoke C. **The Glucose-Lowering Effects of Coconut Oil: A Case Report and Review of the Literature.** Case reports in endocrinology 2020; 2020:8841781.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33425401>

ABSTRACT

BACKGROUND: Coconut oil, a saturated fat comprised mostly of the medium-chain fatty acid, lauric acid, has become increasingly popular over the past few decades due to its touted anti-inflammatory,

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metabolic, and lipid-lowering properties. There have been many studies with mixed results evaluating the effects of coconut oil consumption on lipid metabolism and cardiometabolic risk. However, the effects on glucose metabolism are less clear. There are few trials on the effects of coconut oil on glucose homeostasis but no case reports prior to the current one. **CASE:** We present a case of a 66-year-old man with a history of type 2 diabetes managed with insulin who developed recurrent hypoglycemia and required reduction in insulin therapy quickly after consuming coconut oil supplementation. **CONCLUSION:** This is the first known case report of coconut oil supplementation in a diabetic patient on insulin resulting in hypoglycemia. Review of the literature shows that coconut oil supplementation can have a favorable effect on glycemic control, possibly through phenolic compounds mediating anti-inflammatory effects. This effect is inconsistent throughout the studies reviewed, likely due to variations in types of coconut oil supplementation and scarcity of trials. Further research is required both in animal models and in humans before coconut oil intake is widely advised and popularized. This is especially true in patients with diabetes, who are at increased risk of cardiovascular disease, and in whom reduction in saturated fat intake is advised.

[12] Shen H, Ding L, Baig M et al. **Improving glucose and lipids metabolism: drug development based on bile acid related targets.** *Cell Stress* 2021; 5:1-18.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33447732>

ABSTRACT

Bariatric surgery is one of the most effective treatment options for severe obesity and its comorbidities. However, it is a major surgery that poses several side effects and risks which impede its clinical use. Therefore, it is urgent to develop alternative safer pharmacological approaches to mimic bariatric surgery. Recent studies suggest that bile acids are key players in mediating the metabolic benefits of bariatric surgery. Bile acids can function as signaling molecules by targeting bile acid nuclear receptors and membrane receptors, like FXR and TGR5 respectively. In addition, the composition of bile acids is regulated by either the hepatic sterol enzymes such as CYP8B1 or the gut microbiome. These bile acid related targets all play important roles in regulating metabolism. Drug development based on these targets could provide new hope for patients without the risks of surgery and at a lower cost. In this review, we summarize the most updated progress on bile acid related targets and development of small molecules as drug candidates based on these targets.

[13] Kim H, Oh B, Park-Min KH. **Regulation of Osteoclast Differentiation and Activity by Lipid Metabolism.** *Cells* 2021; 10.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33430327>

ABSTRACT

Bone is a dynamic tissue and is constantly being remodeled by bone cells. Metabolic reprogramming plays a critical role in the activation of these bone cells and skeletal metabolism, which fulfills the energy demand for bone remodeling. Among various metabolic pathways, the importance of lipid metabolism in bone cells has long been appreciated. More recent studies also establish the link between bone loss and lipid-altering conditions-such as atherosclerotic vascular disease, hyperlipidemia, and obesity-and uncover the detrimental effect of fat accumulation on skeletal homeostasis and increased risk of fracture. Targeting lipid metabolism with statin, a lipid-lowering drug, has been shown to improve bone density and quality in metabolic bone diseases. However, the molecular mechanisms of lipid-mediated regulation in osteoclasts are not completely understood.

Thus, a better understanding of lipid metabolism in osteoclasts can be used to harness bone cell activity to treat pathological bone disorders. This review summarizes the recent developments of the contribution of lipid metabolism to the function and phenotype of osteoclasts.

[14] *Schwartz GG, Steg PG, Bhatt DL et al. Clinical Efficacy and Safety of Alirocumab after Acute Coronary Syndrome According to Achieved Level of Low-Density Lipoprotein Cholesterol: A Propensity Score-Matched Analysis of the ODYSSEY OUTCOMES Trial. Circulation* 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33438437>

ABSTRACT

Background: Recent international guidelines have lowered recommended target levels of low-density lipoprotein-cholesterol (LDL-C) for patients at very high risk for major adverse cardiovascular events (MACE). However, uncertainty persists whether additional benefit results from achieved LDL-C levels below conventional targets. Inferences from prior analyses are limited because patients who achieve lower versus higher LDL-C on lipid-lowering therapy differ in other characteristics prognostic for MACE and because few achieved very low LDL-C levels. To overcome these limitations, we performed a propensity score matching (PSM) analysis of the ODYSSEY OUTCOMES trial which compared alirocumab with placebo in 18,924 patients with recent acute coronary syndrome (ACS) receiving intensive or maximum-tolerated statin treatment. Methods: Patients on alirocumab were classified in prespecified strata of LDL-C achieved at 4 months of treatment: <25 (n=3357), 25-50 (n=3692) or >50 mg/dL (n=2197). For each stratum, MACE (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina) after month 4 was compared in patients receiving placebo with similar baseline characteristics and adherence, using 1:1 PSM. Results: Across achieved LDL-C strata of the alirocumab group patients differed by baseline LDL-C, lipoprotein(a), use of intensive statin therapy, study medication adherence, and other demographic, medical history, biometric, and laboratory criteria. After PSM, characteristics were similar in corresponding patients of the alirocumab and placebo groups. Treatment hazard ratio (HR), 95% confidence interval (CI), and absolute risk reduction (ARR, number per 100 patient-years) for MACE were similar in those with achieved LDL-C <25 mg/dL (HR, 0.74; 95% CI, 0.62 to 0.89; ARR, 0.92) or 25-50 mg/dL (HR, 0.74; 95% CI, 0.64 to 0.87; ARR, 1.05). Patients with achieved LDL-C >50 mg/dL had poorer adherence and derived less benefit (HR, 0.87; 95% CI, 0.73 to 1.04; ARR, 0.62). No safety concerns were associated with a limited period of LDL-C levels <15 mg/dL. Conclusions: After accounting for differences in baseline characteristics and adherence, patients treated with alirocumab who achieved LDL-C levels <25 mg/dL did not appear to derive further reduction in the risk of MACE compared to those who achieved LDL-C levels of 25-50 mg/dL. Clinical Trial Registration: URL: <https://www.clinicaltrials.gov> Unique identifier: NCT01663402.

[15] *Kanukula R, Salam A, Rodgers A, Kamel B. Pharmacokinetics of Rosuvastatin: A Systematic Review of Randomised Controlled Trials in Healthy Adults. Clinical pharmacokinetics* 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33428168>

ABSTRACT

BACKGROUND: Rosuvastatin is a lipid-lowering drug that works by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme responsible for producing cholesterol in humans. The pharmacokinetic data of rosuvastatin are considerably variable across studies. OBJECTIVE: To review the pharmacokinetics of rosuvastatin from randomised controlled trials

(RCTs) in healthy adults. **METHODS:** A review of the pharmacokinetics of rosuvastatin was performed using systematic search strategies. The Sheiner method was used to summarise the pharmacokinetics of the drug. **RESULTS:** Randomised controlled studies (n = 70) involving healthy subjects (n = 2355) that examined the pharmacokinetics of rosuvastatin following single and multiple doses were included in the review. Rosuvastatin is given once daily in the dose range of 5-80 mg, with 40 mg being the maximum approved daily dose. Rosuvastatin achieves maximum plasma concentration at a median of 5 h (range: 0.5-6 h) under fasting conditions following single and multiple doses. Following single doses, rosuvastatin has a mean absolute oral availability of 20%, an overall mean total clearance of 28.3 L/h and an average terminal elimination half-life of approximately 20 h. The overall mean total clearance of the drug in Caucasian subjects was 1.7-fold higher than that in healthy Chinese subjects. The systemic exposure of rosuvastatin is characterised by a large coefficient of variation (48%.) There is a small accumulation with repeated dosing. The interaction of rosuvastatin with darunavir/ritonavir was considered statistically and clinically relevant. Interactions of rosuvastatin single doses with erythromycin, fluconazole, itraconazole and antacid were statistically significant. **DISCUSSION AND CONCLUSIONS:** There is considerable variation in the pharmacokinetics of rosuvastatin between races. The clinical relevance of the statistically significant drug interactions is yet to be investigated following repeated co-administration for at least 15 days, consistent with a half-life of low-density lipoprotein of 3 days.

[16] *Petersen KS, Bowen KJ, Tindall AM et al. The Effect of Inflammation and Insulin Resistance on Lipid and Lipoprotein Responsiveness to Dietary Intervention. Current developments in nutrition 2020; 4:nzaa160.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33447695>

ABSTRACT

Lipids and lipoproteins are major targets for cardiovascular disease (CVD) prevention. Findings from a limited number of clinical trials suggest diet-induced atherogenic lipoprotein lowering can be altered in the presence of chronic low-grade inflammation or insulin resistance. This review summarizes results from randomized controlled trials that have examined diet-induced changes in lipids/lipoproteins by inflammatory or insulin sensitivity status. In addition, mechanisms to explain these clinical observations are explored. Post hoc analyses of data from a limited number of randomized controlled trials suggest attenuation of diet-induced lipid/lipoprotein lowering in individuals with inflammation and/or insulin resistance. These findings are supported by experimental studies showing that inflammatory stimuli and hyperinsulinemia alter genes involved in endogenous cholesterol synthesis and cholesterol uptake, reduce cholesterol efflux, and increase fatty acid biosynthesis. Further a priori defined research is required to better characterize how chronic low-grade inflammation and insulin resistance modulate lipid and lipoprotein responsiveness to guide CVD risk reduction in individuals presenting with these phenotypes.

[17] *Korneva V, Kuznetsova T, Julius U. The State of the Problem of Achieving Extremely Low LDL Levels. Current pharmaceutical design 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33430743>

ABSTRACT

Patients who have achieved very low low-density lipoprotein cholesterol (LDL-C) levels in clinical trials have the lowest cardio-vascular risk. The current clinical guidelines set such concentration for

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LDL-C as < 1.4 mmol/L. However, the question of minimum permissible target values of the lipids remains unresolved. A number of experimental and clinical studies showed some unfavorable consequences of low LDL-C levels, at the same time, the modern arsenal of lipid lowering drugs allows reducing LDL-C levels to extremely low values.

[18] *Dopheide JF, Adam L, Wiedmer S et al. Improved lipid target level attainment in patients with peripheral artery disease. Current vascular pharmacology 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33430734>

ABSTRACT

BACKGROUND: Patients with peripheral artery disease (PAD) fall under the category of a very high cardiovascular risk. Although, consequent lipid lowering therapy (LLT) is advised, only sparse data on attained target level in PAD exists. **OBJECTIVES:** We aimed to analyse contemporary guideline recommendations for LLT in symptomatic PAD patients. **METHODS:** monocentric, prospective, observational study involving 200 symptomatic PAD patients. Guideline target level attainment and LLT were analysed between 2017 and 2019. **RESULTS:** Overall 78.5% of the patients were on statin therapy, mainly of high intensity with atorvastatin in 50% and rosuvastatin in 33% of the cases. Average statin dosage adjusted for simvastatin was 55 mg/d. Low density lipoproteincholesterol (LDL-C) was <1.8 mmol/L in 53% and <1.4 mmol/L in 34% of the cases. Mean LDL-C levels were at 1.85 ± 0.88 mmol/L. We observed no difference in the treatment and the target level attainment of patients with a stable PAD (intermittent claudication) or chronic critical PAD. However, patients with ≥ 1 vascular region affected (i.e. coronary and/or cerebrovascular) were treated more intensively and had lower LDL-C levels than patients with PAD alone. **CONCLUSION:** It appears that there is more awareness and improvement of previously documented undertreatment of LDL-C levels in symptomatic PAD patients. Although statin treatment is initiated in the majority of patients, our findings call for a continuously intensified LLT in symptomatic PAD patients.

[19] *Ray KK. Changing the paradigm for post-MI cholesterol lowering from intensive statin monotherapy towards intensive lipid-lowering regimens and individualized care. European heart journal 2021; 42:253-256.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454778>

ABSTRACT

[20] *Sabatine MS, Giugliano RP, Schwartz GG. Letter to the editor re: 'serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review'. Expert Rev Clin Pharmacol 2021:1-2.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33428482>

ABSTRACT

[21] *van Bruggen FH, Nijhuis GBJ, Zuidema SU, Luijendijk HJ. Response to letter to the editor re: 'serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review'. Expert Rev Clin Pharmacol 2021:1-2.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33428485>

ABSTRACT

[22] *Nevola R, Rinaldi L, Zeni L et al. Changes in clinical scenarios, management and perspectives of patients with chronic hepatitis C after viral clearance by direct-acting antivirals. Expert Rev Gastroenterol Hepatol 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33445990>

ABSTRACT

INTRODUCTION: Hepatitis C virus (HCV) causes a systemic infection inducing hepatic and extrahepatic diseases. These latter involve cardiovascular system, kidney, brain, endocrine, glucose and lipid metabolism and the immune system. HCV infection is associated with an increased risk of morbidity and mortality for both hepatic and extrahepatic events. Direct-acting antivirals (DAA), introduced in the most recent years for HCV treatment, are effective in up to 99% of cases and have changed the clinical scenarios and management of these patients. AREAS COVERED: The literature on the impact of HCV clearance by DAA on both hepatic and extrahepatic disease outcomes has been analyzed and discussed in this review in order to summarize the full therapeutic potential and its weaknesses. EXPERT OPINION: Patients achieving HCV clearance have improved hepatic and extrahepatic diseases, quality of life and survival. They have lower incidence of cardiovascular disease, type 2 diabetes, kidney damage, and immuno-mediated manifestations. However, the improvements are related to the degree of pre-treatment organ damage. Therefore, a significant percentage of patients with advanced disease remain at risk of morbidity and mortality and must be monitored in the post-treatment. In addition, data emphasize the importance of starting treatment during the early stages of HCV infection.

[23] *Cong L, Ren Y, Hou T et al. Use of Cardiovascular Drugs for Primary and Secondary Prevention of Cardiovascular Disease Among Rural-Dwelling Older Chinese Adults. Frontiers in pharmacology 2020; 11:608136.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33424613>

ABSTRACT

Cardiovascular risk factors and related disorders are common among older adults, and use of various classes of cardiovascular (CV) drugs could reduce the risk of cardiovascular disease (CVD). However, data are sparse with regard to the use of CV drugs among rural-dwelling older adults in China. Therefore, this population-based study aimed to describe use of CV drugs among older adults living in the rural communities in China, while taking into account the use of CV drugs for primary and secondary prevention of CVDs. This study included 5,246 participants (age ≥ 65 years; 57.17% women; 40.68% illiteracy) in the baseline examination of the MIND-China study. In March-September 2018, data on health-related factors, CVDs (ischemic heart disease, atrial fibrillation, heart failure, and stroke), and CV drug use were collected via face-to-face survey, clinical examination, and laboratory tests. We classified CV drugs according to the Anatomical Therapeutic Chemical classification system for western medications and specific cardiovascular effects for the products of traditional Chinese medicine (TCM). We conducted descriptive analysis. The overall prevalence of major cardiovascular risk factors ranged from 14.30% in diabetes and 23.81% in dyslipidemia to 66.70% in hypertension, and CVDs affected 35.07% of all participants (36.28% in women vs. 33.47% in men, $p = 0.035$). In the total sample, calcium channel blockers (C08) were most commonly used (10.39%), followed by TCM products (7.64%), hypoglycemic agents (A10, 4.73%), renin-angiotensin system (RAS)-acting agents (C09, 4.61%), and lipid-lowering agents (C10, 4.17%). The proportions of CV drugs for primary prevention (i.e., use of CV drugs among people without CVD) were 3.14% for

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antithrombotic agents (mainly aspirin), 1.38% for lipid-lowering agents, and 3.11% for RAS-acting agents; the corresponding figures for secondary prevention (i.e., use of CV drugs among people with CVD) were 13.97%, 9.35%, and 7.39%. In conclusion, despite highly prevalent cardiovascular risk factors and CVDs, a fairly low proportion of the rural-dwelling older adults take CV medications for primary and secondary prevention. Notably, TCM products are among the most commonly used CV drugs. These results call for additional efforts to promote implementation of the evidence-based recommendations for prevention of CVDs in the primary care settings.

[24] *van der Ende MY, Waardenburg IE, Lipsic E et al. The effect of feedback on cardiovascular risk factors on optimization of primary prevention: The PharmLines initiative. Int J Cardiol Hypertens 2020; 6:100042.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33447768>

ABSTRACT

BACKGROUND: It is unknown whether population based single assessment of cardiovascular disease (CVD) risk and feedback to individuals and general practitioners results in initiation of preventive cardiovascular pharmacotherapy in those at risk. **METHODS:** The population based cohort study Lifelines was linked to the IADB.nl pharmacy database to assess information on the initiation of preventive medication (N = 48,770). At the baseline visit, information on cardiovascular risk factors was collected and reported to the participants and their general practitioners. An interrupted-time-series-analysis was plotted, in which the start year of blood pressure and lipid lowering medication was displayed in years before or after the baseline visit. Subsequently, predictors of the initiation of pharmacotherapy were determined and possible reduction in cardiovascular events that could be achieved by optimal treatment of individuals at risk. **RESULTS:** Before the Lifelines baseline visit, 34% (out of 1,527, 95% Confidence interval (CI) 32%-36%) and 30% (out of 1,991, 95%CI 28%-32%) of the individuals at risk had a blood pressure or lipid lowering drug prescription, respectively. In those at risk, the use of blood pressure lowering medication, increased substantially during the year of the baseline visit. Treating individuals at increased risk ($\geq 5\%$ 10-year risk) with lipid or blood pressure lowering medication (N = 8515 and N = 6899) would have prevented 162 and 183 CVD events, respectively, in the upcoming five years. **CONCLUSION:** Primary prevention of CVD in the general population appears suboptimal. Feedback of cardiovascular risk factors resulted in a substantial increase of blood pressure lowering medication and extrapolated health benefits.

[25] *Aguilar-Ballester M, Hurtado-Genovés G, Taberner-Cortés A et al. Therapies for the Treatment of Cardiovascular Disease Associated with Type 2 Diabetes and Dyslipidemia. International journal of molecular sciences 2021; 22.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33440821>

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide and is the clinical manifestation of the atherosclerosis. Elevated LDL-cholesterol levels are the first line of therapy but the increasing prevalence in type 2 diabetes mellitus (T2DM) has positioned the cardiometabolic risk as the most relevant parameter for treatment. Therefore, the control of this risk, characterized by dyslipidemia, hypertension, obesity, and insulin resistance, has become a major goal in many experimental and clinical studies in the context of CVD. In the present review, we summarized experimental studies and clinical trials of recent anti-diabetic and lipid-lowering therapies targeted to

reduce CVD. Specifically, incretin-based therapies, sodium-glucose co-transporter 2 inhibitors, and proprotein convertase subtilisin kexin 9 inactivating therapies are described. Moreover, the novel molecular mechanisms explaining the CVD protection of the drugs reviewed here indicate major effects on vascular cells, inflammatory cells, and cardiomyocytes, beyond their expected anti-diabetic and lipid-lowering control. The revealed key mechanism is a prevention of acute cardiovascular events by restraining atherosclerosis at early stages, with decreased leukocyte adhesion, recruitment, and foam cell formation, and increased plaque stability and diminished necrotic core in advanced plaques. These emergent cardiometabolic therapies have a promising future to reduce CVD burden.

[26] Crane HM, Nance RM, Whitney BM et al. **Brief Report: Differences in Types of Myocardial Infarctions Among People Aging With HIV.** Journal of acquired immune deficiency syndromes (1999) 2021; 86:208-212.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33433123>

ABSTRACT

BACKGROUND: Type 1 myocardial infarctions (T1MIs) result from atherosclerotic plaque instability, rupture, and/or erosion. Type 2 MIs (T2MIs) are secondary to causes such as sepsis and cocaine-induced vasospasm resulting in an oxygen demand-supply mismatch and are associated with higher mortality than T1MIs. T2MIs account for a higher proportion of MIs among people living with HIV (PLWH) compared with the general population. We compared MI rates by type among aging PLWH. We hypothesized that increases in MI rates with older age would differ by MI types, and T2MIs would be more common than T1MIs in younger individuals. **METHODS:** Potential MIs from 6 sites were centrally adjudicated using physician notes, electrocardiograms, procedure results, and laboratory results. Reviewers categorized MIs by type and identified causes of T2MIs. We calculated T1MI and T2MI incidence rates. Incidence rate ratios were calculated for T2MI vs. T1MI rates per decade of age. **RESULTS:** We included 462 T1MIs (52%) and 413 T2MIs (48%). T1MI rates increased with older age, although T1MIs occurred in all age decades including young adults. T2MI rates were significantly higher than T1MI rates for PLWH younger than 40 years. T1MI rates were similar or higher than T2MI rates among those older than 40 years (significantly higher for those aged 50-59 and 60-69 years). **CONCLUSIONS:** Rates of T2MIs were higher than T1MIs until age 40 years among PLWH, differing from the general population, but rates of both were high among older PLWH. Given prognostic differences between MI types, these results highlight the importance of differentiating MI types among PLWH.

[27] Omote K, Yokota I, Nagai T et al. **High-Density Lipoprotein Cholesterol and Cardiovascular Events in Patients with Stable Coronary Artery Disease Treated with Statins: An Observation from the REAL-CAD Study.** Journal of atherosclerosis and thrombosis 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33431716>

ABSTRACT

AIM: The association between high-density lipoprotein cholesterol (HDL-C) level after statin therapy and cardiovascular events in patients with stable coronary artery disease (CAD) remains unclear. Thus, in this study, we sought to determine how HDL-C level after statin therapy is associated with cardiovascular events in stable CAD patients. **METHODS:** From the REAL-CAD study which had shown the favorable prognostic effect of high-dose pitavastatin in stable CAD patients with low-density lipoprotein cholesterol (LDL-C) <120 mg/dL, 9,221 patients with HDL-C data at baseline and

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6 months, no occurrence of primary outcome at 6 months, and reported non-adherence for pitavastatin, were examined. The primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergent admission after 6 months of randomization. Absolute difference and ratio of HDL-C levels were defined as (those at 6 months-at baseline) and (absolute difference/baseline)×100, respectively. RESULTS: During a median follow-up period of 4.0 (IQR 3.2-4.7) years, the primary outcome occurred in 417 (4.5%) patients. The adjusted risk of all HDL-C-related variables (baseline value, 6-month value, absolute, and relative changes) for the primary outcome was not significant (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.91-1.08, HR 1.03, 95% CI 0.94-1.12, HR 1.05, 95% CI 0.98-1.12, and HR 1.08, 95% CI 0.94-1.24, respectively). Furthermore, adjusted HRs of all HDL-C-related variables remained non-significant for the primary outcome regardless of on-treatment LDL-C level at 6 months. CONCLUSIONS: After statin therapy with modestly controlled LDL-C, HDL-C level has little prognostic value in patients with stable CAD.

[28] *Vilar-Gomez E, Gawrieh S, Liang T et al. Interrogation of selected genes influencing serum LDL-Cholesterol levels in patients with well characterized NAFLD. Journal of clinical lipidology 2020.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454241>

ABSTRACT

BACKGROUND: The clinical significance of rare mutations in LDL metabolism genes on nonalcoholic fatty liver disease (NAFLD) severity is not well understood. OBJECTIVE: To examine the significance of mutations in LDL metabolism genes including apolipoprotein B (APOB), proprotein convertase subtilisin kexin 9 (PCSK9) and LDL receptor (LDLR) in patients with NAFLD. METHODS: Patients with biopsy-confirmed NAFLD from the NASH Clinical Research Network studies were stratified into 3 groups of LDL-C (≤ 50 mg/dL, 130-150 mg/dL, ≥ 190 mg/dL) and then 120 (40 per group) were randomly selected from the strata. We examined the presence of mutations on LDL genes and analyzed its association with selected NAFLD-related features. Multivariable analyses were adjusted for age, race, gender and use of statins. RESULTS: Among 40 patients with LDL-C ≤ 50 mg/dL, 7 (18%) patients had heterozygous variants in APOB and 2 had heterozygous variants in PCSK9 (5%). We also found heterozygous mutations in 3 (8%) patients with LDL-C ≥ 190 mg/dL; 2 and 1 located in LDLR and APOE genes, respectively. Compared to wild-type controls with LDL-C ≤ 50 , APOB carriers displayed higher levels of alanine aminotransferase (85.86 ± 35.14 U/L vs 45.61 ± 20.84 U/L, Adj. P = 0.002) and steatosis $>66\%$ (57% vs 24%, Adj. P = 0.050). These associations remained statistically significant after excluding statin users. Other histological features of NAFLD severity were not different between wild-type controls and APOB mutation carriers. CONCLUSION: Mutations in the APOB gene are common among NAFLD patients with very low LDL-C and may be associated with increased aminotransferase levels and steatosis severity.

[29] *Kulkarni AV, Anand L, Vyas AK et al. Omega-3 Fatty Acid Lipid Emulsions are Safe and Effective in Reducing Endotoxemia and Sepsis in Acute-on-Chronic Liver Failure-an open-label randomized controlled trial. Journal of gastroenterology and hepatology 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33450081>

ABSTRACT

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BACKGROUND AND AIM: Sepsis is an important determinant of the outcome of acute-on-chronic liver failure (ACLF) patients. Omega-3 fatty acids (FAs) are known to suppress inflammation, reduce morbidity, and mortality in postoperative and critically ill patients. We aimed to evaluate the effect of intravenous omega-6 and omega-3 FA lipid emulsions in ACLF patients. **METHODS:** Ninety ACLF patients were randomly allocated to 3 groups- Gr. A- received no lipid emulsions, Gr. B- omega-6 FAs, and Gr. C- omega-3 FAs. The primary and secondary aims were to compare the effects of lipid emulsions on immune modulation, the incidence of bacterial sepsis, and mortality at day-28. **RESULTS:** The baseline characteristics of the patients were comparable. Serum endotoxin levels remained suppressed by 22% in Gr. C compared with a 4% and 12% rise in Gr. B and A ($p < 0.001$). Omega-3 FAs also suppressed C-reactive protein levels and neutrophil-to-lymphocyte ratio in Gr. C. Compared with Gr. A, omega-3 FAs reduced sepsis by 86% (HR-0.14(95%CI, 0.04-0.43; $p < 0.001$)). Omega-3 FAs significantly increased the expression of TLR2 and TLR4 on both CD14+ and CD16+ monocytes, and TLR4, on macrophages and neutrophils. There were no serious adverse events, except transient flushing in 20% and 16.6% of patients receiving omega-6 FAs and omega-3 FAs, respectively. **CONCLUSION:** Omega-3 FAs are safe and effective in reducing systemic inflammation, endotoxemia, and sepsis in patients with ACLF. These lipid emulsions could also be considered as effective sources of immunonutrition in such sick patients.

[30] *Stefanick ML, King AC, Mackey S et al. Women's Health Initiative Strong and Healthy (WHISH) Pragmatic Physical Activity Intervention Trial for Cardiovascular Disease Prevention: Design and Baseline Characteristics. J Gerontol A Biol Sci Med Sci 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33433559>

ABSTRACT

BACKGROUND: National guidelines promote physical activity to prevent cardiovascular disease (CVD), yet no randomized controlled trial has tested whether physical activity reduces prevent CVD. **METHODS:** The Women's Health Initiative (WHI) Strong and Healthy (WHISH) pragmatic trial used a randomized consent design to assign women for whom cardiovascular outcomes were available through WHI data collection (N=18,985) or linkage to the Centers for Medicare and Medicaid Services (N30,346), to a physical activity intervention or "usual activity" comparison, stratified by ages 68-99 years (in tertiles), U.S. geographic region, and outcomes data source. Women assigned to the intervention could "opt out" after receiving initial physical activity materials. Intervention materials applied evidence-based behavioral science principles to promote current national recommendations for older Americans The intervention was adapted to participant input regarding preferences, resources, barriers and motivational drivers and was targeted for three categories of women at lower, middle or higher levels of self-reported physical functioning and physical activity. Physical activity was assessed in both arms through annual questionnaires. The primary outcome is major cardiovascular events, specifically myocardial infarction, stroke, or CVD death; primary safety outcomes are hip fracture and non-CVD death. The trial is monitored annually by an independent Data Safety and Monitoring Board. Final analyses will be based on intention-to-treat in all randomized participants, regardless of intervention engagement. **RESULTS:** The 49,331 randomized participants had a mean baseline age of 79.7 years; 84.3% were white, 9.2% black, 3.3% Hispanic, 1.9% Asian/Pacific Islander, 0.3% Native American, and 1% were of unknown race/ethnicity. The mean baseline RAND-36 physical function score was 71.6 (± 25.2 SD). There were no differences between Intervention (N=24,657) and Control (N=24,674) at baseline for age, race/ethnicity, current smoking (2.5%), use of

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blood pressure or lipid-lowering medications, body mass index, physical function, physical activity, or prior CVD (10.1%). **CONCLUSION:** The WHISH trial is rigorously testing whether a physical activity intervention reduces major CV events in a large, diverse cohort of older women.

[31] *Oleaga C, Hay J, Gurcan E et al. Insights into the kinetics and dynamics of the furin-cleaved form of PCSK9. Journal of lipid research 2020; 62:100003.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33429337>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates cholesterol metabolism by inducing the degradation of hepatic low density lipoprotein receptors (LDLRs). Plasma PCSK9 has 2 main molecular forms: a 62 kDa mature form (PCSK9_62) and a 55 kDa, furin-cleaved form (PCSK9_55). PCSK9_55 is considered less active than PCSK9_62 in degrading LDLRs. We aimed to identify the site of PCSK9_55 formation (intracellular vs. extracellular) and to further characterize the LDLR-degradative function of PCSK9_55 relative to PCSK9_62. Coexpressing PCSK9_62 with furin in cell culture induced formation of PCSK9_55, most of which was found in the extracellular space. Under the same conditions, we found that i) adding a cell-permeable furin inhibitor preferentially decreased the formation of PCSK9_55 extracellularly; ii) using pulse-chase analysis, we observed the formation of PCSK9_55 exclusively extracellularly in a time-dependent manner. A recombinant form of PCSK9_55 was efficiently produced but displayed impaired secretion that resulted in its intracellular trapping. However, the nonsecreted PCSK9_55 was able to induce degradation of LDLR, though with 50% lower efficiency than PCSK9_62. Collectively, our data show that 1) PCSK9_55 is formed extracellularly; 2) PCSK9_55 has a shorter half-life; 3) there is a small intracellular pool of PCSK9_55 that is not secreted; and 4) PCSK9_55 retained within the cell maintains a reduced efficiency to cause LDLR degradation.

[32] *Smith LE, Smith DK, Yancey PG et al. Perioperative high-density lipoproteins, oxidative stress, and kidney injury after cardiac surgery. Journal of lipid research 2021:100024.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33453220>

ABSTRACT

Oxidative stress promotes acute kidney injury (AKI). Higher concentrations of HDL cholesterol are associated with less AKI. To test the hypothesis that HDL antioxidant activity is associated with AKI after cardiac surgery, we quantified HDL particle size and number, paraoxonase-1 activity, and isofuran concentrations in 75 patients who developed AKI and 75 matched control patients. Higher preoperative concentrations of HDL particles were associated with lower odds of AKI (OR: 0.80; 95% CI, 0.71-0.91; $p=0.001$), higher paraoxonase-1 activity ($R=0.36$, $p<0.001$), and lower plasma concentrations of isofurans immediately after surgery ($p=0.02$). Similarly, higher preoperative small HDL particle concentrations were associated with less AKI, higher paraoxonase-1 activity, and lower isofuran concentrations. Circulating HDL particle concentrations changed rapidly during the perioperative period. Higher intraoperative particle losses were associated with lower odds of AKI (OR: 0.79; 95% CI 0.67-0.93; $p=0.005$), and increased paraoxonase-1 activity strengthened this association ($p=0.006$). Intraoperative particle loss was also associated with decreased postoperative isofuran concentrations ($p=0.04$). Additionally, higher preoperative small HDL particle concentrations and increased intraoperative small particle loss were associated with improved renal function 3-12 months after surgery ($p=0.003$, 0.01, respectively). In conclusion, a higher preoperative concentration

of HDL particles, particularly small particles, is associated with lower oxidative damage and less AKI. Perioperative changes in HDL particle concentrations are also associated with AKI. Small HDL particles may represent a novel modifiable risk factor for AKI.

[33] *Vieira RFL, Muñoz VR, Junqueira RL et al. Time-restricted feeding combined with aerobic exercise training can prevent weight gain and improve metabolic disorders in mice fed a high-fat diet. The Journal of physiology* 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33450053>

ABSTRACT

KEY POINTS: Time-restricted feeding (TRF, in which energy intake is restricted to 8 h/day during the dark phase) alone or combined with aerobic exercise (AE) training can prevent weight gain and metabolic disorders in Swiss mice fed a high-fat diet. The benefits of TRF+Exe are associated with improved hepatic metabolism and decreased hepatic lipid accumulation. TRF combined with AE training increased fatty acid oxidation and decreased the lipogenic and gluconeogenic genes' expression in the liver of young male Swiss mice. TRF combined with AE training attenuated the detrimental effects of high-fat diet feeding on the insulin signaling pathway in the liver. ABSTRACT: Time-restricted feeding (TRF) or physical exercise have been shown to be efficient in the prevention and treatment of metabolic disorders; however, the additive effects of TRF combined with aerobic exercise (AE) training on liver metabolism have not been widely explored. This study performed TRF (8 h in the active phase), and TRF combined with AE (TRF+Exe) and evaluated the effects on insulin sensitivity and hepatic gene expressions involved in fatty acid oxidation, lipogenesis, and gluconeogenesis in male Swiss mice fed a high-fat diet. As previous reports, we show that TRF alone (eating only between ZT16 and ZT0) was sufficient to reduce weight and adiposity gain, increase fatty acid oxidation, and decrease lipogenesis genes in the liver. In addition, we show that mice of the TRF+Exe group showed additional adaptations such as increased oxygen consumption ($VO(2)$), carbon dioxide production ($VCO(2)$), and production of ketone bodies (β -hydroxybutyrate). Also, TRF+Exe attenuated the negative effects of high-fat diet feeding on insulin signaling pathway (IR, IRS, Akt), and led to increased fatty acid oxidation (Ppara, Cpt1a) as well as decreased gluconeogenic (Fbp1, Pck1, Pgc1a) and lipogenic (Srebp1c, Cd36) genes expression in the liver. These molecular results were accompanied by increased glucose metabolism, lower serum triglycerides, and reduced hepatic lipid content in the TRF+Exe group. The data presented in this study show that TRF alone has benefits but TRF+Exe has additive benefits and can mitigate the harmful effects of consuming a high-fat diet on body adiposity, liver metabolism, and glycemic homeostasis in young male Swiss mice. This article is protected by copyright. All rights reserved.

[34] *Hwang D, Kim HJ, Lee SP et al. Topological Data Analysis of Coronary Plaques Demonstrates the Natural History of Coronary Atherosclerosis. JACC. Cardiovascular imaging* 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454260>

ABSTRACT

OBJECTIVES: This study sought to identify distinct patient groups and their association with outcome based on the patient similarity network using quantitative coronary plaque characteristics from coronary computed tomography angiography (CTA). BACKGROUND: Coronary CTA can noninvasively assess coronary plaques quantitatively. METHODS: Patients who underwent 2

coronary CTAs at a minimum of 24 months' interval were analyzed (n = 1,264). A similarity Mapper network of patients was built by topological data analysis (TDA) based on the whole-heart quantitative coronary plaque analysis on coronary CTA to identify distinct patient groups and their association with outcome. RESULTS: Three distinct patient groups were identified by TDA, and the patient similarity network by TDA showed a closed loop, demonstrating a continuous trend of coronary plaque progression. Group A had the least coronary plaque amount (median 12.4 mm³) [interquartile range (IQR): 0.0 to 39.6 mm³] in the entire coronary tree. Group B had a moderate coronary plaque amount (31.7 mm³) [IQR: 0.0 to 127.4 mm³] with relative enrichment of fibrofatty and necrotic core (32.6% [IQR: 16.7% to 46.2%] and 2.7% [IQR: 0.1% to 6.9%] of the total plaque, respectively) components. Group C had the largest coronary plaque amount (187.0 mm³) [IQR: 96.7 to 306.4 mm³] and was enriched for dense calcium component (46.8% [IQR: 32.0% to 63.7%] of the total plaque). At follow-up, total plaque volume, fibrous, and dense calcium volumes increased in all groups, but the proportion of fibrofatty component decreased in groups B and C, whereas the necrotic core portion decreased in only group B (all p < 0.05). Group B showed a higher acute coronary syndrome incidence than other groups (0.3% vs. 2.6% vs. 0.6%; p = 0.009) but both group B and C had a higher revascularization incidence than group A (3.1% vs. 15.5% vs. 17.8%; p < 0.001). Incorporating group information from TDA demonstrated increase of model fitness for predicting acute coronary syndrome or revascularization compared with that incorporating clinical risk factors, percentage diameter stenosis, and high-risk plaque features. CONCLUSIONS: The TDA of quantitative whole-heart coronary plaque characteristics on coronary CTA identified distinct patient groups with different plaque dynamics and clinical outcomes. (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging [PARADIGM]; NCT02803411).

[35] *Jatem E, Lima J, Montoro B et al. Efficacy and Safety of PCSK9 Inhibitors in Hypercholesterolemia Associated With Refractory Nephrotic Syndrome. Kidney international reports 2021; 6:101-109.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33426389>

ABSTRACT

INTRODUCTION: Treatment of hypercholesterolemia in refractory nephrotic syndrome remains a therapeutic challenge. There is not enough evidence supporting the efficacy of statins, and these drugs can be associated with an increased incidence of adverse effects. Herein we summarize our clinical experience with 12 patients suffering from refractory nephrotic syndrome with associated vascular disease and uncontrolled hypercholesterolemia despite treatment with statins who were treated with proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors. METHODS: Twelve adult patients with primary nephrotic syndrome refractory to multiple lines of immunosuppressive treatment who suffered from clinical atheromatous vascular disease were treated with PCSK9 inhibitors according to the prescription guidelines for secondary prevention of cardiovascular events. Eight patients with refractory nephrotic syndrome without vascular disease treated with atorvastatin comprised the control group. RESULTS: Four weeks after treatment with PCSK9 inhibitors, a statistically significant decrease in total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels was observed without significant changes in serum albumin levels or proteinuria. The mean LDL-C decrease was 36.8% ± 4.9% mmol/L at 4 weeks and remained unchanged throughout the follow-up period. In the control group, there were no significant changes in the levels of total cholesterol or LDL-C during the follow-up period. At the diagnosis of nephrotic syndrome, plasma

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PCSK9 levels were 334 ± 40 ng/mL and correlated significantly with serum LDL-C levels ($r = 0.49$, $P = 0.023$). Six months after starting treatment with PCSK9 inhibitors, plasma PCSK9 levels were significantly reduced to values of 190 ± 36 ng/mL ($P = 0.001$) with a mean relative reduction of $42.3\% \pm 12.6\%$. No local adverse effects were seen at the injection site and no significant changes were seen in the levels of transaminase, creatine phosphokinase, or aldolase. **CONCLUSION:** PCSK9 inhibitors may be an effective and safe alternative for the treatment of hypercholesterolemia associated with refractory nephrotic syndrome.

[36] *Liu Y, Xu J, Wu M et al. Empagliflozin protects against atherosclerosis progression by modulating lipid profiles and sympathetic activity. Lipids in health and disease 2021; 20:5.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33436015>

ABSTRACT

BACKGROUND: Several large clinical trials have confirmed the cardioprotective role of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes. However, whether empagliflozin, as an SGLT2i, could alleviate atherosclerosis progression in non-diabetic states remain unknown. **METHODS:** ApoE^{-/-} mice were fed a Western diet for 12 weeks to induce atherosclerosis. On the 7th week, a group of mice were treated with drinking water containing empagliflozin (10 mg/kg/day), while another group was given normal water. At the 12th week, the whole aortas of each group were harvested. Oil Red O, HE and Movat staining were performed for atherosclerotic lesion area and size. Mouse serum lipid profiles (total cholesterol [TC], triglyceride [TG], low-density lipoprotein-c [LDL], and high-density lipoprotein-c [HDL]), systemic inflammation levels (IL-1 β , IL-6 and IL-10), renin-angiotensin-aldosterone system (RAAS) components and sympathetic activity (norepinephrine and neuropeptide Y) indicators were measured by ELISA. **RESULTS:** Empagliflozin reduced the atherosclerotic lesion burden (-8.6%, $P = 0.004$) at aortic root in ApoE^{-/-} mice. In addition, empagliflozin decreased body weight (-3.27 g, $P = 0.002$), lipid profiles (TC: [-15.3 mmol/L, $P = 0.011$]; TG: [-2.4 mmol/L, $P < 0.001$]; LDL: [-2.9 mmol/L, $P = 0.010$]), RAAS (renin [-9.3 ng/L, $P = 0.047$]; aldosterone [-16.7 ng/L, $P < 0.001$]) and sympathetic activity (norepinephrine [-8.9 ng/L, $P = 0.019$]; neuropeptide Y [-8.8 ng/L, $P = 0.002$]). However, the anti-inflammatory effect of empagliflozin was not significantly evident. **CONCLUSIONS:** The early atherosclerotic lesion size was less visible in empagliflozin-treated mice. Empagliflozin could decrease lipid profiles and sympathetic activity in atherosclerosis.

[37] *Vlad CE, Foia L, Florea L et al. Evaluation of cardiovascular risk factors in patients with familial hypercholesterolemia from the North-Eastern area of Romania. Lipids in health and disease 2021; 20:4.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33430859>

ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH) is one of the most frequent and important monogenic cholesterol pathologies. Traditional and non-traditional cardiovascular risk factors increase the prevalence of atherosclerotic cardiovascular disease (ASCVD) in this population. The aims of the study were: (a) to identify FH patients in the North-Eastern part of Romania and to analyze demographic, clinical and paraclinical data (b) to evaluate the risk of new cardiovascular events at follow-up in FH patients stratified by lipid-lowering agents. **METHODS:** This first prospective study in the North-Eastern part of Romania was carried out between October 2017 and October

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2019; out of 980 patients with dyslipidemia evaluated with the Dutch Lipid Network(DLCN) and Simon Broome(SM) scores, 61 patients with DLCN score above 3 and possible/probable FH(SM score) were included. RESULTS: Nine hundred-eighty patients were examined and 61 (6.2%) were received the clinical diagnosis of FH. The mean age was 48.5 ± 12.5 years, with more female patients than male patients (63.9% versus 36%). Hypertension was the main cardiovascular risk factor for both genders, followed by physical inactivity and obesity for the female group and active smoking for the male group. The measured DLCN score recorded: "possible" FH identified in 39.4%, "probable" FH in 45.9% and "definite" FH in 14.7%. The effective lipid-lowering drugs used were statin alone and statin in association with fenofibrate, which improved both the lipid profile values and the subclinical atherosclerosis markers (ankle-brachial index, carotid intima-media thickness and high-sensitivity C-reactive protein). New ASCVDs that emerged during the study were most commonly represented by coronary heart disease and stroke. At the same time, the new cardiovascular events were delayed in patients receiving the lipid-lowering drugs, without significant differences between them. CONCLUSIONS: In patients with suspected FH, the lipid-lowering agents during the follow-up period delayed the new cardiovascular events, yet failed to reach the goals proposed by the guidelines.

[38] Judge MP, Lucas R, Kuzoian C et al. **Needs Assessment to Inform and Improve Educational Practices Surrounding Omega-3 Consumption during Pregnancy.** Matern Child Health J 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33433741>

ABSTRACT

OBJECTIVES: Adequate dietary consumption of long chain omega-3 fatty acids (n-3 LCPUFA) during pregnancy has been associated with better maternal and infant health outcomes. Given that the primary source of n-3 LCPUFA is fish and fish oils, concerns surrounding contamination and uncertainty of safe fish intake guidelines have negatively affected consumption of fish during pregnancy. Although obstetric healthcare providers are in a unique position to influence dietary intake patterns, a gap exists in their understanding the knowledge and practices surrounding n-3 LCPUFA. This needs assessment investigation evaluated knowledge, attitudes and prescribing/recommending practices of obstetric practitioners surrounding n-3 LCPUFA consumption and/or supplementation to generate evidence supporting the development of targeted educational initiatives. METHODS: A cross-sectional, needs assessment was conducted using anonymous online-survey of affiliate members of the American College of Nurse Midwives (N=105). A 24-item, previously validated ($\alpha=0.86$) needs assessment survey (Obstetric Clinicians Omega-3 Survey, OCOS) was used to assess attitudes, knowledge, and prescribing practices surrounding n-3 LCPUFA. RESULTS: The total OCOS score representing attitudes, knowledge and prescribing patterns collectively was 69.48% (Mean = $79.90 (\pm 12.44)$, score range = 24-115). Scores for the sub-domains included attitude 68.33% (Mean = $20.50 (\pm 3.64)$, score range = 6-30); knowledge 71.40% (Mean = $30.70 (\pm 5.43)$, score range = 9-43); and prescribing patterns 68.31% (Mean = $28.69 (\pm 5.39)$, score range = 9-42). CONCLUSIONS FOR PRACTICE: Although the majority of respondents had fair-moderate n-3 LCPUFA knowledge, attitudes and prescribing/recommending, our results highlight an opportunity for additional research and educational outreach targeting improved n-3 LCPUFA knowledge and practices. Specific areas of educational interest included associated health outcomes, dosing and safe consumption guidelines.

[39] **Drugs for Migraine.** The Medical letter on drugs and therapeutics 2020; 62:153-160.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33434187>

ABSTRACT

[40] *Morales-Palomo F, Moreno-Cabañas A, Ramirez-Jimenez M et al. Exercise Reduces Medication for Metabolic Syndrome Management: A Five-Year Follow-up Study. Med Sci Sports Exerc* 2020; Publish Ahead of Print.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33433153>

ABSTRACT

PURPOSE: To determine the effects of a five-year exercise intervention on metabolic syndrome (MetS) and health related variables, and medication use for MetS management. **METHODS:** Participants were randomly assigned to an exercise intervention (n=25, 54±2y, 20% women) or control group (n=26, 54±2y, 38% women). The intervention lasted four months per year and consisted of high-intensity interval training on a cycloergometer thrice a week. Outcomes were MetS Z- and medication use score, MetS-related variables (including blood pressure, blood glucose homeostasis and lipid profile), and cardiorespiratory fitness (CRF, as determined by maximal oxygen uptake). **RESULTS:** MetS Z-score was similarly reduced over time in both groups (p=0.244 for group*time interaction). A quasi-significant and significant group*time interaction was found for MetS factors (p=0.004) and CRF (p<0.001), respectively. Thus, MetS factors tended to decrease over time only in the exercise group with no change in the control group whereas CRF increased from baseline to five-year assessment in the exercise group (by 1.1 MET, p<0.001) but decreased in the control group (-0.5 MET, p=0.025). Medicine use score increased twofold from baseline to five-year follow-up in the control group (p<0.001) but did not significantly change (10%, p=0.52) in the exercise group (p<0.001 for group*time interaction). The proportion of medicated patients who had to increase antihypertensive (p<0.001), glucose-lowering (p=0.036) or total medication (p<0.0001) over the five-year period was lower in the exercise than in the control group. **CONCLUSIONS:** Exercise training can attenuate the increase in medication that would be otherwise required to manage MetS over a five-year period.

[41] *Cicero AFG, Fogacci F, Kuwabara M, Borghi C. Therapeutic Strategies for the Treatment of Chronic Hyperuricemia: An Evidence-Based Update. Medicina (Kaunas, Lithuania)* 2021; 57.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33435164>

ABSTRACT

This article aims to critically review the evidence on the available therapeutic strategies for the treatment of hyperuricemia. For this reason, several papers were reviewed. Xanthine oxidase inhibitors are the safest and most effective uric acid lowering drugs for the management of chronic hyperuricemia, while the efficacy of uricosuric agents is strongly modulated by pharmacogenetics. Emergent drugs (lesinurad, peglotidase) were found to be more effective for the acute management of refractory hyperuricemia, but their use is supported by a relatively small number of clinical trials so that further well-designed clinical research is needed to deepen their efficacy and safety profile.

[42] *Zhang Q, Wang L, Wang J. Clinical study of atorvastatin combined with milrinone in the treatment of chronic heart failure. Minerva medica* 2021.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33438377>

ABSTRACT

[43] *Hariharan R, Mousa A, de Courten B. Influence of AMY1A copy number variations on obesity and other cardiometabolic risk factors: A review of the evidence. Obes Rev 2021.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33432778>

ABSTRACT

The rising incidence of obesity and type 2 diabetes is contributing to the escalating burden of disease globally. These metabolic disorders are closely linked with diet and in particular with carbohydrate consumption; hence, it is important to understand the underlying mechanisms that influence carbohydrate metabolism. Amylase, the enzyme responsible for the digestion of starch, is coded by the genes AMY1A, AMY1B, and AMY1C (salivary amylase) and AMY2A and AMY2B (pancreatic amylase). Previous studies demonstrate wide variations in AMY1A copy numbers, which can be attributed to several genetic, nutritional, and geographical diversities seen in populations globally. Current literature suggests that AMY1A copy number variations are important in obesity and other cardiometabolic disorders through their effects on glucose and lipid homeostasis, inflammatory markers, and the gut microbiome. This review synthesizes the available evidence to improve understanding of the role of AMY1A in obesity and related cardiometabolic risk factors and disorders including insulin resistance and type 2 diabetes, cardiovascular risk and inflammation, and the gut microbiome.

[44] *Brown RE, Welsh P, Logue J. Systematic review of clinical guidelines for lipid lowering in the secondary prevention of cardiovascular disease events. Open heart 2020; 7.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33443127>

ABSTRACT

BACKGROUND: The WHO recommends that those with established cardiovascular disease should be treated with lipid-lowering therapy, but there is no specific guidance regarding lipid monitoring. Unnecessary general practitioner visits may be a burden for patients and increase healthcare costs. A systematic review of the current guidelines was performed to reveal gaps in the evidence base for optimal lipid monitoring approaches. **METHODS:** For this systematic review, a search of Medline, Cumulative Index to Nursing and Allied Health Literature and Turning Research Into Practice databases was conducted for relevant guidelines published in the 10 years prior to 31 December 2019. Recommendations surrounding the frequency of testing, lipid-lowering therapies and target cholesterol values were compared qualitatively. Each guideline was assessed using the 2009 Appraisal of Guidelines for Research and Evaluation II tool. **RESULTS:** Twenty-two guidelines were included. All recommended statins as the primary lipid-lowering therapy, with a high level of supporting evidence. Considerable variation was found in the recommendations for cholesterol targets. Seventeen guidelines provided at least one cholesterol target, which for low-density lipoprotein (LDL) cholesterol ranged between 1.0 and 2.6 mmol/L, although the most frequently recommended was <1.8 mmol/L (n=12). For long-term follow-up, many recommended reviewing patients annually (n=9), although there was some variation in recommendations for the interval of between 3 and 12 months. Supporting evidence for any approach was limited, often being derived from clinical opinion. **CONCLUSIONS:** Further research is required to provide an evidence base for optimal lipid monitoring of the on-statin secondary prevention population.

[45] *Sun L, Pennells L, Kaptoge S et al. Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. PLoS medicine 2021; 18:e1003498.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33444330>

ABSTRACT

BACKGROUND: Polygenic risk scores (PRSs) can stratify populations into cardiovascular disease (CVD) risk groups. We aimed to quantify the potential advantage of adding information on PRSs to conventional risk factors in the primary prevention of CVD. **METHODS AND FINDINGS:** Using data from UK Biobank on 306,654 individuals without a history of CVD and not on lipid-lowering treatments (mean age [SD]: 56.0 [8.0] years; females: 57%; median follow-up: 8.1 years), we calculated measures of risk discrimination and reclassification upon addition of PRSs to risk factors in a conventional risk prediction model (i.e., age, sex, systolic blood pressure, smoking status, history of diabetes, and total and high-density lipoprotein cholesterol). We then modelled the implications of initiating guideline-recommended statin therapy in a primary care setting using incidence rates from 2.1 million individuals from the Clinical Practice Research Datalink. The C-index, a measure of risk discrimination, was 0.710 (95% CI 0.703-0.717) for a CVD prediction model containing conventional risk predictors alone. Addition of information on PRSs increased the C-index by 0.012 (95% CI 0.009-0.015), and resulted in continuous net reclassification improvements of about 10% and 12% in cases and non-cases, respectively. If a PRS were assessed in the entire UK primary care population aged 40-75 years, assuming that statin therapy would be initiated in accordance with the UK National Institute for Health and Care Excellence guidelines (i.e., for persons with a predicted risk of $\geq 10\%$ and for those with certain other risk factors, such as diabetes, irrespective of their 10-year predicted risk), then it could help prevent 1 additional CVD event for approximately every 5,750 individuals screened. By contrast, targeted assessment only among people at intermediate (i.e., 5% to $<10\%$) 10-year CVD risk could help prevent 1 additional CVD event for approximately every 340 individuals screened. Such a targeted strategy could help prevent 7% more CVD events than conventional risk prediction alone. Potential gains afforded by assessment of PRSs on top of conventional risk factors would be about 1.5-fold greater than those provided by assessment of C-reactive protein, a plasma biomarker included in some risk prediction guidelines. Potential limitations of this study include its restriction to European ancestry participants and a lack of health economic evaluation. **CONCLUSIONS:** Our results suggest that addition of PRSs to conventional risk factors can modestly enhance prediction of first-onset CVD and could translate into population health benefits if used at scale.

[46] Wallentin L, Eriksson N, Olszowka M et al. **Plasma proteins associated with cardiovascular death in patients with chronic coronary heart disease: A retrospective study.** *PLoS medicine* 2021; 18:e1003513.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33439866>

ABSTRACT

BACKGROUND: Circulating biomarkers are associated with the development of coronary heart disease (CHD) and its complications by reflecting pathophysiological pathways and/or organ dysfunction. We explored the associations between 157 cardiovascular (CV) and inflammatory biomarkers and CV death using proximity extension assays (PEA) in patients with chronic CHD. **METHODS AND FINDINGS:** The derivation cohort consisted of 605 cases with CV death and 2,788 randomly selected non-cases during 3-5 years follow-up included in the STabilization of Atherosclerotic plaque By Initiation of darapLadlb Therapy (STABILITY) trial between 2008 and 2010. The replication cohort consisted of 245 cases and 1,042 non-cases during 12 years follow-up included in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study between 1997 and

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2000. Biomarker levels were measured with conventional immunoassays and/or with the OLINK PEA panels CVD I and Inflammation. Associations with CV death were evaluated by Random Survival Forest (RF) and Cox regression analyses. Both cohorts had the same median age (65 years) and 20% smokers, while there were slight differences in male sex (82% and 76%), hypertension (70% and 78%), and diabetes (39% and 30%) in the respective STABILITY and LURIC cohorts. The analyses identified 18 biomarkers with confirmed independent association with CV death by Boruta analyses and statistical significance (all $p < 0.0001$) by Cox regression when adjusted for clinical characteristics in both cohorts. Most prognostic information was carried by N-terminal prohormone of brain natriuretic peptide (NTproBNP), hazard ratio (HR for 1 standard deviation [SD] increase of the log scale of the distribution of the biomarker in the replication cohort) 2.079 (95% confidence interval [CI] 1.799-2.402), and high-sensitivity troponin T (cTnT-hs) HR 1.715 (95% CI 1.491-1.973). The other proteins with independent associations were growth differentiation factor 15 (GDF-15) HR 1.728 (95% CI 1.527-1.955), transmembrane immunoglobulin and mucin domain protein (TIM-1) HR 1.555 (95% CI 1.362-1.775), renin HR 1.501 (95% CI 1.305-1.727), osteoprotegerin (OPG) HR 1.488 (95% CI 1.297-1.708), soluble suppression of tumorigenesis 2 protein (sST2) HR 1.478 (95% CI 1.307-1.672), cystatin-C (Cys-C) HR 1.370 (95% CI 1.243-1.510), tumor necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) HR 1.205 (95% CI 1.131-1.285), carbohydrate antigen 125 (CA-125) HR 1.347 (95% CI 1.226-1.479), brain natriuretic peptide (BNP) HR 1.399 (95% CI 1.255-1.561), interleukin 6 (IL-6) HR 1.478 (95% CI 1.316-1.659), hepatocyte growth factor (HGF) HR 1.259 (95% CI 1.134-1.396), spondin-1 HR 1.295 (95% CI 1.156-1.450), fibroblast growth factor 23 (FGF-23) HR 1.349 (95% CI 1.237-1.472), chitinase-3 like protein 1 (CHI3L1) HR 1.284 (95% CI 1.129-1.461), tumor necrosis factor receptor 1 (TNF-R1) HR 1.486 (95% CI 1.307-1.689), and adrenomedullin (AM) HR 1.750 (95% CI 1.490-2.056). The study is limited by the differences in design, size, and length of follow-up of the 2 studies and the lack of results from coronary angiograms and follow-up of nonfatal events. CONCLUSIONS: Profiles of levels of multiple plasma proteins might be useful for the identification of different pathophysiological pathways associated with an increased risk of CV death in patients with chronic CHD. TRIAL REGISTRATION: ClinicalTrials.gov NCT00799903.

[47] *Cai Z, Yang Y, Zhang J. A systematic review and meta-analysis of the serum lipid profile in prediction of diabetic neuropathy. Scientific reports 2021; 11:499.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33436718>

ABSTRACT

Whether the lipid profile in diabetic patients is associated with diabetic neuropathy (DN) development remains ambiguous, as does the predictive value of serum lipid levels in the risk of DN. Here, we performed the first meta-analysis designed to investigate the relationship between DN and the serum levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL). Candidate studies were comprehensively identified by searching PubMed, Embase, Cochrane Library and Web of Science databases up to May 2020. Observational methodological meta-analysis was conducted to assess the relationships of TG, TC, HDL, and LDL levels with DN. Changes in blood lipids were used to estimate the effect size. The results were pooled using a random-effects or fixed-effects model. Potential sources of heterogeneity were explored by subgroup analysis. Various outcomes were included, and statistical analyses were performed using STATA (Version 12.0). Mean differences (MDs) and odds ratios (ORs) with 95% confidence intervals

(CIs) were estimated. The Newcastle-Ottawa Scale (NOS) was applied to assess the methodological quality. I² statistics were calculated to evaluate statistical heterogeneity. Funnel plots were utilized to test for publication bias. A sensitivity analysis was performed by omitting each study one by one. Thirty-nine clinical trials containing 32,668 patients were included in the meta-analysis. The results demonstrated that DN patients showed higher TG and lower HDL levels (MD=0.34, 95% CI: 0.20-0.48 for TG; MD=-0.05, 95% CI: -0.08--0.02, I(2)=81.3% for HDL) than controls. Subgroup analysis showed that patients with type 1 diabetes mellitus (T1DM) neuropathy had elevated TG levels in their serum (MD=0.25, 95% CI: 0.16-0.35, I(2)=64.4% for T1DM). However, only patients with T1DM neuropathy had reduced serum HDL levels, and there was no significant difference in serum HDL levels between patients with T2DM neuropathy and controls (MD=-0.07, 95% CI: -0.10--0.03, I(2)=12.4% for T1DM; MD=-0.02, 95% CI: -0.07-0.03, I(2)=80.2% for T2DM). TC and LDL levels were not significantly different between DN patients and controls (MD=-0.03, 95% CI: -0.14-0.09, I(2)=82.9% for TC; MD=-0.00, 95% CI: -0.08-0.08, I(2)=78.9% for LDL). In addition, compared with mild or painless DN patients, those with moderate or severe pain DN pain had significantly reduced serum TC and LDL levels (MD=-0.31, 95% CI: -0.49--0.13, I(2)=0% for TC; MD=-0.19, 95% CI: -0.32--0.08, I(2)=0% for LDL). TG levels and HDL levels did not vary considerably between patients with mild or painless DN and those with moderate or severe DN pain patients (MD=0.12, 95% CI: -0.28-0.51, I(2)=83.2% for TG; MD=-0.07, 95% CI: -0.14-0.01, I(2)=58.8% for HDL). Furthermore, people with higher TG and LDL levels had higher risk of DN (OR=1.36, 95% CI: 1.20-1.54, I(2)=86.1% for TG and OR=1.10, 95% CI: 1.02-1.19, I(2)=17.8% for LDL). Conversely, high serum HDL levels reduced the risk of DN (OR=0.85, 95% CI: 0.75-0.96, I(2)=72.6%), while TC levels made no significant difference with the risk of DN (OR=1.02, 95% CI: 1.00-1.04, I(2)=84.7%). This meta-analysis indicated that serum lipid profile changes are among the biological characteristics of DN. Lipid levels should be explored as routine laboratory markers for predicting the risk of DN, as they will help clinicians choose appropriate therapies, and thus optimize the use of available resources.

[48] *Levine JA, Oleaga C, Eren M et al. Role of PAI-1 in hepatic steatosis and dyslipidemia. Scientific reports 2021; 11:430.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33432099>

ABSTRACT

Plasminogen activator inhibitor 1 (PAI-1) is a functional biomarker of the metabolic syndrome. Previous studies have demonstrated that PAI-1 is a mechanistic contributor to several elements of the syndrome, including obesity, hypertension and insulin resistance. Here we show that PAI-1 is also a critical regulator of hepatic lipid metabolism. RNA sequencing revealed that PAI-1 directly regulates the transcriptional expression of numerous genes involved in mammalian lipid homeostasis, including PCSK9 and FGF21. Pharmacologic or genetic reductions in plasma PAI-1 activity ameliorates hyperlipidemia in vivo. These experimental findings are complemented with the observation that genetic deficiency of PAI-1 is associated with reduced plasma PCSK9 levels in humans. Taken together, our findings identify PAI-1 as a novel contributor to mammalian lipid metabolism and provides a fundamental mechanistic insight into the pathogenesis of one of the most pervasive medical problems worldwide.

[49] *Shevchuk SV, Seheda YS, Kuvikova IP et al.* **THE EFFECT OF ATORVASTATINUM IN THE TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS.** *Wiadomosci lekarskie (Warsaw, Poland : 1960)* 2020; 73:2427-2430.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454678>

ABSTRACT

OBJECTIVE: The aim: Was to evaluate the effect of 6-month pathogenetic treatment in combination with atorvastatinum on the endothelium function, lipid and adipokine levels, paraoxonase activity and activity of inflammatory process in RA patients. **PATIENTS AND METHODS:** Materials and methods: The study included 55 patients with RA, dividing into two groups depending on the intended therapy. The first group included 33 patients with "traditional" treatment by methotrexate, glucocorticoids, and non-steroid anti-inflammatory drugs. The second group included 22 patients with "traditional" treatment and additionally prescribed of atorvastatinum 20 mg/day. The lipid profile, leptin, adipokine, paraoxonase activity. C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- α) levels, FMDBA and IMT of carotid artery were determined in all participants of the study. Control parameters were recorded before the start, after 1 and 6 months of treatment. **RESULTS:** Results: The FMDBA has increased by 32% in the second group, compared by only 10.9% in the first group. The dynamics of IMT in the first group was also twice lower than in group with the additional use of atorvastatinum. The leptin levels in the second group significantly decreased by 27% and adiponectin levels increased by 12.8%, than in the first group - by 12.8% and by 7% respectively. The appointment of statins over 6 months resulted in DAS28, TNF- α , ESR and CRP reduction by 15%, 31%, 25% and 21.5% respectively. In the first group the dynamics of indicate rates ranged from 7.8% to 22.5%, and was significantly lower than in the second group. **CONCLUSION:** Conclusions: As a result of the study, it was found that the appointment of atorvastatinum 20 mg/day during 6 months not only reduces dyslipidemia, but also significantly reduces the inflammatory process and adipokine dysregulation, normalizes serum paraoxonase activity and improves the endothelium function.

[50] *Sierkova VK, Romanova V, Lilevska AA, Savytska OO.* **THE ROLE OF LIPOPROTEIN (A) AND PREGNANCY ASSOCIATED PLASMA PROTEIN A IN DIAGNOSTICS CORONARY HEART DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE.** *Wiadomosci lekarskie (Warsaw, Poland : 1960)* 2020; 73:2489-2493.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33454688>

ABSTRACT

OBJECTIVE: The aim: To identify the significance of biomarkers characterizing the role of lipid disorders and the processes of destruction atherosclerotic plaque for the early diagnosis of CHD in patients with COPD. **PATIENTS AND METHODS:** Materials and methods: There were examined 153 patients, men aged 40-70 years, including 53 patients with COPD, 56 with a combination of COPD and CHD and 44 patients with stable CHD. The level of LP (a) and PAPP-A in the serum was determined by ELISA. **RESULTS:** Results: There was increased level of LP (a) and PAPP-A in patients with CHD and with a combination of COPD and CHD. This increased level of LP (a) and PAPP-A was associated with the level of C-reactive protein. The mid level of LP (a) and PAPP-A in patients with COPD did not significantly differ from the reference values. **CONCLUSION:** Conclusions: The increase level of lipoprotein (a) more than 18 mg/dl in patients with COPD may be regarded as a predictor of the development of CHD. The level PAPP-A more than 5 mIU/L in plasma of patients with COPD makes it possible to isolate the groups for CHD risk. The definition of LP (a)

and PAPP-A in patients with COPD may contribute to the early diagnostics of coronary heart disease in the absence of its pronounced clinical manifestations.

[51] *Shafiq M, Walmann T, Nutalapati V et al. Effects of proprotein convertase subtilisin/kexin type-9 inhibitors on fatty liver. World journal of hepatology 2020; 12:1258-1266.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33442452>

ABSTRACT

BACKGROUND: Many studies have investigated the progression of nonalcoholic fatty liver disease (NAFLD) and its predisposing risk factors, but the conclusions from these studies have been conflicting. More challenging is the fact that no effective treatment is currently available for NAFLD. AIM: To determine the effects of proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors on fatty infiltration of the liver. METHODS: This retrospective, chart review-based study was conducted on patients, 18-year-old and above, who were currently on PCSK9 inhibitor drug therapy. Patients were excluded from the study according to missing pre- or post-treatment imaging or laboratory values, presence of cirrhosis or rhabdomyolysis, or development of acute liver injury during the PCSK9 inhibitor treatment period; the latter being due to false elevation of liver function markers, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Radiographic improvement was assessed by a single radiologist, who read both the pre- and post-treatment images to minimize reading bias. Fatty infiltration of the liver was also assessed by changes in ALT and AST, with pre- and post-treatment levels compared by paired t-test (alpha criterion: 0.05). RESULTS: Of the 29 patients included in the study, 8 were male (27.6%) and 21 were female (72.4%). Essential hypertension was present in 25 (86.2%) of the patients, diabetes mellitus in 18 (62.1%) and obesity in 15 (51.7%). In all, patients were on PCSK9 inhibitors for a mean duration of 23.69 ± 11.18 mo until the most recent ALT and AST measures were obtained. Of the 11 patients who received the radiologic diagnosis of hepatic steatosis, 8 (72.73%) achieved complete radiologic resolution upon use of PCSK9 inhibitors (mean duration of 17.6 mo). On average, the ALT level (IU/L) decreased from 21.83 ± 11.89 at pretreatment to 17.69 ± 8.00 at post-treatment (2-tailed $P = 0.042$) and AST level (IU/L) decreased from 22.48 ± 9.00 pretreatment to 20.59 ± 5.47 post-treatment (2-tailed $P = 0.201$). CONCLUSION: PCSK9 inhibitors can slow down or even completely resolve NAFLD.

[52] *Gao YJ, Sun B, Lu L et al. [Prevalence and related factors of dyslipidemia in patients with 21-hydroxylase deficiency]. Zhonghua yi xue za zhi 2021; 101:127-130.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=33455128>

ABSTRACT

Objective: To analyze the prevalence and the related factors of dyslipidemia in 21-hydroxylase deficiency (21-OHD) patients. Methods: A total of 205 patients with 21-OHD were recruited in Peking Union Medical College Hospital from January 2016 to January 2018. The basic information, glucocorticoid replacement therapy, and laboratory examination results of patients were obtained from medical records. The genotypes of CYP21A2 were identified by Sanger sequencing and multiplex ligation dependent probe amplification. The prevalence of dyslipidemia among 21-OHD patients, basic information and related hormone levels of 21-OHD patients with different status of blood lipid were described. Logistic regression model was used to analyze the related factors of dyslipidemia in 21-OHD patients. Results: The age of subjects was 17.0 (8.3, 25.0) years old, including 51 males (24.9%). According to CYP21A2 genotypes, there were 16 cases in Null group, 26

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cases in Group A, 105 cases in group B, 27 cases in group C, and 31 cases in group D. The incidence of dyslipidemia was 29.3% (60/205), among which 37.3% (19/51) in male and 26.6% (41/154) in female patients, respectively. The M (Q(1), Q(3)) of total cortisol level (nmol/L) and body mass index (kg/m²) of male 21-OHD patients with dyslipidemia were 0.17 (0.06, 0.35) and 25.76 (17.01, 30.45), respectively, which were higher than those with ortholiposis [0.04 (0.02, 0.21) and 18.83 (16.53, 23.88)] (all P<0.05). The M (Q(1), Q(3)) of progesterone level (nmol/L), body mass index (kg/m²) and age (years) of female 21-OHD patients with dyslipidemia were 74.40 (50.97, 98.52), 23.09 (21.78, 27.78) and 23.00 (16.50, 28.00), respectively, which were higher than those with ortholiposis [52.81 (33.41, 68.85), 21.55 (18.63, 25.71) and 18.00 (9.50, 25.00)] (all P<0.05). The risk of dyslipidemia increased by 5.0% [OR (95%CI): 1.05 (1.01, 1.09)] for every 1 nmol/L increase of progesterone. Conclusion: The incidence of dyslipidemia is high in 21-OHD patients, and progesterone level is positively correlated with dyslipidemia.