[1] *Zuo LS, Tang XY, Xiong F et al.* **Isoflavone biomarkers are inversely associated with atherosclerosis progression in adults: a prospective study**. The American journal of clinical nutrition 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33709111

ABSTRACT

BACKGROUND: Many studies have examined associations between dietary isoflavones and atherosclerosis, but few used objective biomarkers. OBJECTIVES: We examined the associations of isoflavone biomarkers (primary analyses) and equol production (secondary analyses) with the progression of carotid intima-media thickness (cIMT), and whether inflammation, systolic blood pressure (SBP), blood lipids, and sex hormone-binding globulin (SHBG) mediated these associations, in Chinese adults. METHODS: This 8.8-y prospective study included 2572 subjects (40-75 y old) from the GNHS (Guangzhou Nutrition and Health Study; 2008-2019). The concentrations of daidzein, genistein, and equol were assayed by an HPLC-tandem MS in serum (n = 2572) at baseline and in urine (n = 2220) at 3-y intervals. The cIMT of the common carotid artery (CCA) and bifurcation segment were measured by B-mode ultrasound every 3 y, and the progressions of cIMT (ΔcIMT) were estimated using the regression method. RESULTS: Multivariable linear mixed-effects models (LMEMs) and ANCOVA revealed that subjects with higher serum isoflavones tended to have lower increases of CCA-cIMT. The mean ± SEM differences in 8.8-y ΔCCA-cIMT between extreme tertiles of serum isoflavones were -17.1 ± 8.4, -20.6 ± 8.3, and -23.3 ± 10.4 μm for daidzein, total isoflavone, and equol (P-trends < 0.05), respectively. LMEMs showed that the estimated yearly changes (95% CIs) (μm/y) in CCA-IMT were -2.0 (-3.8, -0.3), -1.9 (-3.6, -0.1), and -2.1 (-3.8, -0.3) in the highest (compared with the lowest) tertile of daidzein, genistein, and total isoflavones, respectively (P-interaction < 0.05). Path analyses indicated that the serum equol-atherosclerosis association was mediated by increased SHBG and decreased SBP. Similar beneficial associations were observed in the secondary analyses. CONCLUSIONS: Serum isoflavones and equol exposure were associated with reduced cIMT progression, mediated by SHBG and SBP.

[2] *Shaw PB.* **Hyperlipidemia: effective disease management with a focus on PCSK9 inhibitors**. The American journal of managed care 2021; 27:S63-s69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33710845

ABSTRACT

Hyperlipidemia is a prevalent condition in the United States and a significant contributor to atherosclerotic cardiovascular disease (ASCVD). ASCVD is a primary cause of morbidity and mortality in the United States. Low-density lipoprotein cholesterol (LDL-C) is a causal factor for the development of ASCVD. Reductions in LDL-C produce a corresponding decrease in ASCVD risk for cardiovascular events. HMG-CoA reductase inhibitors, commonly referred to as statins, remain the gold standard of hyperlipidemia treatment. However, statin monotherapy is often ineffective in reducing LDL-C to treatment guideline-recommended levels, especially in high-risk patients with established ASCVD or familial hypercholesterolemia (FH). Statin therapy causes myalgias in 5% to 10% of patients, which may lead to inadequate dose optimization, nonadherence, or inability to take a statin. Clinical guidelines recommend add-on therapy with ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors when maximally tolerated statin therapy results in suboptimal LDL-C reduction. Hyperlipidemia, especially FH, is associated with substantial clinical and financial burden and is often undertreated. Although undertreatment is partially attributable to failure

to optimize statin therapy, a significant portion of patients will require a PCSK9 inhibitor for adequate LDL-C reduction. Despite this, PCSK9 inhibitor utilization rates remain low. Barriers to treatment may include clinical inertia, high out-of-pocket costs, and pharmacy benefit access issues. Managed care pharmacists can help appropriate patients overcome these barriers to PCSK9 inhibitor use and improve the attainment of LDL-C goals and outcomes, especially in high-risk patients with FH or clinical ASCVD.

[3] *Patel J.* **Managed care pharmacist updates for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors**. The American journal of managed care 2021; 27:S76-s82.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33710847

ABSTRACT

Uncontrolled hyperlipidemia has been associated with serious cardiovascular events. Statin use may not be optimal either due to low adherence or statin intolerance. Although the definition of statin intolerance remains highly debatable, it can generally be viewed as any adverse reaction that limits its use including but not limited to myopathies and myalgias. After initial approval, utilization of PCSK9 inhibitors remained low, possibly due to cost or overly restrictive coverage criteria. With the reduction in list price by 60% to $5850 annually, and updated clinical outcome data, both alirocumab and evolocumab were more in line with the willingness-to-pay threshold. Managed care pharmacists can ensure coverage criteria are appropriately developed to give access to individuals who would benefit the most, while decreasing barriers to access. Additionally, pharmacists are well positioned to collaborate with other healthcare providers to increase adherence to traditional LDL-C-lowering agents and streamline prior authorization processing to increase approval rates.

[4] *Ni X, Yang ZZ, Ye LQ et al.* **Establishment of an in vitro safety assessment model for lipid-lowering drugs using same-origin human pluripotent stem cell-derived cardiomyocytes and endothelial cells**. Acta pharmacologica Sinica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33686244

ABSTRACT

Cardiovascular safety assessment is vital for drug development, yet human cardiovascular cell models are lacking. In vitro mass-generated human pluripotent stem cell (hPSC)-derived cardiovascular cells are a suitable cell model for preclinical cardiovascular safety evaluations. In this study, we established a preclinical toxicology model using same-origin hPSC-differentiated cardiomyocytes (hPSC-CMs) and endothelial cells (hPSC-ECs). For validation of this cell model, alirocumab, a human antibody against proprotein convertase subtilisin kexin type 9 (PCSK9), was selected as an emerging safe lipid-lowering drug; atorvastatin, a common statin (the most effective type of lipid-lowering drug), was used as a drug with reported side effects at high concentrations, while doxorubicin was chosen as a positive cardiotoxic drug. The cytotoxicity of these drugs was assessed using CCK8, ATP, and lactate dehydrogenase release assays at 24, 48, and 72 h. The influences of these drugs on cardiomyocyte electrophysiology were detected using the patch-clamp technique, while their effects on endothelial function were determined by tube formation and Dil-acetylated low-density lipoprotein (Dil-Ac-LDL) uptake assays. We showed that alirocumab did not affect the cell viability or cardiomyocyte electrophysiology in agreement with the clinical results. Atorvastatin (5-50 μM) dose-dependently decreased cardiovascular cell viability over time, and at a high concentration (50 μM, ~100 times the normal peak serum concentration in clinic), it affected the

action potentials of hPSC-CMs and damaged tube formation and Dil-Ac-LDL uptake of hPSC-ECs. The results demonstrate that the established same-origin hPSC-derived cardiovascular cell model can be used to evaluate lipid-lowering drug safety in cardiovascular cells and allow highly accurate preclinical assessment of potential drugs.

[5] *Lindsley J*. **Guideline recommendations, clinical trial data, and new and emerging therapies**. The American journal of managed care 2021; 27:S70-s75.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33710846
ABSTRACT
Nearly 93 million American adults have hyperlipidemia, a major risk factor for the development of atherosclerotic cardiovascular disease. Use of HMG-CoA reductase inhibitors (ie, statins) and ezetimibe have decreased hypercholesterolemia's prevalence in the past decade, but poor adherence is common and leads to scenarios where patients do not derive the greatest possible benefit. In addition, statin resistance may play a role when patients' LDL-C levels are not lowered to the expected extent despite good medication adherence. When statins fail to control hyperlipidemia, guidelines recommend furthering treatment by adding ezetimibe or a PCSK9 inhibitor. In November 2018, the American College of Cardiology and the American Heart Association updated their hyperlipidemia guideline. This revision recommends a more aggressive approach to hyperlipidemia. In patients who fail to respond to or cannot tolerate statins or ezetimibe, PCSK9 inhibitors are a reasonable treatment option. Large outcomes trials have compared the currently approved PCSK9 inhibitors with placebo and established that PCSK9 inhibitors lowered LDL-C by more than 50% below the statin-treated baseline and reduce cardiovascular outcomes. In addition, bempedoic acid, lomitapide, and evinacumab are available options that may be instituted in select patients. In development is inclisiran, a small interfering RNA molecule, which antagonizes PCSK9 production. With good adherence and the use of a greater assortment of medications, patients may experience atherogenic lipoprotein lowering, leading to a decrease in cardiovascular disease.

[6] *Lawrence GD*. **Perspective: The Saturated Fat-Unsaturated Oil Dilemma: Relations of Dietary Fatty Acids and Serum Cholesterol, Atherosclerosis, Inflammation, Cancer, and All-Cause Mortality**. Advances in nutrition (Bethesda, Md.) 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693484
ABSTRACT
PUFAs are known to regulate cholesterol synthesis and cellular uptake by multiple mechanisms that do not involve SFAs. Polymorphisms in any of the numerous proteins involved in cholesterol homeostasis, as a result of genetic variation, could lead to higher or lower serum cholesterol. PUFAs are susceptible to lipid peroxidation, which can lead to oxidative stress, inflammation, atherosclerosis, cancer, and disorders associated with inflammation, such as insulin resistance, arthritis, and numerous inflammatory syndromes. Eicosanoids from arachidonic acid are among the most powerful mediators that initiate an immune response, and a wide range of PUFA metabolites regulate numerous physiological processes. There is a misconception that dietary SFAs can cause inflammation, although endogenous palmitic acid is converted to ceramides and other cell constituents involved in an inflammatory response after it is initiated by lipid mediators derived from PUFAs. This article will discuss the many misconceptions regarding how dietary lipids regulate serum cholesterol, the fact that all-cause death rate is higher in humans with low compared with normal or

moderately elevated serum total cholesterol, the numerous adverse effects of increasing dietary PUFAs or carbohydrate relative to SFAs, as well as metabolic conversion of PUFAs to SFAs and MUFAs as a protective mechanism. Consequently, dietary saturated fats seem to be less harmful than the proposed alternatives.

[7] Donovan GK, Wilson DP. Ethical Dilemmas in Pediatric Lipidology. In: Endotext. Edited by: Feingold KR, Anawalt B, Boyce A *et al.* South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2021, MDText.com, Inc.; 2000.

[8] *Buckler AJ, Karlöf E, Lengquist M et al.* **Virtual Transcriptomics: Noninvasive Phenotyping of Atherosclerosis by Decoding Plaque Biology From Computed Tomography Angiography Imaging**. Arteriosclerosis, thrombosis, and vascular biology 2021:Atvbaha121315969.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33691476

ABSTRACT

OBJECTIVE: Therapeutic advancements in atherosclerotic cardiovascular disease have improved prevention of ischemic stroke and myocardial infarction, but diagnostic methods for atherosclerotic plaque phenotyping to aid individualized therapy are lacking. In this feasibility study, we aimed to elucidate plaque biology by decoding the molecular phenotype of plaques through analysis of computed-tomography angiography images, making a predictive model for plaque biology referred to as virtual transcriptomics. Approach and Results: We employed machine intelligence using paired computed-tomography angiography and transcriptomics from carotid endarterectomies of 40 patients undergoing stroke-preventive surgery for carotid stenosis. Computed tomography angiographies were analyzed with novel software for accurate characterization of plaque morphology and plaque transcriptomes obtained from microarrays, followed by mathematical modeling for prediction of molecular signatures. Four hundred fourteen coding and noncoding RNAs were robustly predicted using supervised models to estimate gene expression based on plaque morphology. Examples of predicted transcripts included ion transporters, cytokine receptors, and a number of microRNAs whereas pathway analyses demonstrated enrichment of several biological processes relevant for the pathophysiology of atherosclerosis and plaque instability. Finally, the ability of the models to predict plaque gene expression was demonstrated using computed tomography angiographies from 4 sequestered patients and comparisons with transcriptomes of corresponding lesions.
CONCLUSIONS: The results of this pilot study show that atherosclerotic plaque phenotyping by image analysis of conventional computed-tomography angiography can elucidate the molecular signature of atherosclerotic lesions in a multiscale setting. The study holds promise for optimized personalized therapy in the prevention of myocardial infarction and ischemic stroke, which warrants further investigations in larger cohorts.

[9] *Yulian ED, Siregar NC, Bajuadji*. **Combination of Simvastatin and FAC Improves Response to Neoadjuvant Chemotherapy in Advanced Local Breast Cancer**. Cancer research and treatment : official journal of Korean Cancer Association 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33705623

ABSTRACT

PURPOSE: The efficacy of neoadjuvant chemotherapy (NAC) for Locally Advanced Breast Cancer (LABC) is limited due to drug resistance and cardiotoxic effects. Pre-clinical studies have shown that statin induces apoptosis and decreases breast cancer cell growth. This study aims to evaluate the

role of statin in combination with Fluorouracil, Adriamycin, and Cyclophosphamide (FAC) therapy in LABC patients. MATERIALS AND METHODS: We undertook a randomized, double-blinded, placebo-controlled trial in two centers of Indonesia. Patients were randomly assigned to FAC plus simvastatin (40 mg/d orally) or FAC plus placebo (40 mg/d) for 21 days. The FAC regimen was repeated every 3 weeks. We evaluated the clinical response, pathological response, and toxicities. RESULTS: The ORR for FAC plus Simvastatin was 90% (95% CI 0.99-1.67) by per-protocol analysis. No complete responses (CR) were recorded, but there were 48 partial responses (PRs). No significant difference was observed between the two groups with the ORR (p=0.103). The pathological complete response rate was 6.25% (2 in Simvastatin group and 1 in placebo group). Adverse events in both arms were generally mild, mainly consisted of myotoxicity. HER-2 expression was a factor related to the success of therapeutic response (OR: 4.2, 95% CI: 1.121-15.731, p=0.033). CONCLUSION: This study suggests that simvastatin combined with FAC shows improvements in ORR and pathological response in patients with LABC. Although no statistically significant difference was documented, there was a trend for better activity and tolerability. The addition of 40 mg simvastatin may improve the efficacy of FAC in LABC patients with HER-2 overexpression.

[10] *Wu N, Bredin SSD, Jamnik VK et al.* **Association between physical activity level and cardiovascular risk factors in adolescents living with type 1 diabetes mellitus: a cross-sectional study**. Cardiovascular diabetology 2021; 20:62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33712025

ABSTRACT

BACKGROUND: Type 1 diabetes mellitus (T1DM) is associated with an increased risk for cardiovascular disease (CVD) related morbidity and premature mortality. Regular physical activity plays an important role in the primary and secondary prevention of CVD, improving overall health and wellbeing. Previous observational studies have examined the associations between self-reported physical activity and CVD risk factors in largely adult Caucasian populations. However, limited work has evaluated the relationship between objectively measured physical activity and CVD risk factors in other ethnicities, particularly Chinese youth living with T1DM. METHODS: This cross-sectional study assessed CVD risk factors, physical activity, and aerobic fitness (and their associations) in Chinese youth living with T1DM (n = 48) and peers (n = 19) without T1DM. Primary outcomes included blood pressure, lipid profiles, and physical activity (accelerometry). Statistical differences between groups were determined with chi-square, independent-samples t-tests, or analysis of covariance. The associations between aerobic fitness, daily physical activity variables, and CVD risk factors were assessed with univariate and multivariate linear regression analyses. RESULTS: Results were summarized using means and standard deviation (SD) for normally distributed variables and medians and 25-75th quartile for non-normally distributed variables. In comparison to peers without diabetes, youth living with T1DM showed higher levels of total cholesterol (3.14 ± 0.67 vs. 4.03 ± 0.81 mmol·L(-1), p = 0.001), low-density lipoprotein cholesterol (1.74 ± 0.38 vs. 2.31 ± 0.72 mmol·L(-1), p = 0.005), and triglycerides (0.60 ± 0.40 vs. 0.89 ± 0.31 mmol·L(-1) p = 0.012), and lower maximal oxygen power (44.43 ± 8.29 vs. 35.48 ± 8.72 mL·kg(-1)·min(-1), p = 0.003), total physical activity counts (451.01 ± 133.52 vs. 346.87 ± 101.97 counts·min(-1), p = 0.004), metabolic equivalents (METs) (2.41 ± 0.60 vs. 2.09 ± 0.41 METs, p = 0.033), moderate-to-vigorous intensity physical activity [MVPA: 89.57 (61.00-124.14) vs (53.19 (35.68-63.16) min, p = 0.001], and the percentage of time spent in MVPA [11.91 (7.74-16.22) vs 8.56 (6.18-10.12) %, p = 0.038]. The level of high-density lipoprotein

cholesterol was positively associated with METs (β = 0.29, p = 0.030, model R(2) = 0.168), and the level of triglycerides was negatively associated with physical activity counts (β = - 0.001, p = 0.018, model R(2) = 0.205) and METs (β = - 0.359, p = 0.015, model R(2) = 0.208), and positively associated with time spent in sedentary behaviour (β = 0.002, p = 0.041, model R(2) = 0.156) in persons living with T1DM. CONCLUSIONS: Chinese youth with T1DM, despite their young age and short duration of diabetes, present early signs of CVD risk, as well as low physical activity levels and cardiorespiratory fitness compared to apparently healthy peers without diabetes. Regular physical activity is associated with a beneficial cardiovascular profile in T1DM, including improvements in lipid profile. Thus, physical activity participation should be widely promoted in youth living with T1DM.

[11] *Rizo-Liendo A, Arberas-Jiménez I, Sifaoui I et al.* **The type 2 statins, cerivastatin, rosuvastatin and pitavastatin eliminate Naegleria fowleri at low concentrations and by induction of programmed cell death (PCD)**. Bioorg Chem 2021; 110:104784.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33684715

ABSTRACT

Primary Amoebic Encephalitis due to Naegleria fowleri species is a fatal infection of the Central Nervous System mostly affecting children and young adults. Infections often occur after performance of risk activities in aquatic habitats such as swimming and splashing. PAḾs therapy remain a key issue to be solved which needs an urgent development. Recently, statins have been highlighted as possible novel compounds to treat PAM. Furthermore, type 2 statins due to improved pharmacological properties and lower toxicity could be use in the future. In the present work, three type 2 statins were checked for their activity against two type strains of N. fowleri. In addition, the effects at the cellular level triggered in treated amoebae were checked in order to evaluate if programmed cell death was induced. The obtained results showed that the tested statins, rosuvastatin, pitavastatin and cerivastatin were able to eliminate N. fowleri trophozoites and also induced PCD. Therefore, type 2 statins could be used in the near future for the treatment of PAM.

[12] *Nishikido T, Fayyad R, Melamed S, Ray KK*. **TRS2P and LDL-C alone or in combination for predicting absolute benefits from additional LDL-C lowering: Analysis from the TNT trial**. Atherosclerosis 2021; 322:8-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33706084

ABSTRACT

BACKGROUND AND AIMS: Despite trial evidence, high intensity statins are underutilized in routine clinical practice. This study sought to assess the individual and joint contributions of the TRS2P score as a measure of residual risk and LDL-C levels to benefits from further LDL-C lowering in the TNT trial. METHODS: A total of 9980 patients were divided into 4 groups based on TRS2P and LDL-C at baseline: <median TRS2P and <median LDL-C (group 1), <median TRS2P and ≥median LDL-C (group 2), ≥median TRS2P and <median LDL-C (group 3), ≥median TRS2P and ≥median LDL-C (group 4). The effect of atorvastatin 80 mg vs. 10 mg on the risk of any cardiovascular event was assessed among the groups. RESULTS: Percentage reductions in LDL-C with atorvastatin 80 mg were consistent across groups, whereas absolute reductions were approximately 11 mg/dL greater when LDL-C was ≥median. Despite atorvastatin 10 mg, either TRS2P ≥ median or LDL-C ≥ median were associated with more events and highest when both were ≥median (groups 1-4; 21.5%, 28.1%, 36.3%, and 40.5%, respectively; p-trend <0.0001. Although relative benefits were similar, absolute

risk reduction from atorvastatin 80 mg was lowest when both scores were <median (1.3%, group 1) and highest when both were >median (7.2%, group 4), NNT 78 vs. 14 (p-interaction <0.0001). CONCLUSIONS: Measures of residual risk as well LDL-C identify patients who remain at high risk despite statins with the combination identifying those who derive the greatest benefits from even modest additional LDL-C lowering. Attention to residual risk as well as LDL-C may further help to optimize guideline implementation.

[13] *Niepolski L, Drzewiecka H, Warchoł W.* **Circulating vascular endothelial growth factor receptor 2 levels and their association with lipid abnormalities in patients on hemodialysis**. Biomedical reports 2021; 14:37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33692900
ABSTRACT
The aim of the present study was to examine the association between the levels of circulating vascular endothelial growth factor receptor (VEGFR)2 levels, serum lipid composition and plasma receptor for advanced glycation end-products (RAGE) expression in patients undergoing hemodialysis (HD). A total of 50 patients on HD (27 men and 23 women; median age, 66 years; age range 28-88 years; HD mean time, 29.0, 3.9-157.0 months) were enrolled. Age-matched healthy subjects (n=26) were used as the control group. Plasma VEGFR2 and RAGE levels were determined using ELISA. Dyslipidemia (D) in patients on HD was diagnosed according to the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. Circulating VEGFR2, RAGE and serum lipids were compared between dyslipidemic and non-dyslipidemic patients on HD and controls. In patients on HD, the plasma VEGFR2 levels were lower compared with those in the healthy population. D was associated with high plasma VEGFR2 levels. The triglyceride/HDL-cholesterol ratio was strongly associated with plasma VEGFR2 levels. The plasma VEGFR2 concentration was associated with circulating RAGE levels. Therefore, circulating VEGFR2 levels may be partly associated with lipid abnormalities and plasma RAGE levels in patients receiving HD.

[14] *Nicholls SJ, Nissen SE, Prati F et al.* **Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study**. Cardiovascular diagnosis and therapy 2021; 11:120-129.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33708484
ABSTRACT
BACKGROUND: Technological advances in arterial wall imaging permit the opportunity to visualize coronary atherosclerotic plaque with sufficient resolution to characterize both its burden and compositional phenotype. These modalities have been used extensively in clinical trials to evaluate the impact of lipid lowering therapies on serial changes in disease burden. While the findings have unequivocally established that these interventions have the capacity to either slow disease progression or promote plaque regression, depending on the degree of lipid lowering achieved, their impact on plaque phenotype is less certain. More recently optical coherence tomography (OCT) has been employed with a number of studies demonstrating favorable effects on both fibrous cap thickness (FCT) and the size of lipid pools within plaque in response to statin treatment. METHODS: The phase 3, multi-center, double-blind HUYGENS study will assess the impact of incremental lipid

lowering with the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, evolocumab, on plaque features using serial OCT imaging, in statin-treated patients following an acute coronary syndrome (ACS). Subjects with non-ST-elevation ACS (n=150) will be randomized 1:1 into two groups to receive monthly injections of evolocumab 420 mg or placebo. RESULTS: The primary endpoint is the effect of evolocumab on coronary atherosclerotic plaques will be assessed by OCT at baseline and at week 50. CONCLUSIONS: The HUYGENS study will determine whether intensified lipid lowering therapy with evolocumab in addition to maximally tolerated statin therapy will have incremental benefits on high-risk features of coronary artery plaques. TRIAL REGISTRATION: This study was registered on Clinicaltrials.gov (NCT03570697).

[15] *Liu C, Schönke M, Zhou E et al.* **Pharmacological treatment with FGF21 strongly improves plasma cholesterol metabolism to reduce atherosclerosis**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693480

ABSTRACT

AIMS: Fibroblast growth factor (FGF) 21, a key regulator of energy metabolism, is currently evaluated in humans for treatment of type 2 diabetes and nonalcoholic steatohepatitis. However, the effects of FGF21 on cardiovascular benefit, particularly on lipoprotein metabolism in relation to atherogenesis, remain elusive. METHODS AND RESULTS: Here, the role of FGF21 in lipoprotein metabolism in relation to atherosclerosis development was investigated by pharmacological administration of a half-life extended recombinant FGF21 protein to hypercholesterolemic APOE*3-Leiden.CETP mice, a well-established model mimicking atherosclerosis initiation and development in humans. FGF21 reduced plasma total cholesterol, explained by a reduction in non-HDL-cholesterol. Mechanistically, FGF21 promoted brown adipose tissue (BAT) activation and white adipose tissue (WAT) browning, thereby enhancing the selective uptake of fatty acids from triglyceride-rich lipoproteins into BAT and into browned WAT, consequently accelerating the clearance of the cholesterol-enriched remnants by the liver. In addition, FGF21 reduced body fat, ameliorated glucose tolerance and markedly reduced hepatic steatosis, related to upregulated hepatic expression of genes involved in fatty acid oxidation and increased hepatic VLDL-triglyceride secretion. Ultimately, FGF21 largely decreased atherosclerotic lesion area, which was mainly explained by the reduction in non-HDL-cholesterol as shown by linear regression analysis, decreased lesion severity and increased atherosclerotic plaque stability index. CONCLUSIONS: FGF21 improves hypercholesterolemia by accelerating triglyceride-rich lipoprotein turnover as a result of activating BAT and browning of WAT, thereby reducing atherosclerotic lesion severity and increasing atherosclerotic lesion stability index. We have thus provided additional support for the clinical use of FGF21 in the treatment of atherosclerotic cardiovascular disease. TRANSLATIONAL PERSPECTIVES: Current therapeutics do not fully block atherosclerosis development, indicating a need for additional effective therapeutics. Here, we demonstrate that pharmacological treatment with recombinant FGF21 potently protects against atherosclerosis in APOE*3-Leiden.CETP mice. Mechanistically, FGF21 reduces hypercholesterolemia by accelerating triglyceride-rich lipoprotein turnover as a result of enhancing adipose tissue thermogenesis, thereby alleviating atherosclerotic lesion formation and severity. Consistent with our animal findings, FGF21 administration in obese patients has shown to reduce several cardiovascular risk factors such as obesity and dyslipidemia. Therefore, our present results, together with available clinical data, suggest that FGF21 is a promising therapeutic for atherosclerotic diseases.

[16] *Karpale M, Käräjämäki AJ, Kummu O et al.* **Activation of nuclear receptor PXR induces atherogenic lipids and PCSK9 through SREBP2-mediated mechanism**. Br J Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33687065

ABSTRACT
BACKGROUND AND PURPOSE: Many drugs and environmental contaminants induce hypercholesterolemia and promote the risk of atherosclerotic cardiovascular disease. The mechanisms involved are poorly defined precluding efficient prediction and prevention. We tested the hypothesis that pregnane X receptor (PXR), a xenobiotic-sensing nuclear receptor, regulates the level of circulating atherogenic lipids in humans and utilized mouse experiments to identify the mechanisms involved. EXPERIMENTAL APPROACH: We performed serum NMR metabolomics in healthy volunteers administered rifampicin, a prototypical human PXR ligand, or placebo in a crossover setting. Furthermore, we used high-fat diet fed wildtype and PXR knockout mice to investigate the mechanisms and pathways mediating the PXR-induced alterations in cholesterol homeostasis. KEY RESULTS: Activation of PXR induced cholesterogenesis both in pre-clinical and clinical settings. In human volunteers, rifampicin increased IDL, LDL and total cholesterol and lathosterol-cholesterol ratio, a marker of cholesterol synthesis, suggesting increased cholesterol synthesis. Mechanistic studies in mice indicated that PXR activation launches widespread induction of the cholesterol synthesis genes including the rate-limiting Hmgcr and upregulates the intermediates in the Kandutsch-Russell cholesterol synthesis pathway in the liver. Additionally, PXR activation induced plasma PCSK9, a negative regulator of hepatic LDL uptake, in both mice and humans. We propose that these effects were mediated through increased proteolytic activation of SREBP2 in response to PXR activation. CONCLUSION AND IMPLICATIONS: PXR activation induces cholesterol synthesis and elevates LDL and total cholesterol in humans. The PXR-SREBP2 pathway is a novel regulator of the cholesterol and PCSK9 synthesis, and a molecular mechanism for drug- and chemical-induced hypercholesterolemia.

[17] *Daghlas I, Gill D.* **Low-density lipoprotein cholesterol and lifespan: a Mendelian randomization study**. British journal of clinical pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33704808

ABSTRACT
BACKGROUND: It is unknown whether long-term low-density lipoprotein cholesterol (LDL-c) lowering increases lifespan and longevity in a general population not selected for elevated cardiovascular risk. The present study aimed to investigate the overall and gene-specific effect of circulating low-density lipoprotein cholesterol (LDL-c) levels on lifespan and longevity in a general population. METHODS AND RESULTS: Leveraging data from the Global Lipids Genetics Consortium (n=173,082), we identified genetic variants to proxy LDL-c levels generally, and also through perturbation of particular drug targets (HMGCR, NPC1L1 and PCSK9). We investigated their association with lifespan (n=1,012,240) using Mendelian randomization, and replicated results using the outcome of longevity to the 90(th) vs. 60(th) percentile age (11,262 cases/25,483 controls). A 1-standard deviation (SD) increase in genetically proxied LDL-c was associated with 1.2 years lower lifespan (95% confidence interval (CI) -1.55- -0.87; P=3.83x10(-12)). Findings were consistent in statistical sensitivity analyses, and when considering the outcome of longevity (odds ratio for survival to the 90(th) vs 60(th) percentile age 0.72, 95% CI 0.64-0.81, P=7.83x10(-8)). Gene-specific MR analyses showed a

significant effect of LDL-c modification through PCSK9 on lifespan (-0.99 years, 95% CI -1.43, -0.55, P=6.80x10(-6)), however estimates for HMGCR and NPC1L1 were underpowered. CONCLUSIONS: This genetic evidence supports that higher LDL-c levels reduce lifespan and longevity. In a general population that is not selected for increased cardiovascular risk, there is likely a net lifespan benefit of LDL-c lowering therapies, particularly for PCSK9 inhibitors, although randomized controlled trials are necessary before modification of clinical practice.

[18] *Yokote K, Ako J, Kitagawa K et al.* **12-Week Effectiveness and Safety of Low-Density Lipoprotein Cholesterol-Lowering Therapy by Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition in Patients With Familial Hypercholesterolemia and Hypercholesterolemia - Data From a Real-World Observational Study of Evolocumab in Japan**. Circ Rep 2019; 1:219-227.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693141

ABSTRACT

Background: Evolocumab is the first monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9) approved in Japan for the treatment of patients with familial hypercholesterolemia (FH) and hypercholesterolemia (HC). This study assessed the 12-week effectiveness and safety of low-density lipoprotein cholesterol (LDL-C)-lowering therapy by PCSK9 inhibition in patients with FH (homozygous [HoFH] or heterozygous [HeFH]) and HC by analyzing evolocumab data collected in the real-world setting in Japan. Methods and Results: Overall, 427 patients (mean±SD age, 61.6±13.8 years; female, 38.4%; 28 HoFH, 320 HeFH, 79 HC), enrolled from 299 clinical sites, were included in the safety analysis set. The major cardiovascular risk factors were coronary artery disease (77.3%), diabetes mellitus/impaired glucose tolerance (38.6%), and hypertension (65.1%). Median follow-up duration was 85.0 days. After 12 weeks of evolocumab treatment, the mean±SD percent change from baseline in LDL-C was -45.5%±27.0% (n=23) in HoFH (P<0.001 vs. baseline; t-test), -54.2%±29.0% (n=280) in HeFH (P<0.001), and -64.6%±22.4% (n=72) in HC (P<0.001) patients. The incidence of adverse drug reactions was 5.4% (23/427). Conclusions: Results suggest that patients receiving evolocumab treatment in the real-world setting were predominantly those with FH and HC in the secondary prevention group. LDL-C-lowering effectiveness with evolocumab was observed in FH (both HoFH and HeFH) and HC patients.

[19] *Otake H, Tanimura K, Sugizaki Y et al.* **Effect of Alirocumab and Rosuvastatin or Rosuvastatin Alone on Lipid Core Plaque in Coronary Artery Disease Seen on Near-Infrared Spectroscopy Intravascular Ultrasound (ANTARES)**. Circ Rep 2019; 1:107-111.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693121

ABSTRACT

Background: Despite evidence of the effects of alirocumab on the incidence of acute coronary events, its impact on plaque stabilization remains uncertain. The present study will investigate the effect of alirocumab on fibroatheroma in patients who underwent recent percutaneous coronary intervention (PCI). Methods and Results: This phase IV, open-label, randomized, blinded near-infrared spectroscopy plus intravascular ultrasound (NIRS-IVUS) analysis, parallel-group, single-center study will enroll Japanese adults recently hospitalized for PCI with suboptimal low-density lipoprotein cholesterol (LDL-C) control (>70 mg/dL) despite stable statin therapy. Thirty patients will be randomized to receive either alirocumab or standard of care. The alirocumab group will receive alirocumab 75 mg every 2 weeks plus 10 mg rosuvastatin per day. The standard-of-care group will

receive 10 mg rosuvastatin per day with dose adjustment to achieve LDL-C <70 mg/dL. Post-treatment NIRS-IVUS will be performed at week 36. The primary endpoint is the change in maximum lipid core burden index in 4-mm pullback compartments (maxLCBI[4 mm]) between baseline and week 36. Secondary endpoints include change in LCBI (lesion), angle of lipid core, plaque burden, and serum lipids and biomarkers related to atherosclerosis and inflammation. Conclusions: The study will clarify the effects of alirocumab on thin-cap fibroatheroma in patients who underwent recent PCI and who have suboptimal LDL-C control with stable statin therapy.

[20] *Ogiso M, Yamaguchi J, Kawada-Watanabe E et al.* **Effect of Aggressive Lipid-Lowering Therapy in Single-Vessel vs. Multivessel Coronary Artery Disease Patients With Acute Coronary Syndrome - Heart Institute of Japan-Proper Level of Lipid Lowering With Pitavastatin and Ezetimibe in Acute Coronary Syndrome (HIJ-PROPER) Substudy**. Circ Rep 2020; 2:128-134.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693218
ABSTRACT
Background: The effects of aggressive lipid-lowering therapy according to the number of diseased coronary arteries in acute coronary syndrome (ACS) are still controversial. This study investigated the efficacy of this therapy in ACS patients with multivessel disease (MVD) and single-vessel disease (SVD). Methods and Results: The subjects were derived from the HIJ-PROPER study, in which ACS patients with dyslipidemia were randomized to receive either pitavastatin+ezetimibe (targeting low-density lipoprotein cholesterol [LDL-C] <70 mg/dL) or pitavastatin monotherapy (targeting LDL-C <90 mg/dL). In this study, treatment efficacy was compared between patients with MVD and SVD. The primary endpoint was a composite of major advanced cardiovascular events (MACE; all-cause death, non-fatal myocardial infarction, non-fatal stroke, and ischemia-driven revascularization). We identified 1,702 eligible patients (MVD, n=869; SVD, n=833; mean age, 65.6 years; male, 75.6%; acute revascularization, 96.2%). MACE incidence was significantly higher in the MVD group than in the SVD group (43.7% vs. 25.9%, HR, 1.95; 95% CI: 1.65-2.31, P<0.001). In the SVD group, pitavastatin+ezetimibe had significantly fewer MACE than pitavastatin monotherapy (34.6% vs. 47.4%, HR, 0.72; 95% CI: 0.55-0.94, P=0.02). Conclusions: The benefits of aggressive lipid-lowering therapy, with the addition of ezetimibe to statins, were enhanced in ACS patients with SVD, but not with MVD, in the early invasive strategy era.

[21] *Nishizaki Y, Daida H.* **Optimal Dose of n-3 Polyunsaturated Fatty Acids for Cardiovascular Event Prevention**. Circ Rep 2020; 2:260-264.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693239
ABSTRACT
Background: The n-3 polyunsaturated fatty acids (PUFA), represented by eicosapentaenoic acid (EPA) and docosahexaenoic acid, have anti-atherogenic effects (e.g., neutral fat-lowering effects) and other beneficial effects such as antiplatelet, anti-inflammatory, plaque stabilizing, vascular endothelial function ameliorative, antihypertensive, and anti-arrhythmic effects. Epidemiological studies and clinical trials have assessed the inhibitory effects of n-3 PUFA on cardiovascular events. Methods and Results: Studies that reported positive outcomes, such as the Japan EPA Lipid intervention Study (JELIS) and the Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT), noted a tendency toward the use of high-dose n-3 PUFA (1.8-4

g/day). The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione (GISSI-Prevenzione) trial and the JELIS had high EPA/arachidonic acid (AA) baseline ratios. In contrast, negative outcome studies, such as the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, Risk and Prevention study, A Study of Cardiovascular Events in Diabetes (ASCEND), and the Vitamin D and Omega-3 Trial (VITAL) had participants who tended to use low-dose n-3 PUFA (0.84-1 g/day) and to have low baseline EPA/AA. Conclusions: Differences in baseline EPA/AA ratio and the EPA/AA ratio threshold for the prevention of cardiovascular events seem to contribute to the different outcomes, together with the dose of n-3 PUFA.

[22] *Miyoshi T, Kawakami H, Kono Y et al.* **Neoatherosclerosis in Sirolimus-Eluting Stents After Paclitaxel-Coated Ballooning Cannot Be Stabilized Despite PCSK9 Inhibitor Therapy**. Circ Rep 2019; 1:196.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693137
ABSTRACT

[23] *Manasirisuk P, Chainirun N, Tiamkao S et al.* **Efficacy of Generic Atorvastatin in a Real-World Setting**. Clinical pharmacology : advances and applications 2021; 13:45-51.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33707972
ABSTRACT
BACKGROUND: The ability of statins to reduce LDL-c plays an important role in both primary and secondary prevention of atherosclerotic cardiovascular diseases. Such treatment can often be costly, but using generic atorvastatin may reduce cost by up to US$2635. In addition, a previous 8-week study found that it exhibited comparable efficacy to the brand-name medication. This study aimed to evaluate the efficacy of generic atorvastatin over a longer period of six months in a real-world setting. METHODS: This was a retrospective cohort study in adult patients who had received brand-name atorvastatin for at least three months and then had switched to generic atorvastatin for at least six months. Lipid and safety profiles were evaluated at six months after switching. Adjusted analyses for age, sex, co-morbid disease, dosage, and indications for statin therapy were also performed. RESULTS: During the study period, there were 488 patients who met the study criteria. The mean (SD) age of the patients was 60.97 (12.26) years, and 48.36% were male (236 patients). At six months, average total cholesterol, HDL-c, and LDL-c were all lower, from 174.43 to 166.15 mg/dL, from 51.64 to 49.51 mg/dL, and from 110.08 to 100.78 mg/dL ($p < 0.001$), respectively. There were no significant differences in terms of any other laboratory test results. LDL-c exhibited the highest significant reduction at 9.30 mg/dL. Stratified analyses by age, sex, co-morbid disease, dose, and indications for statin therapy revealed similar decreases in HDL-c and LDL-c as in the study population as a whole. CONCLUSION: Generic atorvastatin resulted in significantly lower LDL-c than name-brand atorvastatin but less of an increase in HDL-c.

[24] *Kaminskyi V, Zhdanovych O, Kolomiichenko T et al.* **Preeclampsia-associated homeostasis changes in pregnant woman after ART**. Ceska Gynekol 2020; 85:396-402.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33711899
ABSTRACT
OBJECTIVE: To determine the preeclampsia-associated features of homeostasis in pregnant woman after ART to clarify the possible mechanisms and factors of preeclampsia. DESIGN: A prospective

study. SETTING: Department of Obstetrics, Gynecology and Reproductology, Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine. METHODS: The 150 pregnant woman after ART were examined: 48 with preeclampsia (subgroup 1), 102 preeclampsia-free (subgroup 2). The liver enzymes in blood: alanine aminotransferase (ALT), aspartate aminotransferase (AST); the lipid metabolism indices: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), aterogenity index (AI), triglycerides (TG), 25-hydroxy-vitamin D concentration, cytokines: interleukin-1, -2, -6, -8, -10 (IL-1, IL-2,, IL-6, IL-8, IL-10), tumor necrosis factor (TNF), number of platelets, platelet aggregate function, fibrinogen (F), activated partial thrombin time (aPTT), soluble fibrin monomer complexes (SFMC), D-dimer, von Willebrand factor (VWF) activity were measured. To compare the means Students t-test was used. RESULTS: In women with preeclampsia, the transaminase levels and lipidogram indices (TG, LDL, LDL, AI) are elevated. Blood vitamin D are decreased (25.92±4.76 vs. 38.42±5.12 ng/mL, p.

[25] *Joseph P, Glynn R, Lonn E et al.* **Rosuvastatin for the prevention of venous thromboembolism: a pooled analysis of the HOPE-3 and JUPITER randomized controlled trials**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33705531

ABSTRACT

AIMS: To examine the association between rosuvastatin and VTE risk, and whether effects vary in different subpopulations stratified by key demographic, cardiovascular disease (CVD) risk factors and other risk factors associated with VTE. METHODS AND RESULTS: An individual participant data meta-analysis was conducted across two randomized controlled trials in 30,507 participants over a mean follow up of 3.62 years, Individuals had no prior history of vascular disease but were at intermediate CV risk. In both trials, participants were randomized to receive rosuvastatin or matching placebo. The primary outcome was VTE during follow-up, defined as either deep vein thrombosis or pulmonary embolism. Associations between rosuvastatin and VTE were examined in the overall pooled cohort, and subpopulations stratified by demographic risk factors (i.e. age, sex), CVD risk factors (i.e. obesity, smoking, lipid levels, blood pressure levels, C-reactive protein level), and a history of cancer.Mean age was 65.96 (SD 7.19) years of age, and 17,832 (58.45%) were male. 5,434 (17.82%) were smokers, median BMI was 27.6 (Interquartile range [IQR] 24.7 - 31.1) kg/m2, and median CRP level was 3.4 (IQR 2.1 - 6.0) mg/L. There were 139 VTE events. In the pooled cohort, rosuvastatin was associated with a large proportional reduction in the risk of VTE (hazard ratio 0.53, 95% CI 0.37 - 0.75). No significant interactions were observed between treatment with rosuvastatin and the risk of VTE across subpopulations stratified by demographic, CVD risk factors or a history of cancer (p-values for interactions >0.05 for all subgroups). CONCLUSIONS: Rosuvastatin is associated with a 47% proportional reduction in the risk of VTE, and its effect is consistent both in the presence or absence of VTE related clinical risk factors. TRANSLATIONAL PERSPECTIVE: In this individual participant data meta-analysis of two large randomized controlled trials comparing rosuvastatin to placebo, rosuvastatin was associated with a 47% proportional reduction in the risk of VTE. The effect of rosuvastatin was consistent across a broad range of demographic factors, cardiovascular risk factors, and a history of cancer. This study demonstrates that rosuvastatin is broadly affective at reducing the risk of VTE both in the presence or absence of VTE associated clinical risk factors. Results inform future research on the use of statins for this indication.

[26] *Hagisawa K, Ayaori M, Ikewaki K et al.* **5-Aminolevulinic Acid Attenuates Atherosclerotic Plaque Progression in Low-Density Lipoprotein Receptor-Deficient Mice by Heme Oxygenase-1 Induction**. Circ Rep 2019; 2:60-68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33693175

ABSTRACT

Background: Recently, 5-aminolevulinic acid (ALA) has been reported to modulate inflammatory development via an antioxidant effect. Hence, the aim of this study was to determine the anti-atherosclerotic effect of ALA. Methods and Results: Low-density lipoprotein (LDL) receptor knockout mice were fed the following diets for 24 weeks: normal diet (n=6); 1.25% cholesterol diet (high-cholesterol diet, HCD; n=7); HCD+ALA (46 mg/kg/day; n=10); and HCD+ezetimibe (5 mg/kg/day; n=10). At 40 weeks, HCD+ALA had reduced LDL cholesterol (320±68 vs. 379±49 mg/dL), triglyceride (141±44 vs. 195±49 mg/dL) and oxidized LDL (380±40 vs. 422±64 pg/mL) compared with HCD only. En face lesion area for the entire aortic surface was significantly smaller in mice that received HCD+ALA than in mice that received only HCD (32±5% vs. 39±4%, P<0.05). ALA intake exogenously increased tissue heme oxygenase-1 (HO-1) level in plaque composite tissue of the carotid arterial wall compared with HCD only (18±8 vs. 12±3 pg/μL, P<0.05), and HO-1-positive plaque showed modest NADPH oxidase 4 expression. Conclusions: ALA intake induces exogenous production of HO-1 at plaque sites, and improves lipid profiles and attenuation of atherosclerotic plaque progression in vivo.

[27] *Godsman N, Kohlhaas M, Nickel A et al.* **Metabolic alterations in a rat model of Takotsubo syndrome**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33711093

ABSTRACT

AIMS: Cardiac energetic impairment is a major finding in takotsubo patients. We investigate specific metabolic adaptations to direct future therapies. METHODS AND RESULTS: An isoprenaline-injection female rat model (versus sham) was studied at day-3; recovery assessed at day-7. Substrate uptake, metabolism, inflammation and remodelling were investigated by 18F-FDG-PET, metabolomics, qPCR and WB. Isolated cardiomyocytes were patch-clamped during stress protocols for redox states of NAD(P)H/FAD or [Ca2+]c, [Ca2+]m and sarcomere length. Mitochondrial respiration was assessed by seahorse/Clark electrode (glycolytic and β-oxidation substrates).Cardiac 18F-FDG metabolic rate was increased in takotsubo (p=0.006), as were expression of GLUT4-RNA/GLUT1/HK2-RNA and HK activity (all p<0.05), with concomitant accumulation of glucose- and fructose-6-phosphates (p>0.0001). Both lactate and pyruvate were lower (p<0.05) despite increases in LDH-RNA and PDH (p<0.05 both). β-oxidation enzymes CPT1b-RNA and 3KAT were increased (p<0.01) but malonyl-CoA (CPT-1 regulator) was upregulated (p=0.01) with decreased fatty acids and acyl-carnitines levels (p=0.0001-0.02). Krebs cycle intermediates α-ketoglutarate and succinyl-carnitine were reduced (p<0.05) as was cellular ATP reporter dihydroorotate (p=0.003). Mitochondrial Ca2+ uptake during high workload was impaired on day-3 (p<0.0001), inducing oxidation of NAD(P)H and FAD (p=0.03) but resolved by day-7. There were no differences in mitochondrial respiratory function, sarcomere shortening or [Ca2+] transients of isolated cardiomyocytes, implying preserved integrity of both mitochondria and cardiomyocyte. Inflammation and remodelling were upregulated - increased CD68-RNA, collagen RNA/protein and skeletal actin

RNA (all p<0.05). CONCLUSION: Dys-regulation of glucose and lipid metabolic pathways with decreases in final glycolytic and β-oxidation metabolites and reduced availability of Krebs intermediates characterises takotsubo myocardium. The energetic deficit accompanies defective Ca2+ handling, inflammation and upregulation of remodelling pathways, with preservation of sarcomeric and mitochondrial integrity. TRANSLATIONAL PERSPECTIVE: The simultaneous dysregulation in the glycolytic and beta-oxidation pathways which underlies the energetic deficit of the takotsubo heart supports further testing of currently available metabolic modulators as possible candidates for successful therapy, as well as targeting the inflammatory and remodelling pathways.

[28] *Ruscica M, Ferri N, Santos RD et al.* **Lipid Lowering Drugs: Present Status and Future Developments**. Current atherosclerosis reports 2021; 23:17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33694108
ABSTRACT
PURPOSE OF REVIEW: Based on the recent data of the DA VINCI study, it is clear that, besides utilization of statins, there is a need to increase non-statin lipid lowering approaches to reduce the cardiovascular burden in patients at highest risk. RECENT FINDINGS: For hypercholesterolemia, the small synthetic molecule bempedoic acid has the added benefit of selective liver activation, whereas inclisiran, a hepatic inhibitor of the PCSK9 synthesis, has comparable effects with PCSK9 monoclonal antibodies. For hypertriglyceridemia, cardiovascular benefit has been achieved by the use of icosapent ethyl, whereas results with pemafibrate, a selective agonist of PPAR-α, are eagerly awaited. In the era of RNA-based therapies, new options are offered to dramatically reduce levels of lipoprotein(a) (APO(a)L(RX)) and of triglycerides (ANGPTL3L(RX) and APOCIII-L(Rx)). Despite the demonstrated benefits of statins, a large number of patients still remain at significant risk because of inadequate LDL-C reduction or elevated blood triglyceride-rich lipoproteins or lipoprotein(a). The area of lipid modulating agents is still ripe with ideas and major novelties are to be awaited in the next few years.

[29] *Nguyen H, Akamnonu I, Yang T*. **Bempedoic Acid: a cholesterol lowering agent with a novel mechanism of action**. Expert Rev Clin Pharmacol 2021:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33691561
ABSTRACT
INTRODUCTION: Dyslipidemia is a common condition that increases the risk of heart diseases and stroke. High levels of low-density lipoprotein-cholesterol (LDL-C) are correlated with a higher risk for heart disease. A drug class known as 'statins' is the gold standard for LDL-C-lowering, but its use in some patients is limited by its adverse effects of myalgias and myopathies. Use of other LDL-C-lowering agents is frequently limited by cost and degree of efficacy. Additionally, many high-risk atherosclerotic cardiovascular disease patients fail to meet LDL-C goals despite maximally tolerated statin therapy with or without the addition of a non-statin agent. AREAS COVERED: This review covers the pharmacology, pharmacokinetics, clinical trials, and clinical implications of bempedoic acid. A PubMed search was conducted using the terms bempedoic, bempedoic acid, Nexletol, ETC-1002, and adenosine triphosphate citrate lyase inhibitor. Additional data were obtained from the prescribing information and relevant guidelines. All clinical trials were included. EXPERT OPINION: Bempedoic acid has not been shown to cause myalgias or myopathies and is likely to be competitively affordable compared to other LDL-C-lowering agents. Bempedoic acid has been shown

to be superior compared to placebo and provides additional LDL-C lowering on top of maximally tolerated statin therapy or combined with ezetimibe alone.

[30] *Huang AL, Leipsic JA, Zekry SB et al.* **Effects of chronic kidney disease and declining renal function on coronary atherosclerotic plaque progression: a PARADIGM substudy**. European heart journal cardiovascular Imaging 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33709096

ABSTRACT

AIMS : To investigate the change in atherosclerotic plaque volume in patients with chronic kidney disease (CKD) and declining renal function, using coronary computed tomography angiography (CCTA). METHODS AND RESULTS: In total, 891 participants with analysable serial CCTA and available glomerular filtration rate (GFR, derived using Cockcroft-Gault formulae) at baseline (CCTA 1) and follow-up (CCTA 2) were included. CKD was defined as GFR <60 mL/min/1.73 m2. Declining renal function was defined as ≥10% drop in GFR from the baseline. Quantitative assessment of plaque volume and composition were performed on both scans. There were 203 participants with CKD and 688 without CKD. CKD was associated with higher baseline total plaque volume, but similar plaque progression, measured by crude (57.5 ± 3.4 vs. 65.9 ± 7.7 mm3/year, P = 0.28) or annualized (17.3 ± 1.0 vs. 19.9 ± 2.0 mm3/year, P = 0.25) change in total plaque volume. There were 709 participants with stable GFR and 182 with declining GFR. Declining renal function was independently associated with plaque progression, with higher crude (54.1 ± 3.2 vs. 80.2 ± 9.0 mm3/year, P < 0.01) or annualized (16.4 ± 0.9 vs. 23.9 ± 2.6 mm3/year, P < 0.01) increase in total plaque volume. In CKD, plaque progression was driven by calcified plaques whereas in patients with declining renal function, it was driven by non-calcified plaques. CONCLUSION: Decline in renal function was associated with more rapid plaque progression, whereas the presence of CKD was not.

[31] *Gayoso-Rey M, Díaz-Trastoy O, Romero-Ventosa EY et al.* **Effectiveness, Safety, and Adherence to Treatment of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors in Real Practice**. Clinical therapeutics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33712271

ABSTRACT

PURPOSE: To evaluate the effectiveness, adverse reactions, and adherence to treatment of hypolipidemic inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9is) in a context of real clinical practice. METHODS: We present an observational, retrospective, descriptive, multicenter study of patients with hypercholesterolemia who began treatment with PCSK9is between January 2017 and December 2019, with a minimum treatment period of 3 months. The main variable we recorded was the frequency of cardiovascular events (cardiovascular death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina) in patients treated with PCSK9is. We recorded patient demographic characteristics and cardiovascular risk factors at onset of treatment as well as LDL-C levels and their reductions at 3, 6, 12, and 24 months. We calculated adherence to treatment and recorded the adverse reactions during treatment. FINDINGS: A total of 154 patients were studied, 64 (41.6%) of whom were treated with alirocumab and 90 (58.4%) with evolocumab. The initial dose of alirocumab was 75 mg every 14 days in 48 patients (75%) and 150 mg eery 14 days in 16 (25%). All patients who in the evolocumab group received a dose of 140 mg every 14 days. The mean (SD) basal LDL-C level was 159.6 (50.1) mg/dL, the level at 3

months was 87.9 (49.9) mg/dL (mean [SD] decrease, 44.5% [28.2%]), the level at 6 months was 86.7 (49.2) mg/dL (mean [SD] decrease, 46.3% [25.6%]), and the level at 12 months was 80.5 (41.4) (mean [SD] decrease, 48.9% [23.0%]). These values were maintained at 24 months (mean [SD], 80.3 [41.8] mg/dL; mean [SD] decrease, 47.9% [27.8%]). The percentage decrease of LDL-C for both drugs was approximately 50%, which was maintained until 24 months after treatment. Six patients (3.9%) presented with some cardiovascular event: acute myocardial infarction (2 [1.3%]), stroke (1 [0.65%]), coronary revascularization (1 [0.65%]), and hospitalization for unstable angina (2 [1.3%]). We did not see any adverse reactions related to PCSK9i treatment in 76.5% of patients. In the first 6 months, adherence to treatment with PCSK9is, measured as the possession ratio, was a mean (SD) of 99.4% (3.9%). In the rest of the study period (6-24 months), the mean (SD) adherence to treatment was 99.2% (4.7%). IMPLICATIONS: The frequency of cardiovascular events in patients treated with PCSK9is was low and occurred despite adequate adherence to treatment (100% possession ratio) with PCSK9is and concomitant treatment with other hypolipidemics. The effectiveness of PCSK9is is similar to that referred to in other published studies with PCSK9is, and this was maintained in the long term (24 months) with few adverse events, all of which were mild.

[32] *Ferri N.* **Phage display for targeting PCSK9**. EBioMedicine 2021; 65:103267.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33690097
ABSTRACT

[33] *D'Amario D, Cappetta D, Cappannoli L et al.* **Colchicine in ischemic heart disease: the good, the bad and the ugly**. Clinical research in cardiology : official journal of the German Cardiac Society 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33713178
ABSTRACT
Inflammation is the main pathophysiological process involved in atherosclerotic plaque formation, progression, instability, and healing during the evolution of coronary artery disease (CAD). The use of colchicine, a drug used for decades in non-ischemic cardiovascular (CV) diseases and/or systemic inflammatory conditions, stimulated new perspectives on its potential application in patients with CAD. Previous mechanistic and preclinical studies revealed anti-inflammatory and immunomodulatory effects of colchicine exerted through its principal mechanism of microtubule polymerization inhibition, however, other pleiotropic effects beneficial to the CV system were observed such as inhibition of platelet aggregation and suppression of endothelial proliferation. In randomized double-blinded clinical trials informing our clinical practice, low doses of colchicine were associated with the significant reduction of cardiovascular events in patients with stable CAD and chronic coronary syndrome (CCS) while in patients with a recent acute coronary syndrome (ACS), early initiation of colchicine treatment significantly reduced major adverse CV events (MACE). On the other hand, the safety profile of colchicine and its potential causal relationship to the observed increase in non-CV deaths warrants further investigation. For these reasons, postulates of precision medicine and patient-tailored approach with regards to benefits and harms of colchicine treatment should be employed at all times due to potential toxicity of colchicine as well as the currently unresolved signal of harm concerning non-CV mortality. The main goal of this review is to provide a balanced, critical, and comprehensive evaluation of currently available evidence with respect to colchicine use in the setting of CAD.

[34] *Cheng D, Zhao X, Yang S et al.* **Metabolomic Signature Between Metabolically Healthy Overweight/Obese and Metabolically Unhealthy Overweight/Obese: A Systematic Review**. Diabetes, metabolic syndrome and obesity : targets and therapy 2021; 14:991-1010.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33692630

ABSTRACT

The clinical manifestations of overweight/obesity are heterogeneous and complex. In contrast to metabolically unhealthy overweight/obese (MUO), a particular sub-group of obese patients who are considered as metabolically healthy overweight/obese (MHO), display favorable metabolic profiles characterized by high levels of insulin sensitivity, normal blood pressure, as well as favorable lipid, inflammation, hormone, liver enzyme, and immune profiles. While only a few available studies focused on the metabolic files underlying the obese phenotypes, the current review aimed to perform a systematic review of available studies focusing on describing the metabolomic signature between MUO and MHO. We did the systematic search for literature on MEDLINE (PubMed), the Cochrane Library, EMBASE, and searched for the references of relevant manuscripts from inception to 29 May 2020. After critical selection, 20 studies were eligible for this systematic review and evaluated by using QUADOMICS for quality assessment. Eventually, 12 of 20 studies were classified as "high quality". Branched-chain amino acids (isoleucine, leucine, and valine), aromatic amino acids (phenylalanine and tyrosine), lipids (palmitic acid, palmitoleic acid, oleic acid, eicosapentaenoic acid, and docosahexaenoic acid), and acylcarnitines (propionyl carnitine) levels might be elevated in MUO. The current results suggested that MHO showed a favorable trend in the overall metabolic signature. More longitudinal studies are needed to elaborate deeply on the metabolic pathway and the relationship between metabolic patterns and the occurrence of the disease.

[35] *Akoumianakis I, Zvintzou E, Kypreos K, Filippatos TD*. **ANGPTL3 and Apolipoprotein C-III as Novel Lipid-Lowering Targets**. Current atherosclerosis reports 2021; 23:20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33694000

ABSTRACT

PURPOSE OF REVIEW: Despite significant progress in plasma lipid lowering strategies, recent clinical trials highlight the existence of residual cardiovascular risk. Angiopoietin-like protein 3 (ANGPTL3) and apolipoprotein C-III (Apo C-III) have been identified as novel lipid-lowering targets. RECENT FINDINGS: Apo C-III and ANGPTL3 have emerged as novel regulators of triglyceride (TG) and low-density lipoprotein-cholesterol (LDL-C) levels. ANGPTL3 is an inhibitor of lipoprotein lipase (LPL), reducing lipolysis of Apo B-containing lipoproteins. Loss-of-function ANGPLT3 mutations are associated with reduced plasma cholesterol and TG, while novel ANGPLT3 inhibition strategies, including monoclonal antibodies (evinacumab), ANGPLT3 antisense oligonucleotides (IONIS-ANGPTL3-L(Rx)), and small interfering RNA (siRNA) silencing techniques (ARO-ANG3), result in increased lipolysis and significant reductions of LDL-C and TG levels in phase I and II clinical trials. Similarly, Apo C-III inhibits LPL while promoting the hepatic secretion of TG-rich lipoproteins and preventing their clearance. Loss-of-function APOC3 mutations have been associated with reduced TG levels. Targeting of Apo C-III with volanesorsen, an APOC3 siRNA, results in significant reduction in plasma TG levels but possibly also increased risk for thrombocytopenia, as recently demonstrated in phase I, II, and III clinical trials. ARO-APOC3 is a novel siRNA-based agent targeting Apo C-III which is currently under investigation with regard to its lipid-lowering efficiency. ANGPTL3 and Apo C-

III targeting agents have demonstrated striking lipid-lowering effects in recent clinical trials; however, more thorough safety and efficacy data are required. Here, we evaluate the role of ANGPLT3 and Apo C-III in lipid metabolism, present the latest clinical advances targeting those molecules, and outline the remaining scientific challenges on residual lipid-associated cardiovascular risk.

[36] *Ahmad MI, Shapiro MD*. **Preventing Diabetes and Atherosclerosis in the Cardiometabolic Syndrome**. Current atherosclerosis reports 2021; 23:16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33686460
ABSTRACT
PURPOSE OF REVIEW: Cardiometabolic syndrome is characterized by abdominal adiposity, insulin resistance, hypertension, and dyslipidemia. There is a growing burden of cardiometabolic disease in many parts of the world. This review highlights the critical preventive and therapeutic measures that need to be implemented to reduce the impact of cardiometabolic syndrome on cardiovascular health. RECENT FINDINGS: Recent cardiovascular outcome trials demonstrated that newer glucose-lowering medications reduce cardiovascular and renal events in patients with type 2 diabetes mellitus (T2DM). These medications should be considered in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD). These novel drugs may also play a role in primary prevention of cardiovascular disease (CVD) and renal disease in high-risk patients without T2DM. To manage dyslipidemia associated with cardiometabolic syndrome, in addition to lifestyle interventions and statin therapy, ezetimibe, and proprotein convertase subtilisin/Kexin type 9 (PCSK9), inhibitors can be used to reduce the risk of major adverse cardiovascular outcomes (MACE) especially in patients with T2DM and coronary artery disease (CAD). The residual risk of MACE in such a high-risk population can be further mitigated by treatment with an omega-3 fatty acid such as icosapent ethyl. Lifestyle modifications and the use of proven pharmacological therapies are essential for the prevention and progression of diabetes and ASCVD in those with the cardiometabolic syndrome.

[37] *van den Bogaard VAB, Spoor DS, van der Schaaf A et al.* **The Importance of Radiation Dose to the Atherosclerotic Plaque in the Left Anterior Descending Coronary Artery for Radiation-Induced Cardiac Toxicity of Breast Cancer Patients**. International journal of radiation oncology, biology, physics 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33713741
ABSTRACT
IMPORTANCE: Radiation-induced acute coronary events (ACEs) may occur as treatment-related late side effect of breast cancer (BC) radiation. However, the underlying mechanisms behind this radiation-induced cardiac disease remains to be determined. OBJECTIVE: The objective of this study was to test the hypothesis that radiation dose to calcified atherosclerotic plaques in the left anterior descending coronary artery (LAD) is a better predictor for ACEs than radiation dose to the whole heart or left ventricle in BC patients treated with radiotherapy (RT). DESIGN, SETTING, PARTICIPANTS, AND MAIN OUTCOMES AND MEASURES: The study cohort consisted of 910 BC patients treated with postoperative RT after breast conserving surgery. In total, 163 patients had an atherosclerotic plaque in the LAD. The endpoint was the occurrence of an ACE after treatment. For each individual patient, the mean heart dose (MHD), volume of the left ventricle receiving ≥ 5 Gy (LV-V5), mean LAD dose and mean dose to calcified atherosclerotic plaques in the LAD, if present, were acquired based on planning CT-scans. Cox-regression analysis was used to analyse the effects on

the cumulative incidence of ACEs. RESULTS: The median follow-up time was 9.2 years (range: 0.1-14.3 years). In total, 38 patients (4.2%) developed an ACE during follow-up. For patients with an atherosclerotic plaque (n=163) the mean dose to the atherosclerotic plaque was the strongest predictor for ACE, even after correction for cardiovascular risk factors (HR: 1.269 (95% CI: 1.090-1.477), P=0.002). The LV-V5 was associated with ACEs in patients without atherosclerotic plaques in the LAD (n=680) (hazard ratio (HR): 1.021 (95% CI: 1.003-1.039; P=0.023). CONCLUSION AND RELEVANCE: The results of this study suggest that radiation dose to pre-existing calcified atherosclerotic plaques in the LAD is strongly associated with the development of ACEs in BC patients.

[38] *Sundermann EE, Thomas KR, Bangen KJ et al.* **Prediabetes Is Associated With Brain Hypometabolism and Cognitive Decline in a Sex-Dependent Manner: A Longitudinal Study of Nondemented Older Adults**. Frontiers in neurology 2021; 12:551975.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33679574
ABSTRACT
Although type 2 diabetes is a well-known risk factor for Alzheimer's disease (AD), little is known about how its precursor-prediabetes-impacts neuropsychological function and brain health. Thus, we examined the relationship between prediabetes and AD-related biological and cognitive/clinical markers in a well-characterized sample drawn from the Alzheimer's Disease Neuroimaging Initiative. Additionally, because women show higher rates of AD and generally more atherogenic lipid profiles than men, particularly in the context of diabetes, we examined whether sex moderates any observed associations. The total sample of 911 nondemented and non-diabetic participants [normal control = 540; mild cognitive impairment (MCI) = 371] included 391 prediabetic (fasting blood glucose: 100-125 mg/dL) and 520 normoglycemic individuals (age range: 55-91). Linear mixed effects models, adjusted for demographics and vascular and AD risk factors, examined the independent and interactive effects of prediabetes and sex on 2-6 year trajectories of FDG-PET measured cerebral metabolic glucose rate (CMRglu), hippocampal/intracranial volume ratio (HV/IV), cerebrospinal fluid phosphorylated tau-(181)/amyloid-β(1-42) ratio (p-tau(181)/Aβ(1-42)), cognitive function (executive function, language, and episodic memory) and the development of dementia. Analyses were repeated in the MCI subsample. In the total sample, prediabetic status had an adverse effect on CMRglu across time regardless of sex, whereas prediabetes had an adverse effect on executive function across time in women only. Within the MCI subsample, prediabetic status was associated with lower CMRglu and poorer executive function and language performance across time within women, whereas these associations were not seen within men. In the total sample and MCI subsample, prediabetes did not relate to HV/IV, p-tau(181)/Aβ(1-42), memory function or dementia risk regardless of sex; however, among incident dementia cases, prediabetic status related to earlier age of dementia onset in women but not in men. Results suggest that prediabetes may affect cognition through altered brain metabolism, and that women may be more vulnerable to the negative effects of glucose intolerance.

[39] *Schiele F, Quignot N, Khachatryan A et al.* **Clinical impact and room for improvement of intensity and adherence to lipid lowering therapy: Five years of clinical follow-up from 164,565 post-myocardial infarction patients**. International journal of cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33705845
ABSTRACT

BACKGROUND: In patients at risk of cardiovascular (CV) events, the effectiveness of lipid-lowering therapies (LLT) is affected by both intensity and adherence. Our study evaluated the association between LLT intensity (statin and/or ezetimibe) and adherence, and CV events in patients with a history of myocardial infarction (MI) in France. METHODS: Using the French national healthcare database (SNDS), we included patients with a history of MI, an initial LLT prescription in 2011-2013, and a second prescription within one year. LLT intensity was defined using the expected percent reduction in low-density lipoprotein cholesterol; adherence was measured as the proportion of days covered. Cox proportional hazards models were used to assess associations between intensity and/or adherence, and the risk of major adverse CV event (MACE)). RESULTS: 164,565 patients were included; mean (SD) age, 66·3 (13·8) years; 73·6% men. Following an MI, only half of patients were treated with high-intensity LLT and approximately 40% of those on LLT remained non-adherent during follow-up (mean (SD) follow-up, 2·6 (1·4) years). Each 10% increase in treatment intensity, adherence, or adherence-adjusted intensity was respectively associated with a 16% (HR 0.84, 95%CI 0.84-0.85), 7% (HR 0.93, 95%CI 0.93-0.94), and 15% (HR 0.85, 95%CI 0.84-0.86) decrease in the risk of MACE. CONCLUSIONS: Among patients with a history of MI, prescriptions of high-intensity LLT were limited and adherence to LLT was low. Higher intensity and/or adherence to statins was associated with a significantly lower risk of MACE, highlighting the importance of compliance with clinical guidelines to improve patient outcomes.

[40] *Saeed A, Saeed F, Saeed H et al.* **Access to Essential Cardiovascular Medicines in Pakistan: A National Survey on the Availability, Price, and Affordability, Using WHO/HAI Methodology**. Frontiers in pharmacology 2020; 11:595008.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33708114

ABSTRACT

Objective: This national survey was aimed at measuring the access to cardiovascular disease (CVD) medicines in terms of their availability, price, and affordability in Pakistan. This was done by using the standard WHO/Health Action International (HAI) methodology. Methods: The price and availability data for 18 CVD medicines were collected from public sector hospitals (n = 40) and private sector retail pharmacies (n = 40) in eight cities of Pakistan. The outcome measures were availability (calculated as percentage of health facilities stocked with listed medicines), medicine price to the international reference price ratio (i.e., median price ratio (MPR)), and affordability (calculated as number of days' wages (NDWs) of the lowest paid unskilled government worker required to afford one-month treatment of a chronic disease). The affordability of standard treatment in Pakistan with four CVD drugs was compared with data from six other low and middle income countries (LMICs) using HAI database. Findings: The mean percent availability of CVD medicines was significantly low ($p < 0.001$) in the public sector as compared to the private sector, that is, 25.5% vs. 54.6% for originator brands (OBs) and 30.4% vs. 34.9% for lowest price generics (LPGs), respectively. For all OBs and LPGs, the inflation-adjusted mean MPR was 2.72 and 1, respectively. CVD medicines were found to be unaffordable with average NDWs of 6.4 and 2.2 for OBs and LPGs, respectively, that is, NDWs of more than 1. In international comparison with countries such as Sudan, Lebanon, Egypt, India, Afghanistan, and China, the affordability of standard treatment with selected CVD medicines (atenolol, amlodipine, captopril, and simvastatin) in Pakistan was found to be low. Overall, all four OBs and three out of four LPGs of selected CVD drugs were found unaffordable in Pakistan. Conclusion: This data indicated that the availability of selected CVD medicines was low in both public

and private sector medicine outlets. Both OBs and LPGs were found unaffordable in the private sector, necessitating the redressal of pricing policies, structuring, and their implementation.

[41] *Nie P, Yang F, Wan F et al.* **Analysis of MicroRNAs Associated With Carotid Atherosclerotic Plaque Rupture With Thrombosis**. Frontiers in genetics 2021; 12:599350.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33679879

ABSTRACT

Atherosclerosis is a progressive vascular wall inflammatory disease, and the rupture of atherosclerotic vulnerable plaques is the leading cause of morbidity and mortality worldwide. This study intended to explore the potential mechanisms behind plaque rupture and thrombosis in ApoE knockout mice. The spontaneous plaque rupture models were established, and left carotid artery tissues at different time points (1-, 2-, 4-, 6-, 8-, 12-, and 16-week post-surgery) were collected. By the extent of plaque rupture, plaque was defined as (1) control groups, (2) atherosclerotic plaque group, and (3) plaque rupture group. Macrophage (CD68), MMP-8, and MMP-13 activities were measured by immunofluorescence. Cytokines and inflammatory markers were measured by ELISA. The left carotid artery sample tissue was collected to evaluate the miRNAs expression level by miRNA-microarray. Bioinformatic analyses were conducted at three levels: (2) vs. (1), (3) vs. (2), and again in seven time series analysis. The plaque rupture with thrombus and intraplaque hemorrhage results peaked at 8 weeks and decreased thereafter. Similar trends were seen in the number of plaque macrophages and lipids, the expression of matrix metalloproteinase, and the atherosclerotic and plasma cytokine levels. MiRNA-microarray showed that miR-322-5p and miR-206-3p were specifically upregulated in the atherosclerotic plaque group compared with those in the control group. Meanwhile, miR-466h-5p was specifically upregulated in the plaque rupture group compared with the atherosclerotic plaque group. The highest incidence of plaque rupture and thrombosis occurred at 8 weeks post-surgery. miR-322-5p and miR-206-3p may be associated with the formation of atherosclerotic plaques. miR-466h-5p may promote atherosclerotic plaque rupture via apoptosis-related pathways.

[42] *Marchini T, Mitre LS, Wolf D*. **Inflammatory Cell Recruitment in Cardiovascular Disease**. Frontiers in cell and developmental biology 2021; 9:635527.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33681219

ABSTRACT

Atherosclerosis, the main underlying pathology for myocardial infarction and stroke, is a chronic inflammatory disease of middle-sized to large arteries that is initiated and maintained by leukocytes infiltrating into the subendothelial space. It is now clear that the accumulation of pro-inflammatory leukocytes drives progression of atherosclerosis, its clinical complications, and directly modulates tissue-healing in the infarcted heart after myocardial infarction. This inflammatory response is orchestrated by multiple soluble mediators that enhance inflammation systemically and locally, as well as by a multitude of partially tissue-specific molecules that regulate homing, adhesion, and transmigration of leukocytes. While numerous experimental studies in the mouse have refined our understanding of leukocyte accumulation from a conceptual perspective, only a few anti-leukocyte therapies have been directly validated in humans. Lack of tissue-tropism of targeted factors required for leukocyte accumulation and unspecific inhibition strategies remain the major challenges to ultimately translate therapies that modulate leukocytes accumulation into clinical practice. Here, we

carefully describe receptor and ligand pairs that guide leukocyte accumulation into the atherosclerotic plaque and the infarcted myocardium, and comment on potential future medical therapies.

[43] *Khan MA*. **Therapeutic implications of statins beyond lipid lowering: In the perspective of their effects on the antigen presentation, T cells and NKT cells**. Int J Health Sci (Qassim) 2021; 15:1-2.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33708037
ABSTRACT

[44] *Herrett E, Williamson E, Brack K et al.* **The effect of statins on muscle symptoms in primary care: the StatinWISE series of 200 N-of-1 RCTs**. Health technology assessment (Winchester, England) 2021; 25:1-62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33709907
ABSTRACT
BACKGROUND: Uncertainty persists about whether or not statins cause symptomatic muscle adverse effects (e.g. pain, stiffness and weakness) in the absence of severe myositis. OBJECTIVES: To establish the effect of statins on all muscle symptoms, and the effect of statins on muscle symptoms that are perceived to be statin related. DESIGN: A series of 200 double-blinded N-of-1 trials. SETTING: Participants were recruited from 50 general practices in England and Wales. PARTICIPANTS: Patients who were considering discontinuing statin use and those who had discontinued statin use in the last 3 years because of perceived muscle symptoms. INTERVENTIONS: Participants were randomised to a sequence of six 2-month treatment periods during which they received 20 mg of atorvastatin daily or a matched placebo. MAIN OUTCOME MEASURES: The primary outcome was self-reported muscle symptoms rated using a visual analogue scale on the last week of each treatment period. Secondary outcomes included the participant's belief about the cause of their muscle symptoms, the site of muscle symptoms, how the muscle symptoms affected the participant, any other symptoms they experienced, adherence to medication, the participant's decision about statin treatment following the trial, and whether or not they found their own trial result helpful. RESULTS: A total of 151 out of 200 (75.5%) randomised participants provided one or more visual analogue scale measurements in a placebo period and one or more measurements in a statin period, and were included in the primary analysis. There was no evidence of a difference in muscle symptom scores between statin and placebo periods (mean difference statin minus placebo -0.11, 95% confidence interval -0.36 to 0.14; $p = 0.398$). Withdrawals, adherence and missing data were similar during the statin periods and the placebo periods. CONCLUSIONS: Among people who previously reported severe muscle symptoms while taking statins, this series of randomised N-of-1 trials found no overall effect of statins on muscle symptoms compared with the placebo. The slight difference in withdrawals due to muscle symptoms suggests that statins may contribute to symptoms in a small number of patients. The results are generalisable to patients who are considering discontinuing or have already discontinued statins because of muscle symptoms, and who are willing to re-challenge or participate in their own N-of-1 trial. FUTURE WORK: We recommend that additional statins and doses are explored using N-of-1 trials. More broadly, N-of-1 trials present a useful tool for exploring transient symptoms with other medications. LIMITATIONS: This study used 20-mg doses of atorvastatin only. Furthermore, a dropout rate of 43% was observed, but this was accounted for in the power calculations. TRIAL REGISTRATION: Current

Controlled Trials ISRCTN30952488 and EudraCT 2016-000141-31. FUNDING: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 25, No. 16. See the NIHR Journals Library website for further project information.
Statins are one of the most commonly prescribed drugs in the UK. There is strong evidence that they are effective in safely reducing heart disease; however, there is some doubt about whether or not statins cause muscle pain, stiffness or weakness. This research has been carried out to understand the effect of statins on muscle symptoms. To answer our question, we asked 200 volunteers from across England and Wales to participate in the study. Patients who joined the study either had recently stopped taking statins because of muscle symptoms or were considering stopping because of muscle symptoms. Patients who participated were randomly assigned to a sequence of six 2-month treatment periods during which they received either statins or a placebo. Neither patients nor their general practitioner knew which tablet they were receiving. This helped to reduce bias in the data. At the end of each treatment period, patients were asked to report any muscle symptoms, or any other symptoms, that they experienced. The key result of this work is that patients reported no difference, on average, in their muscle symptoms between periods of taking a statin and periods of taking a placebo. We also assessed the impact on the patient's quality of life by looking at how statins affected the following areas: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. As with muscle symptoms, there was no evidence of a difference between statin and placebo periods. The majority of patients who finished the trial decided to continue using statins after the trial. Future research should be carried out to assess different statin doses, as higher doses are often used following a heart attack. In addition, further work is needed to see how the approach we used could be adopted into everyday clinical care.
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[45] *Desai SR, Korula A, Kulkarni UP et al.* **Sitosterolemia: Four Cases of an Uncommon Cause of Hemolytic Anemia (Mediterranean Stomatocytosis with Macrothrombocytopenia)**. Indian J Hematol Blood Transfus 2021; 37:157-161.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33707850
ABSTRACT
Sitosterolemia is a rare autosomal recessively inherited lipid metabolic disorder that is characterized by hyper absorption of plant sterols from the intestinal mucosa leading to toxic levels in the blood. Four patients of age ranging from 11 to 29 years presented to the outpatient department with clinical features of hemolytic anemia. There were no features of hypercholesterolemia in any of the patients. Peripheral smear examination of all four patients showed stomatocytes and macrothrombocytopenia. Qualitative testing for plant sterols was performed in one case. Next generation sequencing revealed a compound heterozygous mutation in ABCG5 gene (c.1222C>T and c.1255C>T) in one case and homozygous mutations in ABCG5 gene (c.727C>T), (c.332G>A (p.G111E)), (c.1222C>T) in the other three cases. Ezetimibe (10 mg/day) was administered in one case, with complete resolution of symptoms. All patients were advised a low plant sterol diet and regular monitoring of hemoglobin and lipid profile. Our cases highlight a rare but important cause of hemolytic anemia that can be suspected from careful peripheral blood examination but only conclusively established by molecular genetic diagnosis.

[46] *Bolognese L.* **[Treatment of ST-elevation myocardial infarction: state of the art and new horizons]**. Giornale italiano di cardiologia (2006) 2021; 22:167-180.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33687367

ABSTRACT

ST-segment elevation myocardial infarction (STEMI) is the most important acute manifestation of coronary artery disease and is associated with high morbidity and mortality. A complete thrombotic occlusion developing from an atherosclerotic plaque in an epicardial coronary vessel is the cause of STEMI in the majority of cases. Early diagnosis and immediate reperfusion are the most effective ways to limit myocardial ischaemia and infarct size and thereby reduce the risk of complications and heart failure. Primary percutaneous coronary intervention has become the preferred reperfusion strategy in these patients; if angioplasty cannot be performed within 120 min of STEMI diagnosis, fibrinolysis therapy should be administered to dissolve the occluding thrombus. The initiation of networks to provide around- the-clock cardiac catheterization availability and the generation of standard operating procedures within hospital systems have helped to reduce the time to reperfusion therapy. Together with new advances in antithrombotic therapy and preventive measures, these developments have resulted in a decrease in mortality. However, a substantial amount of patients still experience recurrent cardiovascular events after STEMI. New insights have been gained regarding the pathophysiology of STEMI and feed into the development of new treatment strategies.

[47] *Shi Z, Zhao M, Li J et al.* **Association of Hypertension With Both Occurrence and Outcome of Symptomatic Patients With Mild Intracranial Atherosclerotic Stenosis: A Prospective Higher Resolution Magnetic Resonance Imaging Study**. Journal of magnetic resonance imaging : JMRI 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33694230

ABSTRACT

BACKGROUND: Intracranial atherosclerotic plaque causing mild luminal stenosis might lead to acute ischemic events. However, the difference between culprit and nonculprit lesions is unclear, as are the factors associated with favorable treatment outcomes. PURPOSE: To quantify characteristics of intracranial atherosclerosis with mild luminal stenosis and to identify factors associated with lesion type (culprit or nonculprit) and with clinical outcomes. STUDY TYPE: Prospective POPULATION: 293 patients who had acute stroke with mild luminal stenosis (<50%) in the middle cerebral or basilar artery. FIELD STRENGTH/SEQUENCE: 3.0 T higher resolution magnetic resonance imaging (hrMRI) of intracranial arteries and whole brain MR images. ASSESSMENT: Morphological and compositional analysis of plaques was performed. This included assessment of plaque volume, plaque burden, remodeling ratio, eccentricity, intraplaque hemorrhage, and enhancement ratio. Clinical outcomes were assessed according to the modified Rankin Scale (mRS) at day 90, with a favorable outcome being defined as a 90-day mRS ≤2. STATISTICAL TESTS: The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by a logistic regression model. RESULTS: Hypertension (OR 5.2; 95% CI 2.6-10.3; $P<0.05$) and hrMRI enhancement ratio (OR 2.7; 95% CI 1.4-5.1; $P<0.05$) were independently associated with lesion type. Patients without hypertension had significantly more ($P<0.05$) favorable outcomes (124/144) than patients with hypertension (97/149). Most hypertensive patients without any previous blood pressure control (54/63) had a favorable outcome. However, these patients were significantly younger ($P<0.05$) than those with adequate blood pressure control. After adjusting for all significant characteristics, hypertension duration (OR 1.19; 95% CI 1.09-1.29;

P<0.05), hypertension management (OR 2.49; 95% CI 1.18-5.26; P<0.05), and enhancement ratio (OR 0.01; 95% CI 0.001-0.157; P<0.05) were found to be independent high-risk factors for outcome prediction. DATA CONCLUSION: hrMRI provided incremental value over traditional risk factors in identifying higher risk intracranial atherosclerosis with mild luminal stenosis. LEVEL OF EVIDENCE: 2 TECHNICAL EFFICACY: Stage 2.

[48] *Ribas SA, Paravidino VB, Brandão JM, Santana da Silva LC*. **The Cardiovascular Health Integrated Lifestyle Diet (CHILD) Lowers LDL-Cholesterol Levels in Brazilian Dyslipidemic Pediatric Patients**. Journal of the American College of Nutrition 2021:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33683168
ABSTRACT
OBJECTIVE: To analyze the impact of the CHILD-2 diet on the lipid profile of Brazilian children and adolescents with dyslipidemia. METHODS: This is a quasi-experimental study, where 149 participants (5-17 years) with mild-to-moderate hypercholesterolemia were divided into two groups (GI: low or normal weight; n = 58 and GII: overweight; n = 91). Both groups underwent the CHILD-2 diet, characterized by 25-30% total fat and less than 7% of low-saturated fat (SF) for 6 months. Changes from baseline in the lipid profile, including Total cholesterol (TC), LDL-C, triacylglycerols and glucose concentrations, dietary and anthropometric data were examined at 3 and 6 months. Longitudinal analyses were performed using linear mixed-effects models in SAS. RESULTS: Serum LDL-C concentrations reduced over time compared with baseline (Δ = -5.1 mg/dL; p<0.01), with no difference between groups (p = 0.35). TC concentrations decreased by -2.0 mg/dL (p<0.01); but no difference was observed between groups. We found no significant changes in body mass index/age Z scores after a dietary intervention compared with baseline in both groups (p = 0.94). CONCLUSION: Despite the modest reduction, our findings confirm that children with dyslipidemia can benefit from the CHILD-2 diet combined with a healthy lifestyle.

[49] *Perry BI, Burgess S, Jones HJ et al.* **The potential shared role of inflammation in insulin resistance and schizophrenia: A bidirectional two-sample mendelian randomization study**. PLoS medicine 2021; 18:e1003455.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33711016
ABSTRACT
BACKGROUND: Insulin resistance predisposes to cardiometabolic disorders, which are commonly comorbid with schizophrenia and are key contributors to the significant excess mortality in schizophrenia. Mechanisms for the comorbidity remain unclear, but observational studies have implicated inflammation in both schizophrenia and cardiometabolic disorders separately. We aimed to examine whether there is genetic evidence that insulin resistance and 7 related cardiometabolic traits may be causally associated with schizophrenia, and whether evidence supports inflammation as a common mechanism for cardiometabolic disorders and schizophrenia. METHODS AND FINDINGS: We used summary data from genome-wide association studies of mostly European adults from large consortia (Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) featuring up to 108,557 participants; Diabetes Genetics Replication And Meta-analysis (DIAGRAM) featuring up to 435,387 participants; Global Lipids Genetics Consortium (GLGC) featuring up to 173,082 participants; Genetic Investigation of Anthropometric Traits (GIANT) featuring up to 339,224 participants; Psychiatric Genomics Consortium (PGC) featuring up to 105,318 participants; and Cohorts for Heart

and Aging Research in Genomic Epidemiology (CHARGE) consortium featuring up to 204,402 participants). We conducted two-sample uni- and multivariable mendelian randomization (MR) analysis to test whether (i) 10 cardiometabolic traits (fasting insulin, high-density lipoprotein and triglycerides representing an insulin resistance phenotype, and 7 related cardiometabolic traits: low-density lipoprotein, fasting plasma glucose, glycated haemoglobin, leptin, body mass index, glucose tolerance, and type 2 diabetes) could be causally associated with schizophrenia; and (ii) inflammation could be a shared mechanism for these phenotypes. We conducted a detailed set of sensitivity analyses to test the assumptions for a valid MR analysis. We did not find statistically significant evidence in support of a causal relationship between cardiometabolic traits and schizophrenia, or vice versa. However, we report that a genetically predicted inflammation-related insulin resistance phenotype (raised fasting insulin (raised fasting insulin (Wald ratio OR = 2.95, 95% C.I, 1.38-6.34, Holm-Bonferroni corrected p-value (p) = 0.035) and lower high-density lipoprotein (Wald ratio OR = 0.55, 95% C.I., 0.36-0.84; p = 0.035)) was associated with schizophrenia. Evidence for these associations attenuated to the null in multivariable MR analyses after adjusting for C-reactive protein, an archetypal inflammatory marker: (fasting insulin Wald ratio OR = 1.02, 95% C.I, 0.37-2.78, p = 0.975), high-density lipoprotein (Wald ratio OR = 1.00, 95% C.I., 0.85-1.16; p = 0.849), suggesting that the associations could be fully explained by inflammation. One potential limitation of the study is that the full range of gene products from the genetic variants we used as proxies for the exposures is unknown, and so we are unable to comment on potential biological mechanisms of association other than inflammation, which may also be relevant. CONCLUSIONS: Our findings support a role for inflammation as a common cause for insulin resistance and schizophrenia, which may at least partly explain why the traits commonly co-occur in clinical practice. Inflammation and immune pathways may represent novel therapeutic targets for the prevention or treatment of schizophrenia and comorbid insulin resistance. Future work is needed to understand how inflammation may contribute to the risk of schizophrenia and insulin resistance.

[50] *Ounjaijean S, Kulprachakarn K, Aurpibul L et al.* **Cardiovascular risks in Asian HIV-infected patients receiving boosted-protease inhibitor-based antiretroviral treatment**. J Infect Dev Ctries 2021; 15:289-296.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33690213

ABSTRACT

INTRODUCTION: Increased risk of cardiovascular disease in HIV-infected patients was tought to be the cause of multiple mechanistic factors, which changing the HIV care landscape. Antiretroviral therapy (ART), especially protease inhibitors (PI), is one of common HIV treatments that may have some association with this. The mechanism of PI in comparison to other regimens, however, are not clearly understood. METHODOLOGY: Age-and gender-match HIV-infected patients treated with either boosted-PI-based regimen (boosted-PI group, N=30) or NNRTI-based ART (non-PI group, N = 30) were recruited for this cross-sectional study. Parameters determined cardiovascular risks, inflammation, endothelial function, and bone metabolic function were evaluated. RESULTS: Compared with non-PI, patients in the boosted-PI group had more evidence of dyslipidemia. No statistical difference in the prevalence of subclinical atherosclerosis was found between the two groups. Circulating levels of inflammatory markers, C-reactive protein (CRP) (5.4±9.1 vs. 14.9 ± 19.4 mg/L, p = 0.019) and lectin-liked oxidized lipoprotein receptor-1 (LOX-1) (387 ± 299 vs. 554 ± 324 pg/mL, p = 0.042) were lower in boosted-PI group. Contrastingly, Vascular adhesion molecules-1

(VCAM-1) (160.2 ± 80.0 vs. 147.8 ± 66.3 ng/mL, p = 0.010), and osteoprotegerin (OPG) (153.7 ± 57.1 vs. 126.4 ± 35.8, p = 0.031) were higher. After adjustment in the multivariate analysis, PI treatment is the only independent parameter associated with the changes of CRP, LOX-1, VCAM-1, and OPG. Subgroup analysis showed that ARV treatment effects differed among participant having dyslipidemia. CONCLUSIONS: The major mechanism in which PI-mediated was triggering atherogenesis could be through alteration of lipid metabolism and endothelial function, but no evidence of accelerated pro-inflammatory response was attested.

[51] *Nouri F, Sadeghi M, Mohammadifard N et al.* **Longitudinal association between an overall diet quality index and latent profiles of cardiovascular risk factors: results from a population based 13-year follow up cohort study**. Nutrition & metabolism 2021; 18:28.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33691729
ABSTRACT
BACKGROUND: Cardiovascular diseases (CVDs) are associated with an unhealthy lifestyle, including poor diet. Indices reflecting the overall quality of diets are more effective than single food or nutrient-based approaches in clarifying the diet disease relationship. The present study aims to use latent variable modeling to examine the longitudinal joint relationships between the latent profiles of CVDs risk factors and the diet quality index (DQI). METHODS: A total of 4390 Iranian adults aged 35 and older within the framework of the Isfahan Cohort Study were included in the current secondary analysis. DQI focused on food groups, including fast foods, sweets, vegetables, fruits, fats, and proteins, based on a validated food frequency questionnaire. The score of DQI has a range between 0 (indicating healthy and high diet quality) and 2 (indicating unhealthy and low diet quality). Blood pressure (BP), anthropometric measurements, blood glucose, serum lipids, and high-sensitivity C-Reactive Protein (hs-CRP) were measured according to standard protocols in 2001, 2007, and 2013 to evaluate the profiles of CVDs risk factors. A Bayesian Multidimensional Graded Responses Linear Mixed Model was used for data analysis. RESULTS: At baseline, the participants' mean ± standard deviation age was 50.09 ± 11.21, and 49.5% of them were male. Three latent profiles of CVDs risk factors were derived: (1) Fit Pre-Metabolic Syndrome (FPMS) profile characterized by normal anthropometric indices and some impaired metabolic risk factors; (2) DysLipoproteinemia Central Obese (DLCO) profile with abdominal obesity and impaired low-density lipoprotein cholesterol as well as other normal risk factors; (3) Impaired Laboratory Inflammatory State (ILIS) profile with impaired high-density lipoprotein cholesterol and hs-CRP and other normal risk factors. In general, higher scores of the extracted latent profiles indicated more impaired function in the related risk factors. After controlling for various potential fixed and time-varying confounding variables, a significant positive longitudinal association was found between FPMS, DLCO, and ILIS profiles and DQI (β (95% CrI): 0.26 (0.03,0.51), 0.14 (0.01,0.27), and 0.24 (0.11,0.38), respectively), demonstrating that lower overall diet quality was associated with more impaired function of the related risk factors. CONCLUSIONS: More adherence to a healthy quality diet is associated with lower levels of all emerging latent profiles of CVDs risk factors. Increasing the knowledge of the community about the importance of the quality of consumed foods may help to prevent CVDs. It is recommended that further investigations, particularly interventional studies, be conducted to confirm our results.

[52] *Kısa PT, Yildirim GK, Hismi BO et al.* **Patients with cerebrotendinous xanthomatosis diagnosed with diverse multisystem involvement**. Metabolic brain disease 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33704661

ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is a lipid storage disease caused by deficiency of sterol 27-hydroxylase enzyme encoded by CYP27A1 gene. This multicenter, cross-sectional descriptive study aimed to document clinical characteristics of CTX patients of different ages, clinical presentations of early-diagnosed patients, and responses to short-term chenodeoxycholic acid (CDCA) treatment. Seven of 11 CTX patients were diagnosed in childhood. Three patients (27%) had neonatal cholestasis, seven (63%) patients had a history of frequent watery defecation started in infantile period, and eight (72.7%) patients had juvenile cataract. Four patients in the adult age group had pyramidal signs and parkinsonism symptoms. The mean Mignarri score at diagnosis was significantly lower in the pediatric patients (267.8 ± 51.4) than in the adult patients (450.0 ± 64.0, p = 0.001). No significant difference was determined between pediatric patients and adult patients regarding plasma cholestanol concentration at diagnosis (p = 0.482). The frequency of defecation decreased with treatment in six children, who had diarrhea at admission. Compared to pretreatment values, patients' body weight and standardized body mass index significantly increased at the 12th month of treatment. In conclusion, Mignarri scores are lower in the pediatric patients than in adult patients since the most determinative signs of the CTX disease are not apparent yet in the childhood. The disease is frequently overlooked in routine practice as the disease presents itself with different clinical combinations both in adults and in children. CTX is potentially a treatable disease; thereby, enhanced awareness is critically important for early diagnosis particularly in children.

[53] *Goldberg RB, Tripputi MT, Boyko EJ et al.* **Hepatic Fat in Participants With and Without Incident Diabetes in the Diabetes Prevention Program Outcome Study**. The Journal of clinical endocrinology and metabolism 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33705543

ABSTRACT

PURPOSE: To characterize hepatic fat content and fatty liver prevalence, their determinants, and effect of interventions to prevent diabetes using computerized tomography in a cohort with prediabetes, in those developing diabetes versus not. METHODS: We measured liver fat as liver attenuation (LA) in Hounsfield units in 1876 participants at ~14 years following randomization into the Diabetes Prevention Program, which tested the effects of lifestyle or metformin interventions versus standard care to prevent diabetes. LA was compared among intervention groups and in those with versus without diabetes, and associations with baseline and follow-up measurements of anthropometric and metabolic covariates were assessed. RESULTS: There were no differences in liver fat between treatment groups at 14 years of follow-up. Participants with diabetes had lower LA (mean ± SD: 46±16 vs. 51±14HU; p<0.001) and a greater prevalence of fatty liver (LA<40HU) (34% vs 17%; p<0.001). Severity of metabolic abnormalities at the time of LA evaluation were associated with lower LA categories in a graded manner and more strongly in those with diabetes. Averaged annual fasting insulin (an index of insulin resistance [OR, 95% CI 1.76, 1.41-2.20]) waist circumference (1.63, 1.17-2.26), and triglyceride (1.42, 1.13-1.78), but not glucose, were independently associated with LA<40HU prevalence. CONCLUSIONS: Fatty liver is common in the early phases of diabetes development. The association of LA with insulin resistance, waist circumference and triglyceride levels emphasizes the importance of these markers for hepatic

steatosis in this population and that assessment of hepatic fat in early diabetes development is warranted.

[54] *Gholami N, Abotorabi S, Lalooha F, Oveisi S*. **Effects of Fish Oil Supplementation on Pregnancy Outcomes in Pregnant Women Referred to Kosar Hospital**. Iranian journal of pharmaceutical research : IJPR 2020; 19:241-247.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33680026

ABSTRACT

The hypothesis of a protective effect of fish oil supplementation in preventing some consequences of pregnancy such as gestational hypertension is put forward which has attracted increasing attention. The aim of the present study was to evaluate the effect of fish oil supplementation on outcomes of pregnancy. This study was a clinical trial performed on 339 women with singleton pregnancy aged 18-35 and gestational age of 20 weeks who visited prenatal clinic at Kosar Hospital in Qazvin during 2015-2016. Patients were randomly divided into two groups marked as intervention group which received soft gelatin capsules (each containing 1000 mg fish oil including 120 mg DHA and 180 mg EPA) on a daily basis from the 20(th) week to the end of pregnancy, and the women in the control group with no fish oil intake. The outcomes of pregnancy including preeclampsia, eclampsia, preterm labor, gestational diabetes, weight, height, head circumference at birth and the gestational age at delivery were evaluated in both groups. Data were analyzed using statistical tests including Mann-Whitney U test and t-test. There was significant difference in gestational age between the two study groups ($P < 0.05$). There was no significant difference in the percentage of preterm birth, preeclampsia, eclampsia, IUGR, and GDM between the two groups ($P > 0.05$). The results of this study showed that consumption of fish oil supplements from 20(th) week of gestation by 18-35 year-old pregnant women increased pregnancy age but failed to decrease the percentage of preterm birth, preeclampsia, eclampsia, IUGR, and GDM.

[55] *Albright RH, Fleischer AE*. **Association of select preventative services and hospitalization in people with diabetes**. Journal of diabetes and its complications 2021:107903.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33691987

ABSTRACT

PURPOSE: The purpose of this study was to assess the utilization rates and trends of preventative outpatient visits to providers in a population of people with diabetes, and evaluate which preventative services may offer protection against poor outcomes (i.e. all-cause hospitalization). METHODS: The National Health and Nutrition Examination Survey (NHANES) was used to examine the relationship between select outpatient services and risk of all-cause hospitalization in people with diabetes. NHANES data from 2011 to 2016 were included. We assessed five outpatient services commonly recommended to prevent future complications in patients with diabetes: (1) routine examination from a physician (2) assessment of hemoglobin A1C (3) eye exam with pupil dilation (4) foot exam and (5) assessment from a diabetes specialist. Logistic regression models were performed to assess the independent association of outpatient services used in the past 1 year, and hospitalization within that same year. RESULTS: The prevalence of diabetes within the NHANES population was 10.5% (n = 3054). Hospitalization was significantly more common among diabetics who were older, had lower income levels (i.e. under $20,000) and those who considered themselves in 'fair' or 'poor health'. After adjustment for important covariates, patients who received a preventative foot exam

within the last year (i.e. 1-4 times per year) were 33% less likely to be hospitalized within that year (OR 0.67, 95%CI 0.46, 0.96). Those visiting a diabetes specialist were 44% less likely to be hospitalized that year (OR 0.56, 95%CI 0.39, 0.82) if the visit was preventative in nature (i.e. occurred more than one year before the hospitalized event). No other outpatient services displayed an independent association with hospitalization. CONCLUSION: Outpatient Services were consistently being used annually by the diabetic population. Receiving a preventative foot exam and visiting a diabetes specialist were associated with protection against hospitalization, resulting in a 33% and 44% decreased risk, respectively. RESEARCH IN CONTEXT: Evidence before this study: Current guidelines focus on preventative care measures to avert diabetes complications. In a 2018 national database study of approximately one-third of the Italian population, guidelines for prevention were not consistently being met among the diabetes population, however, patients who regularly received all the recommended preventative measures experienced a 20% risk reduction in hospitalization. The study's preventative measures included periodic lab monitoring including glycated hemoglobin and lipid profiles and dilated eye exams. Added value of this study: In our study, we used a national database representing the United States' non-institutionalized population to identify the prevalence of prevention measures being utilized in adults with diabetes and further examine their relationship with all-cause hospitalization. Logistic regression analysis identified two preventative measures with inconsistent utilization, however, when these measures were used according to guidelines, they contributed to a risk reduction in all-cause hospitalization. Implications of all the available evidence: Current preventative guidelines can contribute to a risk reduction in hospitalization among adults with diabetes. National guidelines and quality improvement initiatives should be aimed at improving the utilization of foot exams as a preventative measure and referral to a diabetes specialist before complications incur.

[56] *Yan L, Jiaqiong L, Yue G et al.* **Atorvastatin protects against contrast-induced acute kidney injury via upregulation of endogenous hydrogen sulfide**. Renal failure 2020; 42:270-281.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33685337

ABSTRACT

BACKGROUND: Contrast-induced acute kidney injury (CIAKI) is the third leading cause of acute renal failure in hospitalized patients. This study was aimed to investigate whether atorvastatin could upregulate the expression of hydrogen sulfide (H(2)S) and hence protect against CIAKI. METHODS: We treated male rats and NRK-52E cells by iopromide to establish in vivo and in vitro models of CIAKI. Pretreatment with atorvastatin was given in CIAKI rats to investigate its effect on CIAKI. We collected serum and urine samples to detect renal function. We obtained kidney tissue for histological analysis and detection of protein concentration. We tested the serum concentration of H(2)S and renal expression of two H(2)S synthetases [cystathionine γ-lyase (CSE) and cystathionine-β synthase (CBS)]. NaHS was pretreated in NRK-52E cells to testify its underlying effect on contrast-induced injury. RESULTS: Atorvastatin significantly ameliorated renal dysfunction and morphological changes in CIAKI rats, as well as inflammation, apoptosis, and excessive oxidative stress. Atorvastatin also markedly increased the serum concentration of H(2)S and renal expression of CSE and CBS. Moreover, pretreatment with NaHS in NRK-52E cells considerably attenuated contrast-induced cell death and inflammation. CONCLUSION: Atorvastatin protects against CIAKI via upregulation of endogenous hydrogen sulfide.

[57] *van Boheemen L, Turk S, Beers-Tas MV et al.* **Atorvastatin is unlikely to prevent rheumatoid arthritis in high risk individuals: results from the prematurely stopped STAtins to Prevent Rheumatoid Arthritis (STAPRA) trial**. RMD Open 2021; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33685928

ABSTRACT

OBJECTIVES: Persons at high risk of rheumatoid arthritis (RA) might benefit from a low-risk pharmacological intervention aimed at primary prevention. Previous studies demonstrated disease-modifying effects of statins in patients with RA as well as an association between statin use and a decreased risk of RA development. A randomised, double-blind, placebo-controlled trial investigated whether atorvastatin could prevent arthritis development in high-risk individuals. METHODS: Arthralgia patients with anticitrullinated protein antibody (ACPA) >3 xULN or ACPA and rheumatoid factor, without (a history of) arthritis, were randomised to receive atorvastatin 40 mg daily or placebo for 3 years. The calculated sample size was 220 participants. The primary endpoint was clinical arthritis. Cox regression analysis was used to determine the effect of atorvastatin on arthritis development. RESULTS: Due to a low inclusion rate, mainly because of an unwillingness to participate, the trial was prematurely stopped. Data of the 62 randomised individuals were analysed. Median follow-up was 14 (inner quartiles 6-35) months. Fifteen individuals (24%) developed arthritis: 9/31 (29%) in the atorvastatin group; 6/31 (19%) in the placebo group: HR 1.40, 95% CI 0.50 to 3.95. CONCLUSIONS: In this small set of randomised high-risk individuals, we did not demonstrate a protective effect of atorvastatin on arthritis development. The main reason for the low inclusion was unwillingness to participate; this may also impede other RA prevention trials. Further research to investigate and solve barriers for prevention trial participation is needed.

[58] *Valladolid-Acebes I, Åvall K, Recio-López P et al.* **Lowering apolipoprotein CIII protects against high-fat diet-induced metabolic derangements**. Science advances 2021; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33712458

ABSTRACT

Increased levels of apolipoprotein CIII (apoCIII), a key regulator of lipid metabolism, result in obesity-related metabolic derangements. We investigated mechanistically whether lowering or preventing high-fat diet (HFD)-induced increase in apoCIII protects against the detrimental metabolic consequences. Mice, first fed HFD for 10 weeks and thereafter also given an antisense (ASO) to lower apoCIII, already showed reduced levels of apoCIII and metabolic improvements after 4 weeks, despite maintained obesity. Prolonged ASO treatment reversed the metabolic phenotype due to increased lipase activity and receptor-mediated hepatic uptake of lipids. Fatty acids were transferred to the ketogenic pathway, and ketones were used in brown adipose tissue (BAT). This resulted in no fat accumulation and preserved morphology and function of liver and BAT. If ASO treatment started simultaneously with the HFD, mice remained lean and metabolically healthy. Thus, lowering apoCIII protects against and reverses the HFD-induced metabolic phenotype by promoting physiological insulin sensitivity.

[59] *Rajamohan A, Heit B, Cairns E, Barra L*. **Citrullinated and homocitrullinated low- density lipoprotein in rheumatoid arthritis**. Scandinavian journal of rheumatology 2021:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33678128

ABSTRACT

Objective: Antibodies to citrullinated and homocitrullinated (also known as carbamylated) proteins, specific for rheumatoid arthritis (RA), are associated with cardiovascular disease (CVD). Immune complexes containing these proteins have been identified in the atherosclerotic plaque of CVD patients. In mice, homocitrullinated low-density lipoprotein (HomoCitLDL) promotes foam cell formation, which is critical in the pathogenesis of atherosclerosis. We aimed to investigate the atherogenic potential of HomoCitLDL and citrullinated low-density lipoprotein (CitLDL) in RA.Method: Human LDL was homocitrullinated in potassium cyanate and citrullinated by rabbit skeletal muscle peptidyl arginine deiminase-2. The modifications were confirmed by mass spectrometry. Primary human monoctyes from healthy subjects (N = 8) were differentiated to macrophages using macrophage colony-stimulating factor and incubated with modified LDL. Foam cells were visualized using Oil Red O staining. Serum from RA patients (N = 101) and controls (N = 32) was tested for immunoglobulin G antibodies to modified LDL using enzyme-linked immunosorbent assay.Results: HomoCitLDL and CitLDL strongly induced foam cell production (> 90%) versus unmodified LDL (11%) ($p < 0.0001$). The characteristics of the RA subjects were: 73% females, median age 60 [interquartile range (IQR) 17] years and disease duration 7.5 (IQR 13) years; 11% had a prior major cardiovascular event, 66% were ever smokers, 32% had hypertension, 33% dyslipidaemia, and 14% diabetes. Antibodies to HomoCitLDL were detected in 18% of RA patients; they were significantly associated with dyslipidaemia [odds ratio (OR) 3.86; 95% confidence interval (CI) 1.22, 12.17] and antibodies to other homocitrullinated antigens (OR 10.61; 95% CI 1.31, 86.11).Conclusions: HomoCitLDL and CitLDL have atherogenic properties in vitro. Antibody responses to HomoCitLDL, but not CitLDL, were detected in RA patients.

[60] *Li W, Chen SH, Zhao JQ et al.* **[Increased risk of cardiovascular disease in elderly population with carotid plaque and low ankle brachial index]**. Zhonghua xin xue guan bing za zhi 2021; 49:263-268.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33706461
ABSTRACT
Objective: To investigate whether the co-presence of carotid plaques and low ankle-brachial index (ABI) might increase the risks of ischemic cardiovascular and cerebrovascular event in elderly population. Methods: It was a prospective study. Participants from the elderly cohort of the Kailuan Study, who completed a carotid sonography and ABI examination, were included in this study. Participants underwent physical examinations between 2010 and 2011 and were divided into 3 groups: no carotid plaque and ABI>0.9 group (n=526), carotid plaque and ABI>0.9 group (n=1 067), and carotid plaques and ABI≤0.9 group (n=49). Follow up ended on the 31 December 2016. The incidence of ischemic cardiovascular and cerebrovascular event was compared between the 3 groups, the relationship between carotid plaque and low ABI with ischemic cardiovascular and cerebrovascular event was analyzed. Results: A total of 1 642 participants were included (age, (67.1±6.4) years). There were 1 028 males (62.6%) and 1 028 females(37.4%). The average follow-up time was 5.41 years, the incidence of ischemic cardiovascular and cerebrovascular event in the 3 group was 2.1%(11/526), 5.5%(59/1 067), and 12.2%(6/49),respectively; the incidence of myocardial infarction in the 3 group was 0.2%(1/526), 1.6%(17/1 067), 10.2%(5/49), respectively; the incidence of cerebral infarction in the 3 group was 1.9%(10/526), 3.9%(42/1 067) and 2.0%(1/49), respectively. Multivariate Cox risk proportional regression analysis showed that compared with the group without carotid plaque and ABI>0.9, the HR values (95%CI) of ischemic cardiovascular and cerebrovascular

event in the group with carotid plaque and ABI>0.9, carotid plaques and ABI≤0.9 group were 3.52 (1.49-8.35), 7.16(2.11-24.26) respectively, after adjusting for sex,age,systolic blood pressure,fast blood glucose,body mass index,total cholesterol,smoke,alcohol consumption and lipid-lowering medication and antihypertensive medication. Conclusions: Co-presence of carotid plaques and low ankle-brachial index may further increase the risk of ischemic cardiovascular and cerebrovascular event among elderly population in this cohort.