[1] *Wolny R, Mintz GS, Pręgowski J, Witkowski A*. **Mechanisms, Prevention and Treatment of Saphenous Vein Graft Disease**. The American journal of cardiology 2021; 154:41-47.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34256942

ABSTRACT

Saphenous vein grafts are imperfect yet indispensable conduits commonly used for coronary artery bypass grafting. Their degeneration ultimately leading to occlusion results from the pathological response of the vein to altered blood rheology and several types of vascular injury. Surgical techniques minimizing vessel damage, and prolonged antiplatelet and lipid-lowering treatment are established methods of mitigating the degeneration process hence preventing graft occlusions. Percutaneous interventions in degenerated vein grafts carry high risk of embolization, periprocedural myocardial infarction and restenosis. Thus, native vessel should be the preferred treatment target in case of graft failure whenever technically feasible.

[2] *Vogt NM, Hunt JFV, Ma Y et al.* **Effects of simvastatin on white matter integrity in healthy middle-aged adults**. Annals of clinical and translational neurology 2021; 8:1656-1667.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34275209

ABSTRACT

BACKGROUND: The brain is the most cholesterol-rich organ and myelin contains 70% of total brain cholesterol. Statins are potent cholesterol-lowing medications used by millions of adults for prevention of vascular disease, yet the effect of statins on cholesterol-rich brain white matter (WM) is largely unknown. METHODS: We used longitudinal neuroimaging data acquired from 73 healthy, cognitively unimpaired, statin-naïve, middle-aged adults during an 18-month randomized controlled trial of simvastatin 40 mg daily (n = 35) or matching placebo (n = 38). ANCOVA models (covariates: age, sex, APOE-ε4) tested the effect of treatment group on percent change in WM, gray matter (GM), and WM hyperintensity (WMH) neuroimaging measures at each study visit. Mediation analysis tested the indirect effects of simvastatin on WM microstructure through change in serum total cholesterol levels. RESULTS: At 18 months, the simvastatin group showed a significant preservation in global WM fractional anisotropy (β = 0.88%, 95% CI 0.27 to 1.50, P = 0.005), radial diffusivity (β = -1.10%, 95% CI -2.13 to -0.06, P = 0.039), and WM volume (β = 0.72%, 95% CI 0.13 to 1.32, P = 0.018) relative to the placebo group. There was no significant effect of simvastatin on GM or WMH volume. Change in serum total cholesterol mediated approximately 30% of the effect of simvastatin on WM microstructure. CONCLUSIONS: Simvastatin treatment in healthy, middle-aged adults resulted in preserved WM microstructure and volume at 18 months. The partial mediation by serum cholesterol reduction suggests both peripheral and central mechanisms. Future studies are needed to determine whether these effects persist and translate to cognitive outcomes. TRIAL REGISTRATION: NCT00939822 (ClinicalTrials.gov).

[3] *Boccara F*. **Never too old for lipid-lowering therapy**. Archives of cardiovascular diseases 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34257047

ABSTRACT

[4] *Davoudi A, Ahmadi M, Sharifi A et al.* **Studying the Effect of Taking Statins before Infection in the Severity Reduction of COVID-19 with Machine Learning**. BioMed research international 2021; 2021:9995073.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34250095

ABSTRACT

Statins can help COVID-19 patients' treatment because of their involvement in angiotensin-converting enzyme-2. The main objective of this study is to evaluate the impact of statins on COVID-19 severity for people who have been taking statins before COVID-19 infection. The examined research patients include people that had taken three types of statins consisting of Atorvastatin, Simvastatin, and Rosuvastatin. The case study includes 561 patients admitted to the Razi Hospital in Ghaemshahr, Iran, during February and March 2020. The illness severity was encoded based on the respiratory rate, oxygen saturation, systolic pressure, and diastolic pressure in five categories: mild, medium, severe, critical, and death. Since 69.23% of participants were in mild severity condition, the results showed the positive effect of Simvastatin on COVID-19 severity for people that take Simvastatin before being infected by the COVID-19 virus. Also, systolic pressure for this case study is 137.31, which is higher than that of the total patients. Another result of this study is that Simvastatin takers have an average of 95.77 mmHg O(2)Sat; however, the O(2)Sat is 92.42, which is medium severity for evaluating the entire case study. In the rest of this paper, we used machine learning approaches to diagnose COVID-19 patients' severity based on clinical features. Results indicated that the decision tree method could predict patients' illness severity with 87.9% accuracy. Other methods, including the K-nearest neighbors (KNN) algorithm, support vector machine (SVM), Naïve Bayes classifier, and discriminant analysis, showed accuracy levels of 80%, 68.8%, 61.1%, and 85.1%, respectively.

[5] *Zahradnik TM, Cresswell M, Squier K et al.* **Can Achilles tendon xanthoma be distinguished from Achilles tendinopathy using Dixon method MRI? A cross-sectional exploratory study**. BMC musculoskeletal disorders 2021; 22:627.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34271888

ABSTRACT

BACKGROUND: Familial hypercholesterolemia is a genetic condition characterized by life-long elevations of plasma low-density lipoprotein cholesterol. In addition to life-threatening cardiovascular complications, intratendinous cholesterol deposits (xanthomas) can lead to pain and tendon thickening, particularly in the Achilles. Clinical detection of xanthomas currently relies upon visual assessment and palpation, or ultrasound-based measures of tendon thickening or echotexture. Misdiagnosis of xanthoma can delay the commencement of potentially life-saving lipid-lowering therapy. Our primary purpose was to determine whether analysis of separated fat and water magnetic resonance images may be able to differentiate between xanthomatic and nonxanthomatic Achilles tendons through quantification of intratendinous fat content. The main hypothesis was that Achilles tendon xanthomas will demonstrate greater lipid content than Achilles tendinopathy or healthy control tendons. METHODS: Bilateral MRI scans of Achilles tendons from 30 participants (n = 10 Achilles tendon xanthoma, n = 10 Achilles overuse tendinopathy, n = 10 healthy controls) were analyzed for total lipid content using the Dixon method of fat and water signal separation. Secondary outcome measures included tendon water content, as well as ultrasound characterization of tendon tissue organization and thickness. RESULTS: Fat content was greater in Achilles tendon xanthomas compared to the tendinopathy ($p < 0.0001$) and control groups ($p < 0.0001$). Water content was also greater in Achilles tendon xanthomas compared to the tendinopathy ($p < 0.0001$) and control groups ($p = 0.0002$). Ultrasound tissue characterization revealed worse tissue organization in Achilles tendon

xanthoma tendons compared to Achilles tendinopathy ($p<0.05$) but demonstrated largely overlapping distributions. Achilles tendon xanthoma tendons were, on average, significantly thicker than the tendons of the other two groups ($p<0.01$ and $p<0.001$, respectively). CONCLUSION: MRI-derived measures of Achilles tendon fat content may be able to distinguish xanthomas from control and tendinopathic tissue. Dixon method MRI warrants further evaluation in an adequately powered study to develop and test clinically relevant diagnostic thresholds.

[6] *Wang X, Pan J, Ren Z et al.* **Application of a novel hybrid algorithm of Bayesian network in the study of hyperlipidemia related factors: a cross-sectional study**. BMC public health 2021; 21:1375.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34247609
ABSTRACT
BACKGROUND: This article aims to understand the prevalence of hyperlipidemia and its related factors in Shanxi Province. On the basis of multivariate Logistic regression analysis to find out the influencing factors closely related to hyperlipidemia, the complex network connection between various variables was presented through Bayesian networks(BNs). METHODS: Logistic regression was used to screen for hyperlipidemia-related variables, and then the complex network connection between various variables was presented through BNs. Since some drawbacks stand out in the Max-Min Hill-Climbing (MMHC) hybrid algorithm, extra hybrid algorithms are proposed to construct the BN structure: MMPC-Tabu, Fast.iamb-Tabu and Inter.iamb-Tabu. To assess their performance, we made a comparison between these three hybrid algorithms with the widely used MMHC hybrid algorithm on randomly generated datasets. Afterwards, the optimized BN was determined to explore to study related factors for hyperlipidemia. We also make a comparison between the BN model with logistic regression model. RESULTS: The BN constructed by Inter.iamb-Tabu hybrid algorithm had the best fitting degree to the benchmark networks, and was used to construct the BN model of hyperlipidemia. Multivariate logistic regression analysis suggested that gender, smoking, central obesity, daily average salt intake, daily average oil intake, diabetes mellitus, hypertension and physical activity were associated with hyperlipidemia. BNs model of hyperlipidemia further showed that gender, BMI, and physical activity were directly related to the occurrence of hyperlipidemia, hyperlipidemia was directly related to the occurrence of diabetes mellitus and hypertension; the average daily salt intake, daily average oil consumption, smoking, and central obesity were indirectly related to hyperlipidemia. CONCLUSIONS: The BN of hyperlipidemia constructed by the Inter.iamb-Tabu hybrid algorithm is more reasonable, and allows for the overall linking effect between factors and diseases, revealing the direct and indirect factors associated with hyperlipidemia and correlation between related variables, which can provide a new approach to the study of chronic diseases and their associated factors.

[7] *Cai T, Abel L, Langford O et al.* **Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses**. Bmj 2021; 374:n1537.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34261627
ABSTRACT
OBJECTIVE: To assess the associations between statins and adverse events in primary prevention of cardiovascular disease and to examine how the associations vary by type and dosage of statins. DESIGN: Systematic review and meta-analysis. DATA SOURCES: Studies were identified from

previous systematic reviews and searched in Medline, Embase, and the Cochrane Central Register of Controlled Trials, up to August 2020. REVIEW METHODS: Randomised controlled trials in adults without a history of cardiovascular disease that compared statins with non-statin controls or compared different types or dosages of statins were included. MAIN OUTCOME MEASURES: Primary outcomes were common adverse events: self-reported muscle symptoms, clinically confirmed muscle disorders, liver dysfunction, renal insufficiency, diabetes, and eye conditions. Secondary outcomes included myocardial infarction, stroke, and death from cardiovascular disease as measures of efficacy. DATA SYNTHESIS: A pairwise meta-analysis was conducted to calculate odds ratios and 95% confidence intervals for each outcome between statins and non-statin controls, and the absolute risk difference in the number of events per 10 000 patients treated for a year was estimated. A network meta-analysis was performed to compare the adverse effects of different types of statins. An E(max) model based meta-analysis was used to examine the dose-response relationships of the adverse effects of each statin. RESULTS: 62 trials were included, with 120 456 participants followed up for an average of 3.9 years. Statins were associated with an increased risk of self-reported muscle symptoms (21 trials, odds ratio 1.06 (95% confidence interval 1.01 to 1.13); absolute risk difference 15 (95% confidence interval 1 to 29)), liver dysfunction (21 trials, odds ratio 1.33 (1.12 to 1.58); absolute risk difference 8 (3 to 14)), renal insufficiency (eight trials, odds ratio 1.14 (1.01 to 1.28); absolute risk difference 12 (1 to 24)), and eye conditions (six trials, odds ratio 1.23 (1.04 to 1.47); absolute risk difference 14 (2 to 29)) but were not associated with clinically confirmed muscle disorders or diabetes. The increased risks did not outweigh the reduction in the risk of major cardiovascular events. Atorvastatin, lovastatin, and rosuvastatin were individually associated with some adverse events, but few significant differences were found between types of statins. An E(max) dose-response relationship was identified for the effect of atorvastatin on liver dysfunction, but the dose-response relationships for the other statins and adverse effects were inconclusive. CONCLUSIONS: For primary prevention of cardiovascular disease, the risk of adverse events attributable to statins was low and did not outweigh their efficacy in preventing cardiovascular disease, suggesting that the benefit-to-harm balance of statins is generally favourable. Evidence to support tailoring the type or dosage of statins to account for safety concerns before starting treatment was limited. SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42020169955.

[8] *Jaspers NEM, Visseren FLJ, van der Graaf Y et al.* **Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial**. BMJ open 2021; 11:e041673.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34272216

ABSTRACT

OBJECTIVE: To determine whether communicating personalised statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use in patients with stable cardiovascular disease (CVD) compared with standard (non-personalised) therapy-effects. DESIGN: Hypothesis-blinded, three-armed randomised controlled trial SETTING AND PARTICIPANTS: 303 statin users with stable CVD enrolled in a cohort INTERVENTION: Participants were randomised in a 1:1:1 ratio to standard practice (control-group) or one of two intervention arms. Intervention arms received standard practice plus (1) a personalised health profile, (2) educational videos and (3) a structured telephone consultation. Intervention arms received personalised estimates of prognostic changes associated with both discontinuation of current statin and

intensification to the most potent statin type and dose (ie, atorvastatin 80 mg). Intervention arms differed in how these changes were expressed: either change in individual 10-year absolute CVD risk (iAR-group) or CVD-free life-expectancy (iLE-group) calculated with the SMART-REACH model (http://U-Prevent.com). OUTCOME: Primary outcome was patient decisional conflict score (DCS) after 1 month. The score varies from 0 (no conflict) to 100 (high conflict). Secondary outcomes were collected at 1 or 6 months: DCS, quality of life, illness perception, patient activation, patient perception of statin efficacy and shared decision-making, self-reported statin adherence, understanding of statin-therapy, post-randomisation low-density lipoprotein cholesterol level and physician opinion of the intervention. Outcomes are reported as median (25th- 75th percentile). RESULTS: Decisional conflict differed between the intervention arms: median control 27 (20-43), iAR-group 22 (11-30; p-value vs control 0.001) and iLE-group 25 (10-31; p-value vs control 0.021). No differences in secondary outcomes were observed. CONCLUSION: In patients with clinically manifest CVD, providing personalised estimations of treatment-effects resulted in a small but significant decrease in decisional conflict after 1 month. The results support the use of personalised predictions for supporting decision-making. TRIAL REGISTRATION: NTR6227/NL6080.

[9] *Takeshita Y, Terada J, Fujita R et al.* **Coronary artery calcium score may be a novel predictor of COVID-19 prognosis: a retrospective study**. BMJ Open Respir Res 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34272254

ABSTRACT

BACKGROUND: Although several studies have reported an association between atherosclerosis-related diseases and COVID-19, the relationship between COVID-19 severity and atherosclerosis progression remains unclear. The aim of this study is to determine the coronary artery calcium score (CACS) prognostic value in patients with COVID-19 using indices such as deterioration in oxygenation and CT images of the chest. METHODS: This was a single-centre retrospective study of 53 consecutive patients with COVID-19 in Narita who were admitted to our hospital between March 2020 and August 2020. CACS was calculated based on non-gated CT scans of the chest performed on admission day. The patients were divided into the following two groups based on CACS: group 1 (CACS ≥180, n=11) and group 2 (CACS <180, n=42). Following univariate analysis of the main variables, multivariate analysis of variables that may be associated with COVID-19 progression was performed. RESULTS: Multivariable logistic regression analysis of age, sex, smoking history, diabetes, hypertension, dyslipidaemia, number of days from symptom onset to hospitalisation and CACS of ≥180 was performed. It revealed that unlike CACS of <180, CACS of ≥180 is associated with exacerbation of oxygenation or CT images of the chest during hospitalisation (OR: 12.879, 95% CI: 1.399 to 380.401). Furthermore, this model of eight variables showed good calibration (Hosmer-Lemeshow p=0.119). CONCLUSION: CACS may be a prognosis marker of COVID-19 severity. Although coronary artery calcification is not typically assessed in pneumonia cases, it may provide a valuable clinical indicator for predicting severe COVID-19 outcomes.

[10] *Tunbridge MJ, Jardine AG*. **Atherosclerotic Vascular Disease Associated with Chronic Kidney Disease**. Cardiol Clin 2021; 39:403-414.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34247753

ABSTRACT

Cardiovascular risk increases as glomerular filtration rate (GFR) declines in progressive renal disease and is maximal in patients with end-stage renal disease requiring maintenance dialysis. Atherosclerotic vascular disease, for which hyperlipidemia is the main risk factor and lipid-lowering therapy is the key intervention, is common. However, the pattern of dyslipidemia changes with low GFR and the association with vascular events becomes less clear. While the pathophysiology and management of patients with early chronic kidney disease (CKD) is similar to the general population, advanced and end-stage CKD is characterized by a disproportionate increase in fatal events, ineffectiveness of statin therapy, and greatly increased risk associated with coronary interventions. The most effective strategies to reduce atherosclerotic cardiovascular disease in CKD are to slow the decline in renal function or to restore renal function by transplantation.

[11] *Moazzeni SS, Hizomi Arani R, Deravi N et al.* **Weight change and risk of cardiovascular disease among adults with type 2 diabetes: more than 14 years of follow-up in the Tehran Lipid and Glucose Study**. Cardiovascular diabetology 2021; 20:141.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34253199

ABSTRACT

BACKGROUND: To examine the impact of weight change on incident cardiovascular disease and coronary heart disease (CVD/CHD) among an Iranian population with type 2 diabetes mellitus (T2DM). METHODS: The study population included 763 participants with T2DM aged ≥30 years without a history of CVD and cancer at baseline. Two weight measurements done at baseline and about 3 years later. Based on their weight change, they categorized into: >5% loss, 3-5% loss, stable (±<3%), 3-5% gain, >5% gain. Participants were then followed for incident CVD/CHD annually up to 20 March 2018. Multivariable Cox proportional hazard models, adjusted for age, sex, body mass index, educational level, current smoking, glucose-lowering drug use, family history of CVD, hypertension, hypercholesterolemia, chronic kidney disease, and fasting plasma glucose (FPG) were applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of weight change categories for incident CVD/CHD, considering stable weight as reference. RESULTS: After the weight change measurement, during a median follow-up of 14.4 years, 258 CVD and 214 CHD occurred. Over 5% weight gain was associated with reduced risks of CVD and CHD development by the HRs of 0.70 [95% CI 0.48-1.01; P-value: 0.058] and 0.61 [0.40-0.93], respectively, in multivariable analysis. After further adjustment for FPG change, the HRs of weight gain>5% were attenuated to 0.75 [0.51-1.10; P-value: 0.138] and 0.66 [043-1.01; P-value: 0.053] for incident CVD and CHD, respectively. The effect of weight loss>5% was in opposite direction among those older versus younger than 60 years; with suggestive increased risk (not statistically significant) of incident CHD/CVD for the older group. Moreover, weight gain>5% significantly reduced the risk of CHD only among those older than 60 years (P-value for interaction<0.2). Furthermore, weight gain>5% had an association with lower risk of CVD and CHD among sulfonylurea users (0.56 [0.32-0.98] for CVD and 0.54 [0.29-0.99] for CHD). CONCLUSIONS: Our results with a long-term follow-up showed that weight gain>5% was associated with better CVD/CHD outcomes among Iranian participants with T2DM, especially older ones. Moreover, we did not find an unfavorable impact on incident CVD/CHD for sulfonylurea-induced weight gain.

[12] *Morieri ML, Perrone V, Veronesi C et al.* **Improving statin treatment strategies to reduce LDL-cholesterol: factors associated with targets' attainment in subjects with and without type 2 diabetes**. Cardiovascular diabetology 2021; 20:144.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34271920
ABSTRACT
BACKGROUND: This cross-sectional study aimed to identify actionable factors to improve LDL-cholesterol target achievement and overcome underuse of lipid-lowering treatments in high- or very-high-cardiovascular risk patients. METHODS: We evaluated healthcare records of 934,332 subjects from North-Italy, including subjects with available lipid profile and being on statin treatments up to December 2018. A 6-month-period defined adherence with proportion-of-days-covered ≥80%. Treatment was classified as high-intensity-statin (HIS) + ezetimibe, HIS-alone, non-HIS (NHIS) + ezetimibe or NHIS alone. RESULTS: We included 27,374 subjects without and 10,459 with diabetes. Among these, 30% and 36% were on secondary prevention, respectively. Adherence was high (78-100%) and increased with treatment intensity and in secondary prevention. Treatment intensity increased in secondary prevention, but only 42% were on HIS. 2019-guidelines LDL-cholesterol targets were achieved in few patients and more often among those with diabetes (7.4% vs. 10.7%, p < 0.001). Patients in secondary prevention had mean LDL-cholesterol levels aligned slightly above 70 mg/dl (range between 68 and 73 mg/dl and between 73 and 85 mg/dl in patients with and without diabetes, respectively). Moreover, the differences in mean LDL-cholesterol levels observed across patients using treatments with well-stablished different LDL-lowering effect were null or much smaller than expected (HIS vs. NHIS from - 3 to - 11%, p < 0.001, HIS + ezetimibe vs. HIS- from - 4 to + 5% n.s.). These findings, given the observational design of the study, might suggest that a "treat to absolute LDL-cholesterol levels" approach (e.g., targeting LDLc of 70 mg/dl) was mainly used by physicians rather than an approach to also achieve the recommended 50% reduction in LDL-cholesterol levels. Our analyses suggested that female sex, younger age, higher HDL-c, and elevated triglycerides are those factors delaying prescription of statin treatments, both in patients with and without diabetes and in those on secondary prevention. CONCLUSIONS: Among patients on statin treatment and high adherence, only a small proportion of patients achieved LDL-cholesterol targets. Late initiation of high-intensity treatments, particularly among those with misperceived low-risk (e.g., female subjects or those with high HDL-cholesterol), appears as pivotal factors needing to be modified to improve CVD prevention.

[13] *Burnap SA, Mayr M.* **DRP1-a Novel Regulator of PCSK9 Secretion and Degradation**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34264313
ABSTRACT

[14] *Petreski T, Piko N, Petrijan T et al.* **Statin-Associated Necrotizing Myopathy Leading to Acute Kidney Injury: A Case Report**. Case Rep Nephrol Dial 2021; 11:129-135.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34250030
ABSTRACT
Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are a mainstay of cardiovascular disease therapy. In addition to their lipid-lowering capabilities, they exhibit several pleiotropic effects. Their adverse reactions such as myalgias are not uncommon, but in rare cases,

the resulting rhabdomyolysis can be fatal. Recently, more insight has been brought into the pathogenesis of statin-induced rhabdomyolysis, and immune-mediated necrotizing myopathies are diagnosed more frequently. We present a case of a female patient who was on chronic rosuvastatin therapy and developed necrotizing myopathy. The disease progressed to acute kidney and liver injury. We discontinued the drug, started supportive measures, and initiated renal replacement therapy with a high cutoff dialysis membrane once. Her recovery was prompt, with a normal control electromyography 2 weeks after discharge.

[15] *Gao F, Feng GJ, Li H et al.* **Scavenger Receptor BI Induced by HDL From Coronary Heart Disease May Be Related to Atherosclerosis**. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2021; 27:10760296211029710.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34254531
ABSTRACT
This study aims to determine whether dysfunctional High Density Lipoprotein (HDL) influenced the expression of scavenger receptor class B type I (SR-B1) to determine reverse cholesterol transport. Blood samples obtained from coronary heart disease patients confirmed by angiography were collected. HDL was extracted from the blood via ultracentrifugation. Then, the HDL was injected into apoE-/- mice, and the HepG2 cells cultured with Dulbecco's modified eagle medium (DMEM) were added the HDL extracted from coronary heart disease patients. As controls, normal cases without coronary heart disease (CHD) and patients with angina pectoris and acute myocardial infarction were used. The protein expression levels of SR-B1 were detected by western blot, and the lipid accumulation levels were detected by Oil Red O staining in both tissues and cell levels. These results revealed that the HDL obtained from CHD patients downregulate the SR-B1 expression in ex vitro and in vitro studies. In addition, dysfunctional HDL may result in lower SR-B1 expression levels. The degree of SR-B1 expression levels could be relative to the degree of coronary congestion. Along with the increase in severe coronary congestion, such as myocardial infarction, the SR-B1 expression levels were lower. The dysfunctional HDL derived from coronary heart disease patients decreased the expression of SR-B1, and promoted lipid accumulation.

[16] *Hadi A, AlAteeq MA*. **Level of Control of Dyslipidemia Among Patients Followed in Family Medicine Clinics in Riyadh, Saudi Arabia**. Cureus 2021; 13:e15504.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34268035
ABSTRACT
Background Dyslipidemia is a well-established primary risk factor leading to atherosclerotic cardiovascular disease (ASCVD). Treatment with lifestyle modification and lipid-lowering agents has been shown to reduce ASCVD morbidity and mortality. Objectives To explore the level of dyslipidemia control among patients followed in family medicine (FM) clinics and describe the prescribing pattern of lipid-lowering agents. Materials and methods This is a chart review cross-sectional observational study conducted over 382 patients who were followed in FM clinics at King Abdulaziz Medical City for National Guard, Riyadh, Saudi Arabia, from January 2016 to January 2019. The data were extracted from the electronic medical record system (BESTCare) and analyzed using Statistical Package for the Social Sciences (SPSS), version 23 (IBM Corp., Armonk, NY) to look for the association. Result All patients had a reduction in their lipid parameters over the three years

follow-up period. The mean low-density lipoprotein cholesterol (LDL-C) for the total sample was (2.783 ± 0.850) mmol/L. 82.1% were using a statin alone, 6% were using statin plus fenofibrate, and 12.8% were switched from one statin to another. Those who had statin plus fenofibrate and those switched from one statin to another had the most reduction in their LDL, TC, and TG. Conclusion Most of the patients visiting the Ministry of National Guard - Health Affairs (MNG-HA), Riyadh, Saudi Arabia, showed a continuous reduction in their lipid profile over the follow-up period; with better control for high-risk patients. Many factors may have contributed to the reduction, like the number of clinic visits, dietician, and health educator visits, along with the type of medication used.

[17] *Bouabdallaoui N, Tardif JC*. **Colchicine in the Management of Acute and Chronic Coronary Artery Disease**. Current cardiology reports 2021; 23:120.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34269908
ABSTRACT
PURPOSE OF REVIEW: Inflammation is involved in the initiation, progression, and destabilization of atherosclerosis. Anti-inflammatory strategies aimed at reducing residual cardiovascular (CV) risk have gained increasing interest in addition to the traditional management of risk factors. Colchicine is a potent anti-inflammatory therapy that affects the inflammasome and other targets. We will herein review the most recent evidence regarding the usefulness of colchicine in patients with coronary artery disease (CAD). RECENT FINDINGS: Colchicine has recently been repurposed from its traditional use to a number of CV indications. The landmark COLCOT and LoDoCo2 trials have demonstrated that long-term use of colchicine was associated with a reduced rate of CV events in both acute and chronic presentations of CAD, with an overall good safety profile. Colchicine is emerging as a valuable, safe, and cost-effective therapy in addition to standard of care for the prevention of atherothrombotic events in CAD.

[18] *Deshotels MR, Virani SS, Ballantyne CM*. **Lipid Monitoring After Initiation of Lipid-Lowering Therapies: Return of Performance Measures?** Current cardiology reports 2021; 23:116.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34269897
ABSTRACT
PURPOSE OF REVIEW: The 2015 American College of Cardiology (ACC)/American Heart Association (AHA) Focused Update of Secondary Prevention Lipid Performance Measures removed low-density lipoprotein cholesterol (LDL-C) assessment as a performance measure. This review discusses the evidence supporting the importance of lipid monitoring in the secondary prevention of atherosclerotic cardiovascular disease (ASCVD). RECENT FINDINGS: The 2018 AHA/ACC Multisociety cholesterol guideline (as did the 2013 guideline) recommends a lipid panel after initiating lipid-lowering therapy to monitor adherence and medication efficacy. The 2018 guideline also recommends adding nonstatin therapy in very-high-risk ASCVD patients with LDL-C ≥70 mg/dL despite maximally tolerated statin therapy. The removal of LDL-C monitoring as a performance measure is not consistent with the 2018 cholesterol guidelines. Given the importance of monitoring lipid-lowering medication efficacy and adherence and optimally reducing LDL-C in very-high-risk patients with additional evidence-based nonstatin therapy, LDL-C assessment after initiating lipid-lowering therapy should be reinstated as a performance measure for patients with ASCVD.

[19] *Laffin LJ, Bakris GL*. **Intersection Between Chronic Kidney Disease and Cardiovascular Disease**. Current cardiology reports 2021; 23:117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34269921
ABSTRACT
PURPOSE OF REVIEW: The incidence of chronic kidney disease is increasing worldwide, and the previously decreasing incidence of cardiovascular disease has now plateaued. Understanding the intersection of both heart and kidney disease is crucial. RECENT FINDINGS: Chronic kidney disease and cardiovascular disease share common risk factors and specific pathogenic mechanisms and impact a significant segment of the population. Patients with chronic kidney disease are more likely to have cardiovascular disease than progress to end-stage kidney disease requiring renal replacement therapy. We discuss shared risk factors and mechanisms for cardiovascular and chronic kidney disease. The following also addresses contemporary cardiovascular treatment considerations in patients with chronic kidney disease with a focus on atherosclerotic cardiovascular disease and heart failure.

[20] *Magnasco L, Sepulcri C, Antonello RM et al.* **The role of PCSK9 in infectious diseases**. Curr Med Chem 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34269657
ABSTRACT
BACKGROUND: In recent years, many aspects of the physiological role of PCSK9 have been elucidated, particularly regarding its role in lipid metabolism, cardiovascular risk, and its role in innate immunity. Increasing evidence is available about the involvement of PCSK9 in the pathogenesis of viral infections, mainly HCV, and the regulation of host response to bacterial infections, primarily sepsis and septic shock. Moreover, the action of PCSK9 has been investigated as a crucial step in the pathogenesis of malaria infection and disease severity. OBJECTIVE: This paper aims to review the available published literature on the role of PCSK9 in a wide array of infectious diseases. CONCLUSION: Besides the ongoing investigation on PCSK9 inhibition among HIV-infected patients to treat HIV- and ART-related hyperlipidemia, preclinical studies indicate how PCSK9 is involved in reducing the replication of HCV. Interestingly, high plasmatic PCSK9 levels have been described in patients with sepsis. Moreover, a protective role of PCSK9 inhibition has also been proposed against dengue and SARS-CoV-2 viral infections. Finally, a loss of function in the PCSK9-encoding gene has been reported to reduce malaria infection mortality.

[21] *Rezaei A, Neshat S, Heshmat-Ghahdarijani K*. **Alterations of Lipid Profile in COVID-19: A Narrative Review**. Current problems in cardiology 2021:100907.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34272088
ABSTRACT
The COVID-19 pandemic has led to over 100 million infections and over 3 million deaths worldwide. Understanding its pathogenesis is crucial to guide prognostic and therapeutic implications. Viral infections are known to alter the lipid profile and metabolism of their host cells, similar to the case with MERS and SARS-CoV-2002. Since lipids play various metabolic roles, studying lipid profile alterations in COVID-19 is an inevitable step as an attempt to achieve better therapeutic strategies, as well as a potential prognostic factor in the course of this disease. Several studies have reported changes in lipid profile associated with COVID-19. The most frequently reported changes are a

decline in serum cholesterol and ApoA1 levels and elevated triglycerides. The hyper-inflammatory state mediated by the Cytokine storm disturbs several fundamental lipid biosynthesis pathways. Virus replication is a process that drastically changes the host cell's lipid metabolism program and overuses cell lipid resources. Lower HDL-C and ApoA1 levels are associated with higher severity and mortality rates and with higher levels of inflammatory markers. Studies suggest that arachidonic acid omega-3 derivatives might help modulate hyper-inflammation and cytokine storm resulting from pulmonary involvement. Also, statins have been shown to be beneficial when administered after COVID-19 diagnosis via unclear mechanisms probably associated with anti-inflammatory effects and HDL-C rising effects.

[22] *Bellia A, Andreadi A, Giudice L et al.* **Atherogenic Dyslipidemia on Admission Is Associated With Poorer Outcome in People With and Without Diabetes Hospitalized for COVID-19**. Diabetes Care 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34253561

ABSTRACT

OBJECTIVE: Identifying metabolic factors associated with critical disease can help to improve management of patients hospitalized for coronavirus disease 2019 (COVID-19). High triglycerides and low HDL levels characterize the atherogenic dyslipidemia closely related to insulin resistance and diabetes. We examined associations of atherogenic dyslipidemia detected on admission with outcome of COVID-19 during hospitalization. RESEARCH DESIGN AND METHODS: We retrospectively analyzed clinical reports of 118 consecutive patients hospitalized for COVID-19 in Rome, Italy, between March and May 2020. Clinical characteristics, inflammation markers, and glucose and lipid metabolism parameters at admission were collected. Critical disease was defined as in-hospital death or need for endotracheal intubation. Associations were tested using logistic regression analysis. RESULTS: Patients with critical COVID-19 (n = 43) were significantly older than those with noncritical disease (n = 75) and presented higher levels of fasting glucose, triglycerides, C-reactive protein, interleukin-6, procalcitonin, and d-dimer ($P < 0.01$ for all), whereas HDL levels were lower ($P = 0.003$). Atherogenic dyslipidemia was more frequent in patients with critical COVID-19 (46 vs. 24%, $P = 0.011$), as well as diabetes (37 vs. 19%, $P = 0.026$), and significantly associated with death or intubation (odds ratio 2.53 [95% CI 1.16-6.32], $P = 0.018$). Triglycerides were significantly associated with selected inflammatory biomarkers ($P < 0.05$ for all) and poorer outcome of COVID-19 during hospitalization in both the overall population and the subgroup with atherogenic dyslipidemia. CONCLUSIONS: Atherogenic dyslipidemia detected on admission can be associated with critical in-hospital course of COVID-19. Further investigations are needed to elucidate the hypothetical role of insulin resistance and related lipid abnormalities in severe acute respiratory syndrome coronavirus 2 pathogenesis. Assessment of lipid profile should be encouraged in patients hospitalized for COVID-19.

[23] *Da Dalt L, Castiglioni L, Baragetti A et al.* **PCSK9 deficiency rewires heart metabolism and drives heart failure with preserved ejection fraction**. European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34252181

ABSTRACT

AIMS: PCSK9 is secreted into the circulation, mainly by the liver, and interacts with low-density lipoprotein receptor (LDLR) homologous and non-homologous receptors, including CD36, thus

favouring their intracellular degradation. As PCSK9 deficiency increases the expression of lipids and lipoprotein receptors, thus contributing to cellular lipid accumulation, we investigated whether this could affect heart metabolism and function. METHODS AND RESULTS: Wild-type (WT), Pcsk9 KO, Liver conditional Pcsk9 KO and Pcsk9/Ldlr double KO male mice were fed for 20 weeks with a standard fat diet and then exercise resistance, muscle strength, and heart characteristics were evaluated. Pcsk9 KO presented reduced running resistance coupled to echocardiographic abnormalities suggestive of heart failure with preserved ejection fraction (HFpEF). Heart mitochondrial activity, following maximal coupled and uncoupled respiration, was reduced in Pcsk9 KO mice compared to WT mice and was coupled to major changes in cardiac metabolism together with increased expression of LDLR and CD36 and with lipid accumulation. A similar phenotype was observed in Pcsk9/Ldlr DKO, thus excluding a contribution for LDLR to cardiac impairment observed in Pcsk9 KO mice. Heart function profiling of the liver selective Pcsk9 KO model further excluded the involvement of circulating PCSK9 in the development of HFpEF, pointing to a possible role locally produced PCSK9. Concordantly, carriers of the R46L loss-of-function variant for PCSK9 presented increased left ventricular mass but similar ejection fraction compared to matched control subjects. CONCLUSION: PCSK9 deficiency impacts cardiac lipid metabolism in an LDLR independent manner and contributes to the development of HFpEF.

[24] *Sun H, Li Z, Song X et al.* **Revisiting the lipid paradox in ST-elevation myocardial infarction in the Chinese population: findings from the CCC-ACS project**. European heart journal. Acute cardiovascular care 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34263300

ABSTRACT

AIMS: Previous observations revealed a negative association between low-density lipoprotein cholesterol (LDL-C) and clinical outcomes following myocardial infarction, i.e., the lower level the higher mortality, which was referred to as lipid paradox. We sought to re-evaluate this association in ST-elevation myocardial infarction (STEMI) in contemporary practice. METHODS AND RESULTS: We examined the association between admission LDL-C and in-hospital mortality among 44 563 STEMI patients enrolled from 2014 to 2019 in a nationwide registry in China. A total of 43 covariates, which were temporally classified into the following three domains were used for adjustment: (i) pre-admission characteristics; (ii) percutaneous coronary intervention (PCI)-related variables; and (iii) other in-hospital medications. In-hospital mortality was 2.01% (897/44 563). When no covariate adjustment was performed, an inversely 'J-shaped' curve was observed between admission LDL-C levels and in-hospital mortality by restricted cubic spline in logistic regression, with a threshold value of <75 mg/dL that associated with increased risk for in-hospital mortality. However, a gradual attenuation for this association was noted when step-wise adjustments were performed, with the threshold values for LDL-C decreasing from 75 mg/dL to 70 mg/dL after accounting for pre-admission characteristics, further to 65 mg/dL after accounting for PCI-related variables, and finally to no statistical association after further adjustment for other in-hospital medications. CONCLUSIONS: In a nationwide registry in China, our findings do not support the lipid paradox in terms of in-hospital mortality in STEMI patients in contemporary practice. Previous findings in this scenario are possibly due to inadequate control for confounders.

[25] *Frederiksen TC, Mortensen MB, Kanstrup HL*. **Seventeen years of misdiagnosis in rare dyslipidaemia: a case report of sitosterolaemia in a young female**. European heart journal. Case reports 2021; 5:ytab188.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34268478
ABSTRACT
BACKGROUND : Sitosterolaemia is a rare, autosomal recessive dyslipidaemia with increased absorption of dietary plant sterol and often presents with hypercholesterolaemia, xanthomas, and haematologic manifestations. If left untreated, sitosterolaemia can lead to high symptomatic burden and coronary artery disease (CAD). CASE SUMMARY : We describe a case of a young female who initially presented at 4 years of age with classic manifestations of sitosterolaemia. She was misdiagnosed and treated for both juvenile arthritis and later familial hypercholesterolaemia until adulthood, when venous blood samples showed significantly elevated concentrations of plant sterols. DNA analyses showed that the patient was homozygous for a mutation in the ABCG5 gene, [c.1336C>T, p.(Arg446*)], which is known to be associated with sitosterolaemia. DISCUSSION : Sitosterolaemia presents with multiple manifestations, which can initially be misinterpreted leading to prolonged misdiagnosis. Early diagnosis is key in order to relieve symptoms and prevent CAD.

[26] *Bibi M, Ferro A, Guimarães F et al.* **When Should Statins Be Stopped?** European journal of case reports in internal medicine 2021; 8:002661.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34268273
ABSTRACT
Mycobacterium chelonae is a non-tuberculous mycobacterium that can cause skin infections in immunocompetent individuals. We report a case of skin infection by this agent in a woman with dyslipidaemia, that culminated in statin-induced rhabdomyolysis due to the combination of clarithromycin, ciprofloxacin and simvastatin. LEARNING POINTS: Skin infection with Mycobacterium chelonae is an increasing global problem among immunocompetent individuals.Statin-induced rhabdomyolysis is an important and avoidable end-result of drug-drug interaction.Inhibition of cytochrome P450 isoenzyme 3A4 and of organic anion transporting polypeptide 1B1 are two important examples of statin interference with metabolism, and clarithromycin can inhibit both.

[27] *Pareek M, Mason RP, Bhatt DL*. **Icosapent ethyl: safely reducing cardiovascular risk in adults with elevated triglycerides**. Expert opinion on drug safety 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34253137
ABSTRACT
INTRODUCTION: In patients at high cardiovascular risk, the rate of events remains elevated despite traditional, evidence-based lipid-lowering therapy. Residual hypertriglyceridemia is an important contributor to this risk. However, prior medications with triglyceride-lowering effects have not demonstrated an ability to reduce adverse clinical outcomes in the statin era. AREAS COVERED: The present review summarizes evidence and recommendations related to triglyceride-lowering therapy in the primary and secondary preventive settings. We provide an overview of findings from recent meta-analyses, important observational studies, and a detailed description of landmark trials, including the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT). We further review recommendations from current guidelines. EXPERT OPINION: Icosapent ethyl is a stable, highly purified ethyl ester of eicosapentaenoic acid that safely and effectively reduces the

risk of incident cardiovascular events in the contemporary setting. It is prescribed at a dose of 2 grams twice daily and is indicated in patients at high cardiovascular risk who have fasting or non-fasting triglyceride levels ≥150 mg/dl despite maximally tolerated statin treatment, or in individuals with triglyceride levels ≥500 mg/dl. Conversely, n-3 fatty acid medications containing a combination of eicosapentaenoic acid and docosahexaenoic acid are not indicated for reduction of cardiovascular risk and should be actively deprescribed.

[28] *Lazarte J, Hegele RA*. **Volanesorsen for treatment of familial chylomicronemia syndrome**. Expert review of cardiovascular therapy 2021; 19:685-693.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34261380

ABSTRACT

INTRODUCTION: Familial chylomicronemia syndrome (FCS) is a rare subtype of severe hypertriglyceridemia that affects ~1 in 100, 000 to 1,000,000 individuals. The major risk to health is acute pancreatitis. FCS is defined by biallelic loss-of-function mutations in one of five canonical genes that encode proteins critical to lipolysis of large triglyceride-rich lipoprotein particles. Unlike the vast majority of patients with severe hypertriglyceridemia, FCS patients lack any lipolytic capacity and are thus resistant to standard medications. AREAS COVERED: This review focuses on a mechanism that effectively reduces elevated triglyceride levels in FCS, namely interference of synthesis of apolipoprotein (apo) C-III. Volanesorsen is an antisense RNA drug administered subcutaneously that knocks down apo C-III, resulting in dramatic reductions in triglyceride levels both in FCS patients and in the wider population of subjects with severe hypertriglyceridemia. EXPERT OPINION: Volanesorsen is a highly effective treatment to reduce elevated triglycerides in FCS patients, providing proof-of-concept of the validity of targeting apo C-III. However, off target effects of volanesorsen, including thrombocytopenia, may ultimately limit its use. Nonetheless, building on the knowledge derived from the volanesorsen experience, there is intensified interest in promising newer agents that also target apo C-III but have technical modifications that limit potential off target adverse effects.

[29] *Warden BA, Duell PB*. **Evinacumab for treatment of familial hypercholesterolemia**. Expert review of cardiovascular therapy 2021; 19:739-751.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34253139

ABSTRACT

Introduction: Familial hypercholesterolemia (FH) is characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C), early onset coronary atherosclerosis, and premature death. FH is underdiagnosed and undertreated, but requires aggressive LDL-C-lowering to prevent complications. Current treatment strategies such as lifestyle modification and numerous LDL-C-lowering medications are often insufficient to achieve lipid goals in FH.Areas covered: Angiopoietin-like 3 protein (ANGPTL3) is intricately involved in lipid metabolism. Loss-of-function mutations in ANGPTL3 are associated with panhypolipidemia and reduced coronary atherosclerosis. Evinacumab, a fully human monoclonal antibody, inhibits ANGPTL3 and reduces multiple lipoprotein fractions ~50%, including LDL-C. The use of evinacumab within the FH population is described as well as its regulatory journey to an approved therapeutic.Expert opinion: Evinacumab, with its capacity to lower multiple lipoprotein fractions, particularly LDL-C, independently of LDLR function has potential to revolutionize treatment for FH patients. Current FDA-approval is only for homozygous FH (HoFH), arguably the most

impactful indication, but use in other lipid disorders is under investigation. The short-term tolerability of evinacumab is very good, with infrequent, mild, and transient adverse events; however, long-term safety data are needed. The high cost and requirement for intravenous administration may limit adoption of evinacumab, but dramatic LDL-C-lowering and need for new therapeutic options for HoFH will drive interest.

[30] *Meng F, Qiu J, Chen H et al.* **Dietary supplementation with N-3 polyunsaturated fatty acid-enriched fish oil promotes wound healing after ultraviolet B-induced sunburn in mice**. Food Sci Nutr 2021; 9:3693-3700.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34262728

ABSTRACT

N-3 polyunsaturated fatty acids (n-3 PUFA) can alleviate ultraviolet B (UVB)-induced skin cancers, but their effects on sunburn and upcoming wound healing remain controversial. This study aimed to explore the impact of n-3 PUFA-enriched fish oil (n-3 PUFA-FO) on UVB-induced sunburns and subsequent healing. Sixty C57BL/6 female mice were divided into two groups. The treated group mice were fed n-3 PUFA-FO for the entire duration of the experiment. Mice in the control group were fed a standard diet. After two weeks of n-3 PUFA-FO feeding, mice were exposed to UVB for 20 min and sacrificed 20 d later. Skin photodamage and lesion area were recorded during wound healing. Epidermal lesion thickness was quantified in hematoxylin and eosin-stained skin sections. Inflammation and macrophage polarization were assessed by qRT-PCR. Oxidative stress and antioxidant enzyme activity were quantified using specific ELISA kits. N-3 PUFA-FO feeding decreased UVB photodamage and accelerated wound healing progression, both of which were coupled with less intense inflammation and increased macrophage M2 phenotype polarization. Furthermore, n-3 PUFA-FO brought about a decrease in malondialdehyde (MDA) levels but increased the activity of catalase (CAT) and glutathione peroxidase (GP), without changing superoxide dismutase (SOD) activity. N-3 PUFA-FO protects against UVB-induced skin photodamage and promotes wound healing by modulating macrophage phenotypic polarization and antioxidant enzyme activities. N-3 PUFA-FO could be a novel therapeutic approach for both the prevention and treatment of sunburns.

[31] *Miyazaki T, Miyazaki A*. **Hypercholesterolemia and Lymphatic Defects: The Chicken or the Egg?** Frontiers in cardiovascular medicine 2021; 8:701229.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34250049

ABSTRACT

Lymphatic vessels are necessary for maintaining tissue fluid balance, trafficking of immune cells, and transport of dietary lipids. Growing evidence suggest that lymphatic functions are limited under hypercholesterolemic conditions, which is closely related to atherosclerotic development involving the coronary and other large arteries. Indeed, ablation of lymphatic systems by Chy-mutation as well as depletion of lymphangiogenic factors, including vascular endothelial growth factor-C and -D, in mice perturbs lipoprotein composition to augment hypercholesterolemia. Several investigations have reported that periarterial microlymphatics were attracted by atheroma-derived lymphangiogenic factors, which facilitated lymphatic invasion into the intima of atherosclerotic lesions, thereby modifying immune cell trafficking. In contrast to the lipomodulatory and immunomodulatory roles of the lymphatic systems, the critical drivers of lymphangiogenesis and the details of lymphatic insults

under hypercholesterolemic conditions have not been fully elucidated. Interestingly, cholesterol-lowering trials enable hypercholesterolemic prevention of lymphatic drainage in mice; however, a causal relationship between hypercholesterolemia and lymphatic defects remains elusive. In this review, the contribution of aberrant lymphangiogenesis and lymphatic cholesterol transport to hypercholesterolemic atherosclerosis was highlighted. The causal relationship between hypercholesterolemia and lymphatic insults as well as the current achievements in the field were discussed.

[32] *Yue J, Xu H, Zhou Y et al.* **Dyslipidemia Is Related to Mortality in Critical Patients With Coronavirus Disease 2019: A Retrospective Study**. Frontiers in endocrinology 2021; 12:611526.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34248834

ABSTRACT

BACKGROUND: It has been reported that dyslipidemia is related to coronavirus-related diseases. Critical patients with coronavirus disease 2019 (COVID-19) who suffered from multiple organ dysfunctions were treated in the intensive care unit (ICU) in Wuhan, China. Whether the lipids profile was associated with the prognosis of COVID-19 in critical patients remained unclear. METHODS: A retrospective study was performed in critical patients (N=48) with coronavirus disease 2019 in Leishenshan hospital between February and April 2020 in Wuhan. The parameters including lipid profiles, liver function, and renal function were collected on admission day, 2-3days after the admission, and the day before the achievement of clinical outcome. RESULTS: Albumin value and creatine kinase (ck) value were statistically decreased at 2-3 days after admission compared with those on admission day ($P<0.05$). Low density lipoprotein (LDL-c), high density lipoprotein (HDL-c), apolipoprotein A (ApoA), and apolipoprotein A (Apo B) levels were statistically decreased after admission ($P<0.05$). Logistic regression showed that HDL-c level both on admission day and the day before the achievement of clinical outcome were negatively associated with mortality in critical patients with COVID-19. Total cholesterol (TC) level at 2-3days after admission was related to mortality in critical patients with COVID-19. CONCLUSIONS: There were lipid metabolic disorders in the critical patients with COVID-19. Lower levels of HDL-c and TC were related to the progression of critical COVID-19.

[33] *Derosa G, Maffioli P, D'Angelo A, Di Pierro F*. **Nutraceutical Approach to Preventing Coronavirus Disease 2019 and Related Complications**. Frontiers in immunology 2021; 12:582556.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34262553

ABSTRACT

INTRODUCTION: Several months ago, Chinese authorities identified an atypical pneumonia in Wuhan city, province of Hubei (China) caused by a novel coronavirus (2019-nCoV or SARS-CoV-2). The WHO announced this new disease was to be known as "COVID-19". EVIDENCE ACQUISITION: Several approaches are currently underway for the treatment of this disease, but a specific cure remains to be established. EVIDENCE SYNTHESIS: This review will describe how the use of selected nutraceuticals could be helpful, in addition to pharmacological therapy, in preventing some COVID-19-related complications in infected patients. CONCLUSIONS: Even if a specific and effective cure for COVID-19 still has some way to go, selected nutraceuticals could be helpful, in addition to pharmacological therapy, in preventing some COVID-19-related complications in infected patients.

[34] *Awan ZA, Rashidi OM, Al-Shehri BA et al.* **Saudi Familial Hypercholesterolemia Patients With Rare LDLR Stop Gain Variant Showed Variable Clinical Phenotype and Resistance to Multiple Drug Regimen**. Frontiers in medicine 2021; 8:694668.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34249980

ABSTRACT

Familial hypercholesterolemia (FH), a well-known lipid disease caused by inherited genetic defects in cholesterol uptake and metabolism is underdiagnosed in many countries including Saudi Arabia. The present study aims to identify the molecular basis of severe clinical manifestations of FH patients from unrelated Saudi consanguineous families. Two Saudi families with multiple FH patients fulfilling the combined FH diagnostic criteria of Simon Broome Register, and the Dutch Lipid Clinic Network (DLCN) were recruited. LipidSeq, a targeted resequencing panel for monogenic dyslipidemias, was used to identify causative pathogenic mutation in these two families and in 92 unrelated FH cases. Twelve FH patients from two unrelated families were sharing a very rare, pathogenic and founder LDLR stop gain mutation i.e., c.2027delG (p.Gly676Alafs(*)33) in both the homozygous or heterozygous states, but not in unrelated patients. Based on the variant zygosity, a marked phenotypic heterogeneity in terms of LDL-C levels, clinical presentations and resistance to anti-lipid treatment regimen (ACE inhibitors, β-blockers, ezetimibe, statins) of the FH patients was observed. This loss-of-function mutation is predicted to alter the free energy dynamics of the transcribed RNA, leading to its instability. Protein structural mapping has predicted that this non-sense mutation eliminates key functional domains in LDLR, which are essential for the receptor recycling and LDL particle binding. In conclusion, by combining genetics and structural bioinformatics approaches, this study identified and characterized a very rare FH causative LDLR pathogenic variant determining both clinical presentation and resistance to anti-lipid drug treatment.

[35] *Deroissart J, Porsch F, Koller T, Binder CJ.* **Anti-inflammatory and Immunomodulatory Therapies in Atherosclerosis**. Handbook of experimental pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34251531

ABSTRACT

Hypercholesterolemia is a major risk factor in atherosclerosis development and lipid-lowering drugs (i.e., statins) remain the treatment of choice. Despite effective reduction of LDL cholesterol in patients, a residual cardiovascular risk persists in some individuals, highlighting the need for further therapeutic intervention. Recently, the CANTOS trial paved the way toward the development of specific therapies targeting inflammation, a key feature in atherosclerosis progression. The pre-existence of multiple drugs modulating both innate and adaptive immune responses has significantly accelerated the number of translational studies applying these drugs to atherosclerosis. Additional preclinical research has led to the discovery of new therapeutic targets, offering promising perspectives for the treatment and prevention of atherosclerosis. Currently, both drugs with selective targeting and broad unspecific anti-inflammatory effects have been tested. In this chapter, we aim to give an overview of current advances in immunomodulatory treatment approaches for atherosclerotic cardiovascular diseases.

[36] *Wang ZH, Zheng KI, Wang XD et al.* **LC-MS-based lipidomic analysis in distinguishing patients with nonalcoholic steatohepatitis from nonalcoholic fatty liver**. Hepatobiliary Pancreat Dis Int 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34256994

ABSTRACT

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is one of the main liver diseases, and its pathologic profile includes nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). However, there is no reliable non-invasive parameter in distinguishing NASH from NAFL in clinical practice. The present study was to find a non-invasive way to differentiate these two categories of NAFLD via lipidomic analysis. METHODS: Lipidomic analysis was used to determine the changes of lipid moieties in blood from 20 NAFL and 10 NASH patients with liver biopsy. Liver histology was evaluated after hematoxylin and eosin staining and Masson's trichrome staining. The profile of lipid metabolites in correlation with steatosis, inflammation, hepatocellular necroptosis, fibrosis, and NAFLD activity score (NAS) was analyzed. RESULTS: Compared with NAFL patients, NASH patients had higher degree of steatosis, ballooning degeneration, lobular inflammation. A total of 434 different lipid molecules were identified, which were mainly composed of various phospholipids and triacylglycerols. Many lipids, such as phosphatidylcholine (PC) (P-22:0/18:1), sphingomyelin (SM) (d14:0/18:0), SM (d14:0/24:0), SM (d14:0/22:0), phosphatidylethanolamine (PE) (18:0/22:5), PC (O-22:2/12:0), and PC (26:1/11:0) were elevated in the NASH group compared to those in the NAFL group. Specific analysis revealed an overall lipidomic profile shift from NAFL to NASH, and identified valuable lipid moieties, such as PCs [PC (14:0/18:2), PE (18:0/22:5) and PC (26:1/11:0)] or plasmalogens [PC (O-22:0/0:0), PC (O-18:0/0:0), PC (O-16:0/0:0)], which were significantly altered in NASH patients. In addition, PC (14:0/18:2), phosphatidic acid (18:2/24:4) were positively correlated with NAS; whereas PC (18:0/0:0) was correlated positively with fibrosis score. CONCLUSIONS: The present study revealed overall lipidomic profile shift from NAFL to NASH, identified valuable lipid moieties which may be non-invasive biomarkers in the categorization of NAFLD. The correlations between lipid moieties and NAS and fibrosis scores indicate that these lipid biomarkers may be used to predict the severity of the disease.

[37] *Fuah KW, Lim C*. **First Reported Case of Rhabdomyolysis Associated with Concomitant Use of Cyclosporin, Diltiazem, and Simvastatin**. Indian J Nephrol 2021; 31:173-175.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34267441

ABSTRACT

Rhabdomyolysis is a syndrome with a wide range of symptoms ranging from asymptomatic raised serum creatinine kinase to life-threatening metabolic disturbances and acute kidney injury. A careful history taking and high clinical suspicion on drug-drug interaction are crucial to identify the etiology of rhabdomyolysis. Here, we present a case of rhabdomyolysis due to a rare drug-to-drug interaction of simvastatin, diltiazem, and cyclosporin in a patient with IgA nephropathy. Early renal replacement therapy was initiated, and the insulting agents were withheld. Despite the metabolic disturbances were corrected, the patient succumbed to possible venous thromboembolism event during the prolonged hospital stay. Therefore, heightened awareness is required in dealing with patients with glomerulonephritis who are frequently prescribed on polypharmacy, in order to reduce unwarranted adverse events.

[38] *Nikalji R, Sen S*. **Rosuvastatin-Induced Rhabdomyolysis: A Case Report**. Indian J Nephrol 2021; 31:190-193.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34267446

ABSTRACT
Rosuvastatin is a recently approved statin and used widely across the globe for primary and secondary prevention of atherosclerotic cardiovascular heart disease. It has the highest lipid-lowering property among all statins and relatively well tolerated. Rhabdomyolysis is a rare but potentially serious adverse effect. The present report highlights the case of a patient admitted with proximal myopathy with severe rhabdomyolysis and acute kidney injury associated with life-threatening hyperkalemia. The symptoms appeared within 1 month of starting rosuvastatin. He required temporary dialysis to overcome the crisis. His myopathy and kidney injury were completely reversible after a few months of stopping the drug. In this report, we have also discussed the various risk factors for developing myopathy with statins and the importance of strict pharmacovigilance, and a greater caution among physicians while using this drug.

[39] *Eskerud I, Gerdts E, Larsen TH et al.* **Total coronary atherosclerotic plaque burden is associated with myocardial ischemia in non-obstructive coronary artery disease**. International journal of cardiology. Heart & vasculature 2021; 35:100831.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34258383
ABSTRACT
AIM: Whether the total coronary atherosclerotic plaque burden is independently associated with myocardial ischemia in non-obstructive coronary artery disease (CAD) is not well established. We aimed to test the association of total plaque burden quantified by coronary computed tomography angiography (CCTA) with myocardial ischemia in patients with chronic coronary syndrome and non-obstructive CAD. METHODS: We included 125 patients (age 62 ± 9 years, 58% women) with chronic coronary syndrome and non-obstructive CAD (stenosis < 50%) by CCTA, who were grouped according to presence or absence of myocardial ischemia by myocardial contrast stress echocardiography. Total plaque burden was quantified by CCTA as the total plaque volume in the main coronary arteries, and positive remodelling was defined as remodelling index > 1.10. RESULTS: Patients with myocardial ischemia (n = 66) had higher total plaque burden (847 ± 245 mm(3) vs. 758 ± 251 mm(3), p = 0.049) and higher left ventricular (LV) mass index (42.1 ± 9.9 g/m(2.7) vs. 37.3 ± 8.0 g/m(2.7), p = 0.004), while age, sex, prevalence of hypertension, diabetes, calcium score and positive remodelling did not differ between the groups (all p > 0.05). In multivariable regression analysis, total plaque burden remained associated with presence of myocardial ischemia (OR 1.02, 95% CI 1.00-1.04, p = 0.045) independent of age, sex, hypertension, diabetes, LV mass index, coronary calcium score and positive remodelling. CONCLUSION: Total coronary artery plaque burden by CCTA was independently associated with myocardial ischemia in patients with non-obstructive CAD. Whether plaque quantification is useful for clinical management of patients with non-obstructive CAD should be tested in prospective studies.ClinicalTrials.gov: Identifier NCT01853527.

[40] *Eisavi M, Mazaheri E, Rezapour A et al.* **The Cost-Effectiveness and Cost-Utility of Statin Drug for the Treatment of Patients with Cardiovascular Disease, A Systematic Review**. International journal of preventive medicine 2021; 12:39.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34249288
ABSTRACT

Cardiovascular diseases impose a burden of disease and economic burden on society. With regard to different drugs are used to treat cardiovascular disease; these interventions should be economically evaluated and them that the most cost-effective were selected. The aim of this study was to investigate the studies carried on the cost-effectiveness and cost-utility of statin drugs for the treatment of patients with cardiovascular disease between 2004 and 2020. Quality assessment of the articles was examined by Drummond's checklist. Given that the inclusion criteria, 26 articles included in the review. The results of this review showed that many articles related to the economic evaluation of statin drugs adhered international standards for performing economic evaluation studies. All the studies mentioned the source of effectiveness (the second criteria) and alternative options for the comparison (the third criteria). Atorvastatin and rosuvastatin drugs were the main options for the comparison in the studies. Although the results of the studies were different in some aspects, such as the type of modeling, costs items and the study perspective, they reached the same results which the use of statin drugs versus no-drug can decrease cost, cardiovascular events and deaths and increase QALY. The results were nearly different due to study design, time horizon, efficacy, and drug prices.

[41] *Ozdemir S, Ozdemir E, Birlik B, Demirdal T*. **The Value of Carotid Intima-Media Thickness in the Detection of Atherosclerosis in HIV (+) Patients Subclinical Atherosclerosis in HIV (+)**. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 2021; 30:759-764.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34271772

ABSTRACT

BACKGROUND: To evaluate the role of the traditional risk scoring system (TRSS) in detecting subclinical atherosclerosis in HIV (+) patients. STUDY DESIGN: Cohort study. PLACE AND DURATION OF STUDY: Infectious Diseases Clinic, Izmir Katip Çelebi University, Atatürk Training and Research Hospital, from March 2017 to January 2018. METHODOLOGY: The patient group was formed with 52 HIV (+) patients, aged 18-60 years, and a control group was formed with 52 HIV (-) healthy volunteers. For all groups, there was no comorbid diseases or family history. Diabetes mellitus, hypertension, chronic kidney disease and cardiovascular disease were excluded from the two groups. Carotid intima-media thickness (CIMT) measurements were performed with high resolution B mode Doppler USG and patients with subclinical atherosclerosis were identified by the presence of atheroma plaque. RESULTS: The median right CIMT measurement was 0.91 (0.73-0.97) mm and the median left CIMT was 0.90 (0.73-0.98) mm in HIV (+) patients. The median values of CIMT on right and left sides in the control group were 0.77 (0.67-0.81) mm and 0.76 (0.70-0.81) mm. Atheroma plaque was detected in 13.5% of the HIV (+) patients and in none of the control group. Subclinical atherosclerosis was found in 51.9% of HIV (+) patients and this rate was 7.7% in the HIV (-) group ($p<0.001$). There was a weak correlation between CIMT and TRSS. CONCLUSION: In this study, the scoring systems (Framingham, ACC/AHA CVHRS) that determine the risk of cardiovascular disease recommended in current practice and the results of CIMT measurements were not found to be compatible. The development of new scoring systems including CIMT testing for the determination of this risk will open important new horizons. Key Words: AIDS, Cardiovascular disease, Subclinical atherosclerosis, CIMT.

[42] *Santiago-Hernandez A, Martin-Lorenzo M, Martínez PJ et al.* **Early renal and vascular damage within the normoalbuminuria condition**. Journal of hypertension 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34261953

ABSTRACT
OBJECTIVE: A continuous association between albuminuria and cardiorenal risk exists further below moderately increased albuminuria ranges. If only based in albumin to creatinine ratio (ACR) higher than 30 mg/g, a significant percentage of individuals may be out of the scope for therapeutic management. Despite epidemiological outcomes, the identification of biochemical changes linked to early albuminuria is underexplored, and normoalbuminuric individuals are usually considered at no risk in clinical practice. Here, we aimed to identify early molecular alterations behind albuminuria development. METHODS: Hypertensive patients under renin-angiotensin system (RAS) suppression were classified as control, (ACR<10 mg/g) or high-normal (ACR=10-30 mg/g). Urinary protein alterations were quantified and confirmed by untargeted and targeted mass spectrometry. Coordinated protein responses with biological significance in albuminuria development were investigated. Immunohistochemistry assays were performed in human kidney and arterial tissue to in situ evaluate the associated damage. RESULTS: A total of 2663 identified proteins reflect inflammation, immune response, ion transport and lipids metabolism (P value≤0.01). A1AT, VTDB and KNG1 varied in high-normal individuals (P value<0.05), correlated with ACR and associated with the high-normal condition (odds ratio of 20.76, 6.00 and 7.04 were found, respectively (P value<0.001)). After 12 months, protein variations persist and aggravate in progressors to moderately increased albuminuria. At tissue level, differential protein expression was found in kidney from individuals with moderately increased albuminuria and atherosclerotic aortas for the three proteins, confirming their capacity to reflect subclinical organ damage. CONCLUSION: Early renal and vascular damage is molecularly evidenced within the normoalbuminuria condition.

[43] *Masuda R, Lodge S, Nitschke P et al.* **Integrative Modeling of Plasma Metabolic and Lipoprotein Biomarkers of SARS-CoV-2 Infection in Spanish and Australian COVID-19 Patient Cohorts**. J Proteome Res 2021; 20:4139-4152.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34251833

ABSTRACT
Quantitative plasma lipoprotein and metabolite profiles were measured on an autonomous community of the Basque Country (Spain) cohort consisting of hospitalized COVID-19 patients (n = 72) and a matched control group (n = 75) and a Western Australian (WA) cohort consisting of (n = 17) SARS-CoV-2 positives and (n = 20) healthy controls using 600 MHz (1)H nuclear magnetic resonance (NMR) spectroscopy. Spanish samples were measured in two laboratories using one-dimensional (1D) solvent-suppressed and T(2)-filtered methods with in vitro diagnostic quantification of lipoproteins and metabolites. SARS-CoV-2 positive patients and healthy controls from both populations were modeled and cross-projected to estimate the biological similarities and validate biomarkers. Using the top 15 most discriminatory variables enabled construction of a cross-predictive model with 100% sensitivity and specificity (within populations) and 100% sensitivity and 82% specificity (between populations). Minor differences were observed between the control metabolic variables in the two cohorts, but the lipoproteins were virtually indistinguishable. We observed highly significant infection-related reductions in high-density lipoprotein (HDL) subfraction 4 phospholipids, apolipoproteins A1 and A2,that have previously been associated with negative regulation of blood coagulation and fibrinolysis. The Spanish and Australian diagnostic SARS-CoV-2 biomarkers were mathematically and biologically equivalent, demonstrating that NMR-based technologies are suitable for the study of the comparative pathology of COVID-19 via plasma phenotyping.

[44] *Kidokoro T, Edamoto K*. **Improvements in Physical Fitness are Associated with Favorable Changes in Blood Lipid Concentrations in Children**. J Sports Sci Med 2021; 20:404-412.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34267579

ABSTRACT

Although accumulating evidence suggests the benefits of cardiorespiratory fitness and muscular fitness, little knowledge exists on how other physical fitness (PF) components are associated with cardiovascular disease (CVD) risk markers in children. Additionally, much of the relevant evidence is from longitudinal studies with CVD risk markers at a single time point (i.e., baseline) rather than changes in PF. The purpose of the present study was to examine whether initial 1-year changes in different performance measures of PF (i.e., endurance performance, muscular strength/endurance, flexibility, agility, and speed) can predict the subsequent changes (2-year change) in blood lipid concentrations in children. This 2-year longitudinal study included a total of 251 Japanese children (mean age 9.2 ± 0.4). PF tests were performed to comprehensively evaluate the participant's fitness levels (handgrip strength [upper body muscular strength], bent-leg sit-ups [muscular endurance], sit-and-reach [flexibility], side-step [agility], 20-meter shuttle run [endurance performance], 50-meter sprint [speed], standing long jump [lower body muscular strength], and softball throw [explosive arm strength and throwing ability]). Fasting lipid profile was assayed for triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C concentration. Multilevel linear regressions were used to examine the associations between the preceding changes (over 1-year) in PF and subsequent changes (over 2-years) in blood lipid concentrations. We also examined the simultaneous associations between 2-year changes in PF and 2-year changes in blood lipid concentrations. For boys, preceding improvement in handgrip strength was negatively associated with TG concentration (β = -0.260, p = 0.030); improvements in bent-leg sit-ups were negatively associated with clustered lipid scores (β = -0.301, p = 0.038) and non-HDL-C (β = -0.310, p = 0.044); and improvements in 50m sprinting were associated with subsequent changes in non-HDL-C (β = 0.348, p = 0.006) and LDL-C (β = 0.408, p = 0.001). For girls, improvements in handgrip strength was negatively associated with TG concentration (β = -0.306, p = 0.017); and improvements in standing long jump were negatively associated with non-HDL-C (β = -0.269, p = 0.021) and LDL-C (β = -0.275, p = 0.019). For boys and girls, there were no significant simultaneous associations between 2-year changes in PF and 2-year changes in blood lipid concentrations. In conclusion, preceding change in physical fitness in relation to change in blood lipid concentration likely reflect a physiological adaptation to growth and maturation since these associations diminished in the subsequent year.

[45] *Freedland SJ, Howard LE, Ngo A et al.* **Low Carbohydrate Diets and Estimated Cardiovascular and Metabolic Syndrome Risk in Prostate Cancer**. The Journal of urology 2021:101097ju0000000000002112.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34259565

ABSTRACT

PURPOSE: A low carbohydrate diet (LCD) was shown to suggestively slow prostate cancer (PC) growth. In non-cancer patients, LCDs improve metabolic syndrome (MetS) without weight loss. However, concerns about negative impact on cardiovascular disease (CVD) risk remain. The objective of this secondary analysis is to determine the impact of an LCD on risk of MetS and

estimated CVD risk in PC patients. MATERIALS AND METHODS: Pooled data were analyzed from two randomized trials testing LCD vs. control on 1) preventing insulin resistance after starting hormone therapy (CAPS1) and 2) slowing PC growth in recurrent PC after failed primary treatment (CAPS2). Both trials included a usual care control vs LCD intervention in which patients were instructed to limit carbohydrate intake to ≤20gram/day, and in CAPS1 only, to walk for ≥30 minutes/day for ≥5 days/week. MetS components (hypertension, high triglycerides, low HDL, central obesity and diabetes), ten-year CVD risk estimated using the Framingham Score with either BMI or lipids, and remnant cholesterol were compared between arms using mixed models adjusting for trial. RESULTS: and Conclusions: LCD resulted in a significantly reduced risk of MetS (p=0.004) and remnant cholesterol (p<0.001). Moreover, LCD resulted in significantly lower estimated CVD risk using BMI (p=0.002) over the study with no difference in estimated CVD risk using lipids (p=0.14). Limitations include small sample size, short follow-up, and inability to distinguish effects of carbohydrate restriction and weight loss. Long-term studies are needed to confirm this finding. TRIAL REGISTRATION: NCT00932672 (CAPS1); NCT01763944 (CAPS2).

[46] *Tang BL*. **Cholesterol synthesis inhibition or depletion in axon regeneration**. Neural regeneration research 2022; 17:271-276.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34269187
ABSTRACT
Cholesterol is biosynthesized by all animal cells. Beyond its metabolic role in steroidogenesis, it is enriched in the plasma membrane where it has key structural and regulatory functions. Cholesterol is thus presumably important for post-injury axon regrowth, and this notion is supported by studies showing that impairment of local cholesterol reutilization impeded regeneration. However, several studies have also shown that statins, inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase, are enhancers of axon regeneration, presumably acting through an attenuation of the mevalonate isoprenoid pathway and consequent reduction in protein prenylation. Several recent reports have now shown that cholesterol depletion, as well as inhibition of cholesterol synthesis per se, enhances axon regeneration. Here, I discussed these findings and propose some possible underlying mechanisms. The latter would include possible disruptions to axon growth inhibitor signaling by lipid raft-localized receptors, as well as other yet unclear neuronal survival signaling process enhanced by cholesterol lowering or depletion.

[47] *Macías-García D, Periñán MT, Muñoz-Delgado L et al.* **Serum lipid profile among sporadic and familial forms of Parkinson's disease**. NPJ Parkinsons Dis 2021; 7:59.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34272400
ABSTRACT
Brain cholesterol metabolism has been described as altered in Parkinson's disease (PD) patients. Serum lipid levels have been widely studied in PD with controversial results among different populations and age groups. The present study is aimed at determining if the serum lipid profile could be influenced by the genetic background of PD patients. We included 403 PD patients (342 sporadic PD patients, 30 GBA-associated PD patients, and 31 LRRK2-associated PD patients) and 654 healthy controls (HCs). Total cholesterol, HDL, LDL, and triglycerides were measured in peripheral blood. Analysis of covariance adjusting for sex and age (ANCOVA) and post hoc tests were applied to determine the differences within lipid profiles among the groups. Multivariate ANCOVA revealed

significant differences among the groups within cholesterol and LDL levels. GBA-associated PD patients had significantly lower levels of total cholesterol and LDL compared to LRRK2-associated PD patients and HCs. The different serum cholesterol levels in GBA-associated PD might be related to diverse pathogenic mechanisms. Our results support the hypothesis of lipid metabolism disruption as one of the main PD pathogenic mechanisms in patients with GBA-associated PD. Further studies would be necessary to explore their clinical implications.

[48] *Matsushita Y, Takahashi T, Asahi K et al.* **Validation of improved 24-hour dietary recall using a portable camera among the Japanese population**. Nutrition journal 2021; 20:68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34266425

ABSTRACT

BACKGROUND: The collection of weighed food records (WFR) is a gold standard for dietary assessment. We propose using the 24-h recall method combined with a portable camera and a food atlas (24hR-camera). This combination overcomes the disadvantages of the 24-h dietary recall method. Our study examined the validity of the 24hR-camera method against WFR by comparing the results. METHODS: Study subjects were 30 Japanese males, aged 31-58 years, who rarely cook and reside in the Tokyo metropolitan area. For validation, we compared the estimated food intake (24hR-camera method) and weighed food intake (WFR method). The 24hR-camera method uses digital photographs of all food consumed during a day, taken by the subjects, and a 24-h recall questionnaire conducted by a registered dietitian, who estimates food intake by comparing the participant's photographs with food atlas photographs. The WFR method involves a registered dietitian weighing each food item prepared for the subject to consume and any leftovers. Food intake was calculated for each food group and nutrient using the 24hR-camera vs. weighed methods. RESULTS: Correlation coefficients between the estimated vs. weighed food intake were 0.7 or higher in most food groups but were low in food groups, such as oils, fats, condiments, and spices. The estimated intake of vegetables was significantly lower for the 24hR-camera method compared to the WFR method. For other food groups, the percentages of the mean difference between estimated vs. weighed food intake were -22.1% to 5.5%, with no significant differences between the methods (except for algae, which had a very low estimated intake). The correlation coefficients between the two methods were 0.774 for energy, and 0.855, 0.769, and 0.763 for the macronutrients, proteins, lipids, and carbohydrates, respectively, demonstrating high correlation coefficients: greater than 0.75. The correlation coefficients between the estimated vs. weighed for salt equivalents and potassium intake were 0.583 and 0.560, respectively, but no significant differences in intake were observed. CONCLUSIONS: The 24hR-camera method satisfactorily estimated the intake of energy and macronutrients (except salt equivalents and potassium) in Japanese males and was confirmed as a useful method for dietary assessment.

[49] *Wang IE, Yi S, Block RC, Mousa SA*. **Aspirin and omega-3 polyunsaturated fatty acid use and their interaction in cardiovascular diseases and colorectal adenomas**. Nutrition research reviews 2021:1-13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34253265

ABSTRACT

Aspirin (acetylsalicylic acid, ASA) is inexpensive and is established in preventing cardiovascular disease (CVD) and colorectal adenomas. Omega-3 (n3) polyunsaturated fatty acids (PUFA),

eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have also shown benefit in preventing CVD. The combination could be an effective preventative measure in patients with such diseases. ASA and n3 PUFA reduced the risk of CVD in ASA-resistant or diabetic patients. EPA- and DHA-deficient patients also benefited the most from n3 PUFA supplementation. Synergistic effects between ASA and EPA and DHA are 'V-shaped' such that optimal ASA efficacy is dependent on EPA and DHA concentrations in blood. In colorectal adenomas, ASA (300 mg/d) and EPA reduced adenoma burden in a location- and subtype-specific manner. Low doses of ASA (75-100 mg/d) were used in CVD prevention; however, ultra-low doses (30 mg/d) can also reduce thrombosis. EPA-to-DHA ratio is also important with regard to efficacy. DHA is more effective in reducing blood pressure and modulating systemic inflammation; however, high-dose EPA can lower CVD events in high-risk individuals. Although current literature has yet to examine ASA and DHA in preventing CVD, such combination warrants further investigation. To increase adherence to ASA and n3 PUFA supplementation, combination dosage form may be required to improve outcomes.

[50] *Yetmar ZA, Chesdachai S, Kashour T et al.* **Prior Statin Use and Risk of Mortality and Severe Disease From Coronavirus Disease 2019: A Systematic Review and Meta-analysis**. Open Forum Infect Dis 2021; 8:ofab284.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34258316
ABSTRACT
BACKGROUND: Statins up-regulate angiotensin-converting enzyme 2, the receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while also exhibiting pleiotropic antiviral, antithrombotic, and anti-inflammatory properties. Uncertainties exist about their effect on the course of SARS-CoV-2 infection. We sought to systematically review the literature and perform a meta-analysis to examine the association between prior statin use and outcomes of patients with coronavirus disease 2019 (COVID-19). METHODS: We searched Ovid Medline, Web of Science, Scopus, and the preprint server medRxiv from inception to December 2020. We assessed the quality of eligible studies with the Newcastle-Ottawa quality scale. We pooled adjusted relative risk (aRRs) of the association between prior statin use and outcomes of patients with COVID-19 using the DerSimonian-Laird random-effects model and assessed heterogeneity using the I (2) index. RESULTS: Overall, 19 (16 cohorts and 3 case-control) studies were eligible, with a total of 395 513 patients. Sixteen of 19 studies had low or moderate risk of bias. Among 109 080 patients enrolled in 13 separate studies, prior statin use was associated with a lower risk of mortality (pooled aRR, 0.65 [95% confidence interval {CI}, .56-.77], I (2) = 84.1%) and a reduced risk of severe COVID-19 was also observed in 48 110 patients enrolled in 9 studies (pooled aRR, 0.73 [95% CI, .57-.94], I (2) = 82.8%), with no evidence of publication bias. CONCLUSIONS: Cumulative evidence suggests that prior statin use is associated with lower risks of mortality or severe disease in patients with COVID-19. These data support the continued use of statins medications in patients with an indication for lipid-lowering therapy during the COVID-19 pandemic.

[51] *Jakubiak GK, Osadnik K, Lejawa M et al.* **Oxidative Stress in Association with Metabolic Health and Obesity in Young Adults**. Oxidative medicine and cellular longevity 2021; 2021:9987352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34257828
ABSTRACT

INTRODUCTION: Obesity is one of the most important public health problems in the world. Among obese people, there are those who, apart from excessive body weight, do not exhibit other metabolic dysfunctions, have a lower risk of developing cardiovascular diseases (CVDs), and show lower mortality. According to the theory, they are referred as metabolically healthy obese (MHO), in contrast to metabolically unhealthy obese (MUO). Metabolic disturbances occurring with obesity have been well established to be associated with oxidative stress. AIM: The purpose of this study was to analyse the association between selected anthropometric and biochemical parameters with oxidative stress in MHO, MUO, and normal weight young adults. Material and Methods. Individuals with age between 18 and 36 years with no history of chronic diseases and use of medicaments, with or without obesity, participated in the study. Complete blood counts, biochemical measurements, and parameters of oxidative stress such as total antioxidant capacity (TAC), total oxidative status (TOS), oxidative stress index (OSI), serum concentration of malondialdehyde (MDA), ceruloplasmin, thiol groups and lipid hydroperoxides (LPH), concentration of lipofuscin (LPS) in erythrocytes, and the activity of superoxide dismutase (SOD) were measured. RESULTS: 422 patients who met the inclusion criteria were enrolled in the study. Among the study participants, 208 people (49.29%) were offspring of patients with angiographically confirmed coronary artery disease. Among the participants, 16 patients have been included in the group of metabolically healthy obese (MHO) people and 61 patients in the group of metabolically unhealthy obese (MUO) people and 345 patients had normal body weight. Significant differences between metabolically unhealthy obese and normal weight patients, as well as between women and men, have been found. CONCLUSIONS: We showed significant differences in the selected parameters of oxidative stress between metabolically unhealthy obese (MUO) individuals and young volunteers with normal body weight as well as without significant medical history.

[52] *Ma D, Jiang P, Jiang Y et al.* **Effects of Lipid Peroxidation-Mediated Ferroptosis on Severe Acute Pancreatitis-Induced Intestinal Barrier Injury and Bacterial Translocation**. Oxidative medicine and cellular longevity 2021; 2021:6644576.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34257815

ABSTRACT

Ferroptosis is a recently recognized type of regulated cell death characterized by iron- and lipid peroxidation-mediated nonapoptotic cell death. However, whether ferroptosis is involved in severe acute pancreatitis- (SAP-) induced intestinal barrier injury is unknown. The aim of this study was to investigate whether ferroptosis is involved in SAP-induced intestinal barrier injury, particularly intestinal epithelial cell (IEC) death, and determine whether the inhibition of ferroptosis would ameliorate intestinal barrier injury and prevent bacterial translocation (BT). Sodium taurocholate (5%) was retrogradely perfused into the biliopancreatic duct to establish a rat model of SAP. The rats were divided into three groups: sham operation (SO), SAP-induced intestinal barrier injury (SAP), and ferroptosis inhibitor liproxstatin-1 (SAP + Lip). Serum indexes were measured in the rats. In addition, the biochemical and morphological changes associated with ferroptosis were observed, including iron accumulation in intestinal tissue, lipid peroxidation levels, and mitochondrial shrinkage. Hematoxylin staining and eosin staining were used to assess histological tissue changes. Western blot, RT-PCR, and immunofluorescent staining were performed to analyze the expression of ferroptosis-related proteins and genes as well as tight junction. BT was detected by 16S rDNA sequencing analysis. The results indicated that ferroptosis was significantly induced in the IECs from rats with SAP and ferroptosis was mediated by lipid peroxidation. The specific lipid peroxidation of IECs clearly

upregulated ferroptosis and exacerbated intestinal barrier injury. Furthermore, treatment with liproxstatin-1 lowered the levels of serum damage markers, decreased lipid peroxidation, and alleviated intestinal and acute remote organ injury in SAP rats. In addition, inhibition of ferroptosis reduced BT. Our findings are the first to demonstrate that ferroptosis contributes to SAP-induced intestinal barrier injury via lipid peroxidation-mediated IEC death. These results suggest that ferroptosis is a potential therapeutic target for SAP-induced intestinal barrier injury.

[53] *Vukicevic P, Klisic A, Neskovic V et al.* **New Markers of Platelet Activation and Reactivity and Oxidative Stress Parameters in Patients Undergoing Coronary Artery Bypass Grafting**. Oxidative medicine and cellular longevity 2021; 2021:8915253.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34257821
ABSTRACT
OBJECTIVE: Recent studies have shown that the red cell distribution width- (RDW-) to-platelet (PLT) count ratio (i.e., RPR) and the mean platelet volume (MPV)/PLT ratio (i.e. MPR) are more sensitive markers of atherosclerosis-connected risk than RDW and PLT alone. The present study is aimed at investigating the oxidative stress status and these two new markers of platelet activation in two different heart surgery modalities: cardiopulmonary bypass (CPB) and off-pump coronary artery bypass (OPCAB). We also aimed to test the possible relationship between RPR and MPR, respectively, and the severity and complexity of atherosclerotic plaque, measured as Syntax Score. Patients and Methods. A total of 107 patients encompassed this prospective study (i.e., 60 patients in CPB group and 47 patients in OPCAB). Blood samples were drawn at several time intervals: before skin incision (t1), immediately after intervention (t2), 6 h (t3), 24 h (t4), 48 h (t5), and 96 h after cessation of the operation (t6). RESULTS: The values of RPR and MPR were similar in CPB and OPCAB before surgery and started to rise in t2 (i.e., immediately after the intervention). This increase lasted to t5 (i.e., 48 hours after the intervention), when it became the highest. After that, both markers started to regress about the 96(th) hour after the beginning of surgery. Nominal values of both indices were higher in CPB than in OPCAB in all study points after the surgery. Furthermore, a significantly higher level of antioxidative parameters (i.e., total sulfhydryl groups and paraoxonase 1) in the OPCAB group compared to the CPB group was noted at t5 study point (i.e., 48 hours after the surgery), whereas no significant difference was noted in prooxidant levels (i.e., lipid hydroperoxides and advanced oxidation protein products) between these groups at this study point. MPR and RPR correlated positively with Syntax Score at several study points after the surgery completion. Syntax Score, MPR, and RPR showed good clinical accuracy in surgery-related complication prediction ((AUC = 0.736), 95(th) CI (0.616-0.856), P = 0.003)). CONCLUSION: When combined, MPV, RDW, and platelet count, such as MPR and RPR, could be good predictors of coronary artery disease status, regarding the aspect of joint inflammation, oxidative stress, and thrombosis.

[54] *Sampietro T, Sbrana F, Dal Pino B et al.* **Acute coronary syndrome and lipid-lowering therapy in a realistic diagnostic-therapeutic care pathway**. Pharmacological research : the official journal of the Italian Pharmacological Society 2021; 171:105763.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34252553
ABSTRACT

[55] *Kajingulu FM, Lepira FB, Nkodila AN et al.* **Circulating Proprotein Convertase Subtilisin/Kexin Type 9 Levels Predict Future Cardiovascular Event Risks in Hemodialyzed Black African Patients**. Rambam Maimonides Med J 2021; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34270402

ABSTRACT
CONTEXT AND OBJECTIVE: Cardiovascular diseases are the leading cause of mortality in patients. In this context, proprotein convertase subtilisin/kexin type 9 (PCSK9) appears to be the new biomarker identified as interfering in lipid homeostasis. This study aimed to investigate the association between PCSK9, dyslipidemia, and future risk of cardiovascular events in a population of black Africans. METHODS: A cross-sectional study was conducted between August 2016 and July 2020 in six hemodialysis centers in the city of Kinshasa, Democratic Republic of the Congo. Serum PCSK9 was measured by ELISA; lipid levels of 251 chronic kidney disease grade 5 (CKD G5) hemodialysis patients and the Framingham predictive instrument were used for predicting cardiac events. RESULTS: Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG) were significantly increased in the tertile with the highest PCSK9. By contrast, high-density lipoprotein cholesterol (HDL-c) was significantly decreased in the same tertile. A strong positive and significant correlation was found between PCSK9 and TC, TG, and LDL-c. Negative and significant correlation was observed between PCSK9 and HDL-c. The levels of PCSK9, smoking, overweight, and atherogenic dyslipidemia were associated with future risks for cardiovascular events in univariate analysis. After adjustment, all these variables persisted as independent determinants of future risk for cardiovascular events. The probability of having a cardiovascular event in this population was independently associated with PCSK9 levels. Compared to the patients in the lowest PCSK9 tertile, patients with PCSK9 levels in the middle (aOR 5.9, 95% CI 2.06-17.3, P<0.001) and highest tertiles (aOR 8.9, 95% CI 3.02-25.08, P<0.001) presented a greater risk of cardiac event. CONCLUSION: Increased PCSK9 serum levels are associated with higher levels of TC, LDL-c, and TG and lower levels of HDL-c in black African hemodialysis patients. Serum PCSK9 levels in these patients predict increased risk of cardiovascular events, independent of traditional potential confounders.

[56] *Porges T, Shafat T, Sagy I et al.* **Clinical Characteristics and Prognosis of Idiopathic Acute Pancreatitis**. Rambam Maimonides Med J 2021; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34270401

ABSTRACT
OBJECTIVE: Acute pancreatitis is a serious diagnosis with an increasing incidence in the Western world. In this study we sought to investigate the incidence of idiopathic AP and to compare clinical and prognostic characteristics of idiopathic cases with cases of AP with known etiology. METHODS: In this retrospective study of adult hospitalized patients diagnosed with acute pancreatitis between 2012 and 2015, a comparison was made between admissions of patients with known etiology and those for whom no cause was found. Primary outcome was defined as composite outcome of 30-day mortality and complications. RESULTS: Among 560 admissions of 437 patients with a primary diagnosis of acute pancreatitis, the main factors identified were gallstones (51.2%) and idiopathic pancreatitis (35.9%), with alcohol ranked third at only 4.8%. Mortality rate within 30 days of hospitalization was 2.9% and within one year was 7.1%. Use of lipid-lowering, anti-hypertensive, and anti-diabetic medications was more frequent among patients with "idiopathic" disease (70%, 68%,

and 33% versus 59%, 56%, and 27%, respectively). Patients admitted with idiopathic AP, in comparison to patients with known AP etiology, had milder disease with shorter hospital stay (3 days versus 4, respectively), and less re-admission in 30 days (7.5% versus 21.2%). Idiopathic AP patients had better prognosis in terms of 30-day death and complication (HR 0.33, 95% CI 0.08-0.40, P<0.001). CONCLUSION: Idiopathic disease is common among acute pancreatitis patients; the two study groups differed in severity of disease and prognosis. Common use of medications with doubtful value suggests possible under-diagnosis of drug-induced acute idiopathic pancreatitis.

[57] *Huang K, Wen XQ, Ren N et al.* **Lipidomic profile in patients with a very high risk of atherosclerotic cardiovascular disease on PCSK9 inhibitor therapy**. Reviews in cardiovascular medicine 2021; 22:461-467.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34258913
ABSTRACT
We evaluated the lipidomic profile of patients with very high-risk atherosclerotic cardiovascular disease (ASCVD) by ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-MS). A total of 64 patients with a very high risk of ASCVD were recruited and randomLy divided into the atorvastatin group (20 mg, every night, 4 weeks) or the combined group (evolocumab, 140 mg, once every 2 weeks on top of atorvastatin (20 mg per day)). The level of serum lipids was detected before and after treatment for 4 weeks. The lipid classes of triacylglycerols, cholesteryl esters, and sphingomyelins were analyzed using an ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry system. There were 32 patients in each group. After 4 weeks of treatment, the levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in both groups and the level of lipoprotein-a (Lp-a) in the combined group were lower. In the combined treatment group, the levels of TC, LDL-C, and Lp-a decreased significantly ($P < 0.05$) after 4 weeks of treatment. Most of the lipid classes in plasma decreased in the combined group at 4 weeks, especially sphingolipids. Only 1 patient had an adverse event (a rash) in the combined group, which improved after anti-allergic treatment. PCSK9 inhibitors can rapidly and effectively reduce most lipid classes in patients with very-high-risk ASCVD.

[58] *Xi Y, Cao N, Niu L et al.* **Prevalence and treatment of high cardiovascular disease risk in Inner Mongolia, China**. Reviews in cardiovascular medicine 2021; 22:521-529.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34258921
ABSTRACT
Early identification of individuals with high risk is crucial to preventing cardiovascular disease (CVD). We aimed to determine the prevalence of high CVD risk in Inner Mongolia and to analyze the treatment of major risk factors among individuals with high CVD risk. We selected 70,380 participants aged 35-75 years in Inner Mongolia between 2015 and 2017 using multistage stratified sampling. All participants completed a questionnaire and their blood pressure, blood glucose and lipid levels, height, weight and waist circumference were measured. Participants without a history of CVD were defined as high CVD risk if the predicted 10-year risk for CVD exceeded 10%. We assessed rates of high CVD risk and the prevalence and treatment of major risk factors among individuals with high CVD risk. After excluding participants with previous CVD, 68,083 participants remained. The overall prevalence of high CVD risk was 24.96%. The age- and sex-standardized rate of high CVD risk was 22.92%. Among high-risk participants, the prevalence of risk factors was hypertension (91.9%),

dyslipidemia (54.1%), obesity (34.6%), diabetes (27.6%), and smoking (24.5%); clustering of these risk factors was common. The percentage of high-risk individuals taking antihypertensive drugs was 45.94% in those with hypertension; 27.99% of those with diabetes took hypoglycemic drugs and only 5.01% of those with dyslipidemia took lipid-lowering drugs. Control rates of hypertension, diabetes, and dyslipidemia were 1.20%, 4.43%, and 2.78%, respectively. Therefore, the prevalence of high CVD risk was elevated in Inner Mongolia, and treatment and control rates were low.

[59] *Hu M, Yang F, Huang Y et al.* **Structural insights into the mechanism of human NPC1L1-mediated cholesterol uptake**. Science advances 2021; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34272236
ABSTRACT
Niemann-Pick C1-like 1 (NPC1L1) protein plays a central role in the intestinal cholesterol absorption and is the target of a drug, ezetimibe, which inhibits NPC1L1 to reduce cholesterol absorption. Here, we present cryo-electron microscopy structures of human NPC1L1 in apo state, cholesterol-enriched state, and ezetimibe-bound state to reveal molecular details of NPC1L1-mediated cholesterol uptake and ezetimibe inhibition. Comparison of these structures reveals that the sterol-sensing domain (SSD) could respond to the cholesterol level alteration by binding different number of cholesterol molecules. Upon increasing cholesterol level, SSD binds more cholesterol molecules, which, in turn, triggers the formation of a stable structural cluster in SSD, while binding of ezetimibe causes the deformation of the SSD and destroys the structural cluster, leading to the inhibition of NPC1L1 function. These results provide insights into mechanisms of NPC1L1 function and ezetimibe action and are of great significance for the development of new cholesterol absorption inhibitors.

[60] *Sharma A, Sharma C, Raina S et al.* **A randomized open-label trial to evaluate the efficacy and safety of triple therapy with aspirin, atorvastatin, and nicorandil in hospitalised patients with SARS Cov-2 infection: A structured summary of a study protocol for a randomized controlled trial**. Trials 2021; 22:451.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34266452
ABSTRACT
OBJECTIVES: The pathophysiology of SARS-Cov-2 is characterized by inflammation, immune dysregulation, coagulopathy, and endothelial dysfunction. No single therapeutic agent can target all these pathophysiologic substrates. Moreover, the current therapies are not fully effective in reducing mortality in moderate and severe disease. Hence, we aim to evaluate the combination of drugs (aspirin, atorvastatin, and nicorandil) with anti-inflammatory, antithrombotic, immunomodulatory, and vasodilator properties as adjuvant therapy in covid- 19. TRIAL DESIGN: Single-centre, prospective, two-arm parallel design, open-label randomized control superiority trial. PARTICIPANTS: The study will be conducted at the covid centre of Dr. Rajendra Prasad Government Medical College Tanda Kangra, Himachal Pradesh, India. All SARS-CoV-2 infected patients requiring admission to the study centre will be screened for the trial. All patients >18years who are RT-PCR/RAT positive for SARS-CoV-2 infection with pneumonia but without ARDS at presentation (presence of clinical features of dyspnoea hypoxia, fever, cough, spo2 <94% on room air and respiratory rate >24/minute) requiring hospital admission and consenting to participate in the trial will be included. Patients with documented significant liver disease/dysfunction (AST/ALT > 240), myopathy and rhabdomyolysis (CPK > 5x normal), allergy or intolerance to statins, allergy or intolerance to aspirin, patients taking medications

with significant interaction with statins, prior statin use (within 30 days), prior aspirin use (within 30 days), history of active GI bleeding in past three months, coagulopathy, thrombocytopenia (platelet count < 100000/ dl), pregnancy, active breastfeeding, patient unable to take oral or nasogastric medications, patients in altered mental status, shock, acute renal failure, acute coronary syndrome, sepsis and ARDS at presentation will be excluded. INTERVENTION AND COMPARATOR: After randomization, participants in the intervention group will receive aspirin, atorvastatin, and nicorandil (Fig. 1). Atorvastatin will be prescribed as 40 mg starting dose followed by 40 mg oral tablets once daily for ten days or till hospital discharge whichever is later. Aspirin dose will be 325 starting dose followed by 75 mg once daily for ten days or till hospital discharge whichever is later. Nicorandil will be given as 10 mg starting dose followed by 5mg twice daily ten days or till hospital discharge whichever is later. All patients in the intervention and control group will receive a standard of care for covid management as per national guidelines. All patients will receive symptomatic treatment with antipyretics, adequate hydration, anticoagulation with low molecular weight heparin, intravenous remdesivir, corticosteroids (intravenous dexamethasone for 5 days or more duration if oxygen requirement increasing or inflammatory markers are raised), and oxygen support. Patients will receive treatment for comorbid conditions as per guidelines. Fig. 1 Schematic study design MAIN OUTCOMES: The patients will be followed up for outcomes during the hospital stay or for ten days whichever is longer. The primary outcome will be in-hospital mortality. Any progression to ARDS, shock, acute kidney injury, impaired consciousness, length of hospital stay, length of mechanical ventilation (invasive plus non-invasive) will be secondary outcomes. Changes in serum markers (CRP, D -dimer, S ferritin) will be other secondary outcomes. The safety endpoints will be hepatotoxicity (ALT/AST > 3x ULN; hyperbilirubinemia), myalgia-muscle ache, or weakness without creatine kinase (CK) elevation, myositis-muscle symptoms with increased CK levels (3-10) ULN, rhabdomyolysis-muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin) observed during the hospital stay. RANDOMIZATION: Computer-generated block randomization will be used to randomize the participants in a 1:1 ratio to the active intervention group A (Aspirin, Atorvastatin, Nicorandil) plus conventional therapy and control group B conventional therapy only. BLINDING (MASKING): The study will be an open-label trial. NUMBERS TO BE RANDOMIZED (SAMPLE SIZE): A total of 396 patients will participate in this study, which is randomly divided with 198 participants in each group. TRIAL STATUS: The first version of the protocol was approved by the institutional ethical committee on 1(st) February 2021, IEC /006/2021. The recruitment started on 8/4/2021 and will continue until 08/07/2021. A total of 281 patients have been enrolled till 21/5/2021. TRIAL REGISTRATION: The trial has been prospectively registered in Clinical Trial Registry - India (ICMR- NIMS): CTRI/2021/04/032648 [Registered on: 8 April 2021]. FULL PROTOCOL: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this letter serves as a summary of the key elements of the full protocol. The study protocol has been reported under the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines.