[1] *Abe M, Ozaki Y, Takahashi H et al.* **Relation of renal function to mid-term prognosis of stable angina patients with high- or low-dose pitavastatin treatment: REAL-CAD substudy**. American heart journal 2021; 240:89-100.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34174217

ABSTRACT

BACKGROUND: It has not yet been established whether higher-dose statins have beneficial effects on cardiovascular events in patients with stable coronary artery disease (CAD) and renal dysfunction. METHODS: The REAL-CAD study is a prospective, multicenter, open-label trial. As a substudy, we categorized patients by an estimated glomerular filtration rate (eGFR) as follows: eGFR ≥60 (n = 7,768); eGFR ≥45 and <60 (n = 3,176); and eGFR <45 mL/Min/1.73 m(2) (n = 1,164), who were randomized to pitavastatin 4mg or 1mg therapy. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina, and was assessed by the log-rank test and Cox proportional hazards model. RESULTS: The baseline characteristics and medications were largely well-balanced between two groups. The magnitude of low-density lipoprotein cholesterol (LDL-C) reduction at 6 months in high- and low-dose pitavastatin groups was comparable among all eGFR categories. During a median follow-up of 3.9 years, high- compared with low-dose pitavastatin significantly reduced cardiovascular events in patients with eGFR ≥60 (hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.58-0.91; P = .006), and reduced but not significant for patients with eGFR ≥45 and <60 (HR 0.85; 95% CI, 0.63-1.14; P = .27) or eGFR <45 mL/Min/1.73 m(2) (HR 0.90; 95% CI 0.62-1.33; P = .61). An interaction test of treatment by eGFR category was not significant (P value for interaction = .30). CONCLUSION: Higher-dose pitavastatin therapy reduced LDL levels and cardiovascular events in stable CAD patients irrespective of eGFR level, although the effect on events appeared to be numerically lower in patients with lower eGFR.

[2] *Falkenhain K, Roach LA, McCreary S et al.* **Effect of carbohydrate-restricted dietary interventions on LDL particle size and number in adults in the context of weight loss or weight maintenance: a systematic review and meta-analysis**. The American journal of clinical nutrition 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34159352

ABSTRACT

BACKGROUND: LDL particle size and number (LDL-P) are emerging lipid risk factors. Nonsystematic reviews have suggested that diets lower in carbohydrates and higher in fats may result in increased LDL particle size when compared with higher-carbohydrate diets. OBJECTIVES: This study aimed to systematically review available evidence and conduct meta-analyses of studies addressing the association of carbohydrate restriction with LDL particle size and LDL-P. METHODS: We searched 6 electronic databases on 4 January, 2021 for randomized trials of any length that reported on dietary carbohydrate restriction (intervention) compared with higher carbohydrate intake (control). We calculated standardized mean differences (SMDs) in LDL particle size and LDL-P between the intervention and control groups of eligible studies, and pooled effect sizes using random-effects models. We performed prespecified subgroup analyses and examined the effect of potential explanatory factors. Internal validity and publication bias were assessed using Cochrane's risk-of-bias tool and funnel plots, respectively. Studies that could not be meta-analyzed were summarized qualitatively. RESULTS: This review summarizes findings from 38 randomized trials including a total of 1785 participants. Carbohydrate-restricted dietary interventions were associated with an increase

in LDL peak particle size (SMD = 0.50; 95% CI: 0.15, 0.86; P < 0.01) and a reduction in LDL-P (SMD = -0.24; 95% CI: -0.43, -0.06; P = 0.02). The effect of carbohydrate-restricted dietary interventions on LDL peak particle size appeared to be partially explained by differences in weight loss between intervention groups and exploratory analysis revealed a shift from small dense to larger LDL subclasses. No statistically significant association was found between carbohydrate-restricted dietary interventions and mean LDL particle size (SMD = 0.20; 95% CI: -0.29, 0.69; P = 0.37). CONCLUSIONS: The available evidence indicates that dietary interventions restricted in carbohydrates increase LDL peak particle size and decrease the numbers of total and small LDL particles.This review was registered at www.crd.york.ac.uk/prospero/ as CRD42020188745.

[3] *Kuznetsov MR, Reshetov IV, Sapelkin SV et al.* **[Methods of decreasing the risk of repeat interventions in patients after arterial revascularization]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2021; 27:169-175.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34166358
ABSTRACT
Discussed in the article are the main problems related to surgical treatment of patients with peripheral artery disease, particularly taking into consideration that in the world there are from 160 to 202 million people suffering from this disease, with two thirds of such patients having signs of lesions of coronary or cerebral arteries. Vascular reconstructive interventions cannot completely eliminate the problem, since in the postoperative period there may develop cardiovascular complications related to both the limb involved as either acute or progressing chronic ischaemia and arteries of other localization (coronary, cerebral). The risk of serious cardiovascular complications in patients with a history of endured adverse ischaemic events on the part of limbs is severalfold higher. To solve these problems and decrease complications, salicylic acid is used as basic therapy. Attempts at replacing it by another drug or combined therapy with an alternative antiaggregant showed no advantages in increased risk of massive haemorrhage. On the other hand, a combination of salicylic acid with an anticoagulant at a low dose, i. e., rivaroxaban 2.5 mg twice daily as compared with acetylsalicylic acid monotherapy made it possible to significantly decrease the incidence of various cardiovascular complications in the form of myocardial infarction, stroke, adverse ischaemic events on the part of the extremity, limb amputation.

[4] *Alves AC, Azevedo S, Benito-Vicente A et al.* **LDLR variants functional characterization: Contribution to variant classification**. Atherosclerosis 2021; 329:14-21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34167030
ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolaemia (FH) is an autosomal disorder of lipid metabolism presenting with increased cardiovascular risk. LDLR mutations are the cause of disease in 90% of the cases but functional studies have only been performed for about 15% of all LDLR variants. In the Portuguese Familial Hypercholesterolemia Study (PFHS), 142 unique LDLR alterations were identified and 44 (30%) lack functional characterization. The aim of the present work is to increase evidence for variant classification by performing functional characterization of 13 LDLR missense alterations found in Portugal and in 20 other countries. METHODS: Different LDLR mutants were generated by site-directed mutagenesis and expressed in CHO-ldlA7 cells lacking endogenous expression of LDLR. To determine the effects of alterations on LDLR function, cell surface

expression, binding and uptake of FITC-LDL were assessed by flow cytometry and Western blot. RESULTS: Of the 13 variants studied 7 were shown to affect LDLR function - expression, binding or uptake, with rates lower than 60%: p.(Cys184Tyr), p.(Gly207_Ser213del); p.(His211Asp); p.(Asp221Tyr); p.(Glu288Lys); p.(Gly592Glu) and p.(Asp601Val)). The remaining 6 variants do not alter the LDLR function. CONCLUSIONS: These studies contributed to an update of these variants classification: from the 9 variants classified as variants of unknown significance, 7 have reached now a final classification and 3 variants have improved classification from likely pathogenic to pathogenic. In Portugal, an additional 55 patients received an FH definite diagnosis thanks to these studies. Since only likely pathogenic and pathogenic variants are clinically actionable, this work shows the importance of functional studies for variant classification.

[5] *Orlowski S, Mourad JJ, Gallo A, Bruckert E*. **Coronaviruses, cholesterol and statins: Involvement and application for Covid-19**. Biochimie 2021; 189:51-64.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34153377

ABSTRACT

The infectious power of coronaviruses is dependent on cholesterol present in the membranes of their target cells. Indeed, the virus enters the infected cell either by fusion or by endocytosis, in both cases involving cholesterol-enriched membrane microdomains. These membrane domains can be disorganized in-vitro by various cholesterol-altering agents, including statins that inhibit cell cholesterol biosynthesis. As a consequence, numerous cell physiology processes, such as signaling cascades, can be compromised. Also, some examples of anti-bacterial and anti-viral effects of statins have been observed for infectious agents known to be cholesterol dependent. In-vivo, besides their widely-reported hypocholesterolemic effect, statins display various pleiotropic effects mediated, at least partially, by perturbation of membrane microdomains as a consequence of the alteration of endogenous cholesterol synthesis. It should thus be worth considering a high, but clinically well-tolerated, dose of statin to treat Covid-19 patients, in the early phase of infection, to inhibit virus entry into the target cells, in order to control the viral charge and hence avoid severe clinical complications. Based on its efficacy and favorable biodisposition, an option would be considering Atorvastatin, but randomized controlled clinical trials are required to test this hypothesis. This new therapeutic proposal takes benefit from being a drug repurposing, applied to a widely-used drug presenting a high efficiency-to-toxicity ratio. Additionally, this therapeutic strategy avoids any risk of drug resistance by viral mutation since it is host-targeted. Noteworthy, the same pharmacological approach could also be proposed to address different animal coronavirus endemic infections that are responsible for heavy economic losses.

[6] *Awad K, Mohammed M, Zaki MM et al.* **Association of statin use in older people primary prevention group with risk of cardiovascular events and mortality: a systematic review and meta-analysis of observational studies**. BMC medicine 2021; 19:139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34154589

ABSTRACT

BACKGROUND: Current evidence from randomized controlled trials on statins for primary prevention of cardiovascular disease (CVD) in older people, especially those aged >75 years, is still lacking. We conducted a systematic review and meta-analysis of observational studies to extend the current evidence about the association of statin use in older people primary prevention group with risk of

CVD and mortality. METHODS: PubMed, Scopus, and Embase were searched from inception until March 18, 2021. We included observational studies (cohort or nested case-control) that compared statin use vs non-use for primary prevention of CVD in older people aged ≥ 65 years; provided that each of them reported the risk estimate on at least one of the following primary outcomes: all cause-mortality, CVD death, myocardial infarction (MI), and stroke. Risk estimates of each relevant outcome were pooled as a hazard ratio (HR) with a 95% confidence interval (CI) using the random-effects meta-analysis model. The quality of the evidence was rated using the GRADE approach. RESULTS: Ten observational studies (9 cohorts and one case-control study; n = 815,667) fulfilled our criteria. The overall combined estimate suggested that statin therapy was associated with a significantly lower risk of all-cause mortality (HR: 0.86 [95% CI 0.79 to 0.93]), CVD death (HR: 0.80 [95% CI 0.78 to 0.81]), and stroke (HR: 0.85 [95% CI 0.76 to 0.94]) and a non-significant association with risk of MI (HR 0.74 [95% CI 0.53 to 1.02]). The beneficial association of statins with the risk of all-cause mortality remained significant even at higher ages (>75 years old; HR 0.88 [95% CI 0.81 to 0.96]) and in both men (HR: 0.75 [95% CI: 0.74 to 0.76]) and women (HR 0.85 [95% CI 0.72 to 0.99]). However, this association with the risk of all-cause mortality remained significant only in those with diabetes mellitus (DM) (HR 0.82 [95% CI 0.68 to 0.98]) but not in those without DM. The level of evidence of all the primary outcomes was rated as "very low." CONCLUSIONS: Statin therapy in older people (aged ≥ 65 years) without CVD was associated with a 14%, 20%, and 15% lower risk of all-cause mortality, CVD death, and stroke, respectively. The beneficial association with the risk of all-cause mortality remained significant even at higher ages (>75 years old), in both men and women, and in individuals with DM, but not in those without DM. These observational findings support the need for trials to test the benefits of statins in those above 75 years of age.

[7] *Kim EJ, Wierzbicki AS*. **Investigating raised creatine kinase**. Bmj 2021; 373:n1486.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34162592
ABSTRACT

[8] *Döbert M, Varouxaki AN, Mu AC et al.* **Pravastatin versus Placebo in Pregnancies at High Risk of Term Preeclampsia**. Circulation 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34162218
ABSTRACT
Background: Effective screening for term preeclampsia is provided by a combination of maternal factors with measurements of mean arterial pressure, serum placental growth factor and serum soluble fms-like tyrosine kinase-1 at 35 to 37 weeks of gestation, with detection rate of about 75%, at screen positive rate of 10%. However, there is no known intervention to reduce the incidence of the disease. Methods: In this multicenter, double-blind, placebo-controlled trial, we randomly assigned 1,120 women with singleton pregnancies at high-risk of term preeclampsia to receive pravastatin, at a dose of 20 mg per day, or placebo from 35 to 37 weeks of gestation until delivery or 41 weeks. The primary outcome was delivery with preeclampsia at any time after randomization. The analysis was performed according to intention-to-treat. Results: A total of 29 women withdrew consent during the trial. Preeclampsia occurred in 14.6% (80/548) participants in the pravastatin group and in 13.6% (74/543) in the placebo group. Allowing for the effect of risk at the time of screening and participating centre, the mixed effects Cox regression showed no evidence of an effect of pravastatin; hazard ratio (statin/placebo) 1.08 (95% confidence interval: 0.78, 1.49; p=0.65). There was no evidence of

interaction between the effect of pravastatin, estimated risk of preeclampsia, previous pregnancy history, adherence and aspirin treatment. There was no significant between-group difference in the incidence of any secondary outcomes, including gestational hypertension, stillbirth, abruption, delivery of small for gestational age neonates, neonatal death or neonatal morbidity. There was no significant between-group difference in the treatment effects on serum placental growth factor and soluble fms-like tyrosine kinase-1 concentrations 1 and 3 weeks after randomization Adherence was good, with reported intake of 80% or more of the required number of tablets in 89% of participants. There were no significant between-group differences in neonatal adverse outcomes or other adverse events. Conclusions: Pravastatin in women at high risk of term preeclampsia did not reduce the incidence of delivery with preeclampsia. Clinical Trial Registration: URL: https://www.isrctn.com Unique Identifier ISRCTN16123934.

[9] *Jabor A, Vacková T, Kubíček Z et al.* **Biological variation of proprotein convertase subtilisin/kexin type 9 (PCSK9) in human serum**. Clinica chimica acta; international journal of clinical chemistry 2021; 521:59-63.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34153278
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is involved in the regulation of LDL receptors. Inhibition of PCSK9 increase uptake of LDL-particles and pathogen-associated molecular patterns (PAMPs). The aim of our study was to evaluate biological variation of serum PCSK9. METHODS: Within-subject (CV(I)) and between-subject (CV(G)) biological variations were assessed in 14 healthy volunteers in a 6-week protocol (7 samples, equidistant time intervals). Serum concentration of PCSK9 was measured by a Quantikine ELISA assay (R&D systems, Bio-Techne Ltd., UK) on a DS2 ELISA reader (Dynex Technologies GmbH, Germany). Precision (CV(A)) was assessed by duplicate measurements. Two methods with different levels of robustness were used for the estimation of CV(I), SD-ANOVA and CV-ANOVA method. We calculated the index of individuality and reference change values. The experiment was fully compliant with EFLM database checklist. RESULTS: The within-subject values of PCSK9 in healthy persons, as calculated by two statistical methods, were 23.2% (SD-ANOVA with CV(A) of 5.6%) and 26.6% (CV-ANOVA with CV(A) of 4.8%). The CV(G) was 10.9% (SD-ANOVA), index of individuality and RCV were 2.13 and 66.3%, respectively. CONCLUSIONS: The high index of individuality indicates that common reference intervals can be used to interpret serum PSCK9 values.

[10] *Li F, Li D, Yu J et al.* **Silent Myocardial Infarction and Long-Term Risk of Frailty: The Atherosclerosis Risk in Communities Study**. Clin Interv Aging 2021; 16:1139-1149.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34168437
ABSTRACT
BACKGROUND: Silent myocardial infarction (SMI) accounts for more than half of all MIs, and common risk factors and pathophysiological pathways coexist between SMI and frailty. The risk of frailty among patients with SMI is not well established. This study aimed to examine the association between SMI and frailty. METHODS AND RESULTS: This analysis included data from the Atherosclerosis Risk in Communities study. Patients without MI at baseline were eligible for inclusion. SMI was defined as electrocardiographic evidence of MI without clinical MI (CMI) after the baseline and until the fourth visit. Frailty was assessed during the fifth visit. A total of 4953 participants were

included with an average age of 52.2±5.1 years. Among these participants, 2.7% (n=135) developed SMI, and 2.9% (n=146) developed CMI. After a median follow-up time of 14.7 (14.0-15.3) years, 6.7% (n=336) of the participants developed frailty. Patients with SMI and CMI were significantly more likely to become frail than those without MI (15.6% vs 6.2%, P<0.001 and 16.4% vs 6.2%, P<0.001, respectively). After adjusting for confounders, SMI and CMI were found to be independent predictors of frailty (odds ratio [OR]=2.243, 95% confidence interval [CI]=1.307-3.850, P=0.003 and OR=2.164, 95% CI=1.259-3.721, P=0.005, respectively). The association was consistent among the subgroups of age, sex, race, diabetes, and hypertension. CONCLUSION: In conclusion, both SMI and CMI were found to be associated with a higher risk of frailty. Future studies are needed to confirm the beneficial effects of screening for SMI as well as to implement standardized preventive treatment to reduce the risk of frailty. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00005131.

[11] *Salib M, Girerd S, Girerd N et al.* **Serum markers of fibrosis, cardiovascular and all-cause mortality in hemodialysis patients: the AURORA trial**. Clinical research in cardiology : official journal of the German Cardiac Society 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34170371
ABSTRACT
BACKGROUND: Biomarkers of fibrosis are associated with outcome in several cardiovascular diseases. However, their relevance to chronic kidney disease and dialysis is uncertain, as it remains unclear how the kidneys and the dialysis procedure itself affect their elimination and degradation. We aimed to investigate the relationship of the blood levels of two markers associated with fibrosis: procollagen type I C-terminal pro-peptide (PICP) and galectin-3 (Gal-3) with mortality in dialysis patients. METHODS: Procollagen type I C-terminal pro-peptide and galectin-3 were measured at baseline in 2773 patients enrolled in the AURORA trial, investigating the effect of rosuvastatin on cardiovascular outcomes, in patients on hemodialysis, and their interaction with CV death or all-cause mortality using survival models. The added prognostic value of these biomarkers was assessed by the net reclassification improvement (NRI). RESULTS: The median follow-up period was 3.8 years. Blood concentrations of PICP and Gal-3 were significantly associated with CV death [adjusted HR per 1 SD = 1.11 (1.02-1.20) and SD = 1.20 (1.10-1.31), respectively] and all-cause mortality (all adjusted p < 0.001). PICP and Gal-3 had a synergistic effect with regard to CV death and all-cause mortality (interaction p = 0.04 and 0.01, respectively). Adding PICP, Gal-3 and their interaction on top of clinical and biological covariates, resulted in significantly improved prognostic accuracy NRI = 0.080 (0.019-0.143) for CV death. CONCLUSION: In dialysis patients, concomitant increase in PICP and Gal-3 concentrations are associated with higher rates of CV death. These results suggest that concomitantly raised PICP and Gal-3 may reflect an activated fibrogenesis relevant to risk stratification in dialysis, raising the hypothesis that anti-fibrotic therapy may be beneficial for cardiovascular protection in such patients.

[12] *Abdelmasih R, Abdelmaseih R, Reed J.* **A Rare Case of Statin-Induced Diplopia: An Often-Overlooked but Reported Side Effect**. Cureus 2021; 13:e15117.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34159019
ABSTRACT

Statins are a class of medications indicated for atherosclerotic cardiovascular diseases and dyslipidemia. Ever since their introduction, various side effects have been reported with their use. Statin-induced myopathy is a well-established side effect of the medication, ranging in severity from mild myotoxicity to fatal rhabdomyolysis, with or without an increase in creatine kinase levels. Statin-induced diplopia, ptosis, or ophthalmoplegia are very rare, but they have been reported as adverse events in a handful of cases. These adverse events typically result from the progressive weakening of the external ocular musculature or the levator palpebrae superioris muscle. In this report, we present a rare case of statin-induced diplopia in a patient who had been on atorvastatin therapy for years. We believe this report will increase awareness among physicians about such an adverse event related to statins.

[13] *Deng F, Tuomi SK, Neuvonen M et al.* **Comparative hepatic and intestinal efflux transport of statins**. Drug metabolism and disposition: the biological fate of chemicals 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34162690

ABSTRACT

Previous studies have shown that lipid-lowering statins are transported by various ATP-binding cassette (ABC) transporters. However, due to varying methods, it is difficult to compare the transport profiles of statins. Therefore, we investigated the transport of ten statins or statin metabolites by six ABC transporters using human embryonic kidney cell-derived membrane vesicles. The transporter protein expression levels in the vesicles were quantified with liquid chromatography-tandem mass spectrometry, and used to scale the measured clearances to tissue levels. In our study, apically expressed breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) transported atorvastatin, fluvastatin, pitavastatin, and rosuvastatin. Multidrug resistance-associated protein 3 (MRP3) transported atorvastatin, fluvastatin, pitavastatin, and to a smaller extent, pravastatin. MRP4 transported fluvastatin and rosuvastatin. The scaled clearances suggest that BCRP contributes to 84-90% and 82% of the total active efflux of rosuvastatin in the small intestine and the liver, respectively. For atorvastatin, the corresponding values for P-gp-mediated efflux were 32-73% and 56%, respectively. MRP3, on the other hand, may contribute to 33-38% and 35-51% of total active efflux of atorvastatin, fluvastatin, and pitavastatin in jejunal enterocytes and liver hepatocytes, respectively. These data indicate that BCRP may play an important role in limiting the intestinal absorption and facilitating the biliary excretion of rosuvastatin and that P-gp may restrict the intestinal absorption and mediate the biliary excretion of atorvastatin. Moreover, the basolateral MRP3 may enhance the intestinal absorption and sinusoidal hepatic efflux of several statins. Taken together, the data show that statins differ considerably in their efflux transport profiles. Significance Statement This study characterized and compared the transport of atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin acid, and four atorvastatin metabolites by six ABC transporters (BCRP, MRP2, MRP3, MRP4, MRP8, P-gp). Based on in vitro findings and protein abundance data, we conclude that BCRP, MRP3 and P-gp have a major impact in the efflux of various statins. Together with in vitro metabolism, uptake transport and clinical data, our findings are applicable for use in comparative systems pharmacology modelling of statins.

[14] *Shashu BA*. **The Management of Coronary Artery Disease in Ethiopia: Emphasis on Revascularization**. Ethiop J Health Sci 2021; 31:439-454.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34158796

ABSTRACT

Cardiovascular diseases are number one cause of death worldwide. Over half of the cardiovascular diseases, 51%, are due to coronary artery disease. Coronary artery disease is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial coronary arteries. Rupture of the fibrous cap of the plaque causes the majority of the deaths due to myocardial infarction. Angina pectoris is a discomfort in the chest or adjacent areas caused by myocardial ischemia usually precipitated by exertion. In acute coronary syndrome, the chest discomfort is either of low threshold or appears at rest and when it evolves on the background of established angina pectoris, the discomfort becomes more frequent and prolonged. Exercise electrocardiography which has been the most frequently used non-invasive test to diagnose obstructive coronary artery disease is currently shown to have inferior diagnostic performance compared with diagnostic imaging tests. The pivotal tests in patients presenting with clinical features of acute coronary syndrome are electrocardiography and determination of serum troponin I and/or T. Revascularization is the mainstay of treatment in patients with acute coronary syndrome. In chronic coronary syndrome, on top of optimal medical treatment, revascularization reduces mortality in:- 1) left main stenosis, 2) three-vessel coronary artery disease, particularly with ejection fraction of less than 40%, 3) two vessel disease with more than 75% stenosis of the proximal left anterior descending coronary artery disease.

[15] *Sahebkar A, Momtazi-Borojeni AA, Banach M*. **PCSK9 vaccine: so near, yet so far!** European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34151957
ABSTRACT

[16] *Moriya S, Isoda K, Dohi T, Okazaki S*. **Significant decrease in lipid core burden index following balloon dilation was associated with the leakage of cholesterol crystals in a patient: a case report**. European heart journal. Case reports 2020; 4:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34151139
ABSTRACT

BACKGROUND: Near-infrared spectroscopy (NIRS) has been used for analysis the composition of the atherosclerotic plaque in coronary arteries. However, meaning of significant decrease in max lipid core burden index at 4 mm (max LCBI(4mm)) during percutaneous coronary intervention (PCI) is poorly understood. CASE SUMMARY: A 64-year-old male with unstable angina underwent coronary angiography, which demonstrated a hazy tight culprit lesion in the mid-right coronary artery. Pre-intervention NIRS-intravascular ultrasound (NIRS-IVUS) and chemogram showed plaque with high lipid burden at the culprit lesion. Then, we used a distal protection device before PCI because of high max LCBI(4mm) in the lesion. After pre-dilation with a scoring balloon, repeat NIRS-IVUS interrogation revealed an almost complete disappearance of the yellow signal and decrease in max LCBI(4mm) (from 537 to 44) significantly, suggesting decrease in the lipid content of the plaque. Finally, a drug-eluting stent deployment followed by inflation of a non-compliant balloon led to an excellent result. After PCI, we detected trapped large amounts of debris on retrieval of the filter. Pathological diagnosis confirmed that trapped material was lipid-rich plaque including cholesterol crystals. DISCUSSION: This is the first report directly demonstrated that significant decrease in max LCBI(4mm) at culprit lesion should be associated with the leakage of cholesterol crystals from lipid-rich plaque during PCI in the clinical patient.

[17] *Diaz-Arocutipa C, Benites-Meza JK, Chambergo-Michilot D et al.* **Efficacy and Safety of Colchicine in Post-acute Myocardial Infarction Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Frontiers in cardiovascular medicine 2021; 8:676771.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34169101

ABSTRACT

Background: Inflammation plays a key role in atherosclerotic plaque destabilization and adverse cardiac remodeling. Recent evidence has shown a promising role of colchicine in patients with coronary artery disease. We evaluated the efficacy and safety of colchicine in post-acute myocardial infarction (MI) patients. Methods: We searched five electronic databases from inception to January 18, 2021, for randomized controlled trials (RCTs) evaluating colchicine in post-acute MI patients. Primary outcomes were cardiovascular mortality and recurrent MI. Secondary outcomes were all-cause mortality, stroke, urgent coronary revascularization, levels of follow-up high-sensitivity C-reactive protein (hs-CRP), and drug-related adverse events. All meta-analyses used inverse-variance random-effects models. Results: Six RCTs involving 6,005 patients were included. Colchicine did not significantly reduce cardiovascular mortality [risk ratio (RR), 0.91; 95% confidence interval (95% CI), 0.52-1.61; p = 0.64], recurrent MI (RR, 0.87; 95% CI, 0.62-1.22; p = 0.28), all-cause mortality (RR, 1.06; 95% CI, 0.61-1.85; p = 0.78), stroke (RR, 0.28; 95% CI, 0.07-1.09; p = 0.05), urgent coronary revascularization (RR, 0.46; 95% CI, 0.02-8.89; p = 0.19), or decreased levels of follow-up hs-CRP (mean difference, -1.95 mg/L; 95% CI, -12.88 to 8.98; p = 0.61) compared to the control group. There was no increase in any adverse events (RR, 0.97; 95% CI, 0.89-1.07; p = 0.34) or gastrointestinal adverse events (RR, 2.49; 95% CI, 0.48-12.99; p = 0.20). Subgroup analyses by colchicine dose (0.5 vs. 1 mg/day), time of follow-up (<1 vs. ≥1 year), and treatment duration (≤30 vs. >30 days) showed no changes in the overall findings. Conclusion: In post-acute MI patients, colchicine does not reduce cardiovascular or all-cause mortality, recurrent MI, or other cardiovascular outcomes. Also, colchicine did not increase drug-related adverse events.

[18] *Provenzano M, Pelle MC, Zaffina I et al.* **Sodium-Glucose Co-transporter-2 Inhibitors and Nephroprotection in Diabetic Patients: More Than a Challenge**. Frontiers in medicine 2021; 8:654557.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34150796

ABSTRACT

Diabetic nephropathy is the most common cause of end-stage renal disease worldwide. Control of blood glucose and blood pressure (BP) reduces the risk of developing this complication, but once diabetic nephropathy is established, it is then only possible to slow its progression. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a novel class of oral hypoglycemic agents that increase urinary glucose excretion by suppressing glucose reabsorption at the renal proximal tubule. SGLT2is lower glycated hemoglobin (HbA1c) without increasing the risk of hypoglycemia, induce weight loss and improve various metabolic parameters including BP, lipid profile, albuminuria and uric acid. Several clinical trials have shown that SGLT2is (empagliflozin, dapagliflozin canagliflozin, and ertugliflozin) improve cardiovascular and renal outcomes and mortality in patients with type 2 diabetes. Effects of SGLT2is on the kidney can be explained by multiple pathways. SGLT2is may improve renal oxygenation and intra-renal inflammation thereby slowing the progression of kidney function decline. Additionally, SGLT2is are associated with a reduction in glomerular hyperfiltration,

an effect which is mediated by the increase in natriuresis, the re-activation of tubule-glomerular feedback and independent of glycemic control. In this review, we will focus on renal results of major cardiovascular and renal outcome trials and we will describe direct and indirect mechanisms through which SGLT2is confer renal protection.

[19] *Al-Kuraishy HM, Al-Gareeb AI, Samy OM*. **Statin therapy improves serum Annexin A1 levels in patients with acute coronary syndrome: A case-controlled study**. Int J Crit Illn Inj Sci 2021; 11:4-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34159129
ABSTRACT
BACKGROUND: The objective of the study is to estimate the protective role of statins in patients with acute coronary syndrome (ACS) through modulation of annexin A1 (AnxA1) serum levels. METHODS: A total number of 63 patients with ACS were recruited compared with 25 healthy control subjects. The enrolments were divided into - Group (A): Patients with ACS on atorvastatin (n = 20), Group (B): Patients with ACS on rosuvastatin (n = 20), Group (C): Patients with ACS but not on statin therapy (n = 23), and Group (D): Healthy controls (n = 25). Body mass index and both systolic blood pressure and diastolic blood pressures were measured. Lipid profile, atherogenic index, cardiac risk ratio, cardiovascular risk index, and human AnxA1 level were estimated. RESULTS: AnxA1 serum level was higher in patients with ACS (3.35 ± 0.84) compared with healthy controls (1.71 ± 0.91) and nonstatin using patients (1.47 ± 0.76) (P = 0.005). CONCLUSION: AnxA1 serum level is reduced in patients with ACS compared with healthy controls. Patients with ACS on statins therapy showed a higher level of AnxA1 compared with patients with ACS but not on statin therapy.

[20] *Tinius RA, Yoho K, Blankenship MM, Maples JM*. **Postpartum Metabolism: How Does It Change from Pregnancy and What are the Potential Implications?** International journal of women's health 2021; 13:591-599.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34168507
ABSTRACT
BACKGROUND: Metabolic dysfunction after pregnancy may have serious consequences for a new mother. The purpose of the study was to characterize basic changes that occur in metabolic profiles from late pregnancy through 4-6 months postpartum. A secondary purpose was to determine metabolic factors that may be contributing to postpartum weight retention. METHODS: Participants (n=25) came in for 2 visits: late pregnancy (~34 weeks gestation) and postpartum (4-6 months). Resting metabolic rate (RMR), respiratory quotient (RQ), and substrate oxidation values were assessed for 15 minutes during fasted conditions. Blood was drawn and skinfold anthropometry was performed to assess additional outcomes (inflammation, insulin resistance, lipid profiles, body composition). The participants completed a number of surveys that examined other lifestyle and demographic data of interest. At the postpartum visit, additional assessments regarding sleep and breastfeeding habits were administered. RESULTS: RMR was lower during postpartum (1517.2±225.1 kcal/day) compared to pregnancy (1867.9±302.6 kcal/day) ($p<0.001$), and remained lower when expressing RMR per kg body weight (postpartum: 22.3±2.7 vs pregnant: 23.7±3.4 kcal/kg, ($p=0.034$). Relative RMR (RMR per kg body weight) was negatively correlated to insulin resistance (HOMA-IR) during postpartum ($r=-.463$, $p=0.034$). Maternal HOMA-IR, inflammation (CRP), triglycerides (TAG), and carbohydrate oxidation were all positively correlated to postpartum

weight retention (HOMA-IR: r=0.617, p=0.004; CRP: r=0.477, p=0.039, TAG: r=0.463, p=0.040; Carbohydrate Oxidation: (r=0.469, p=0.018). CONCLUSION: Metabolic rate is lower during postpartum compared to pregnancy, and may be connected to insulin resistance. Maternal insulin resistance, inflammation, blood lipids, and substrate metabolism are all related to postpartum weight retention.

[21] *Black DM, Miller M, Heinonen TM, Zhang G*. **Advancing Beyond Failed HDL Clinical Trials to Pharmacogenetic Studies of ADCY9 and CETP inhibition**. Journal of cardiovascular pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34173811
ABSTRACT
Atherosclerosis has been effectively avoided with many therapies that lower LDL-cholesterol. However significant cardiovascular burden remains. The effect of raising HDL has been confounded by other factors (such as lowering triglycerides or LDL), and unsuccessful when attempting to solely increase HDL. Reviewing the available data, the failures of prior strategies may reflect the complexity of HDL in human metabolism, as well as the heterogeneity of human genetics. dal-GenE (NCT02525939) represents the first large cardiovascular outcomes study to utilize a selective genomic test to identify the target population most likely to receive therapeutic benefit and utilizes a cholesterol ester transfer protein (CETP) inhibitor, dalcetrapib. Both the CETP target and the ADCY9 polymorphism identified by the diagnostic test are based on inheritance and an evolving understanding of inborn risk. Selective treatment of sub-populations may be the key to the conundrum of HDL as an actionable risk factor.

[22] *Russo V, Silverio A, Scudiero F et al.* **Preadmission Statin Therapy and Clinical Outcome in Hospitalized Patients With COVID-19: An Italian Multicenter Observational Study**. Journal of cardiovascular pharmacology 2021; 78:e94-e100.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34173802
ABSTRACT
Statin therapy has been recently suggested as possible adjuvant treatment to improve the clinical outcome in patients with coronavirus disease 2019 (COVID-19). The aim of this study was to describe the prevalence of preadmission statin therapy in hospitalized patients with COVID-19 and to investigate its potential association with acute distress respiratory syndrome (ARDS) at admission and in-hospital mortality. We retrospectively recruited 467 patients with laboratory-confirmed COVID-19 admitted to the emergency department of 10 Italian hospitals. The study population was divided in 2 groups according to the ARDS diagnosis at admission and in-hospital mortality. A multivariable regression analysis was performed to assess the risk of ARDS at admission and death during hospitalization among patients with COVID-19. A competing risk analysis in patients taking or not statins before admission was also performed. ARDS at admission was reported in 122 cases (26.1%). There was no statistically significant difference for clinical characteristics between patients presenting with and without ARDS. One hundred seven patients (18.5%) died during the hospitalization; they showed increased age (69.6 ± 13.1 vs. 66.1 ± 14.9; P = 0.001), coronary artery disease (23.4% vs. 12.8%; P = 0.012), and chronic kidney disease (20.6% vs. 11.1%; P = 0.018) prevalence; moreover, they presented more frequently ARDS at admission (48.6% vs. 19.4%; P < 0.001). At multivariable regression model, statin therapy was not associated neither with ARDS at

admission nor with in-hospital mortality. Preadmission statin therapy does not seem to show a protective effect in severe forms of COVID-19 complicated by ARDS at presentation and rapidly evolving toward death.

[23] *Liu QK*. **Triglyceride-lowering and anti-inflammatory mechanisms of omega-3 polyunsaturated fatty acids for atherosclerotic cardiovascular risk reduction**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34172393
ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death globally. Omega-3 polyunsaturated fatty acids (PUFAs) including eicosapentaenoic acid and docosahexaenoic acid have been extensively studied as both dietary supplement and pharmaceutical agent for the prevention of ASCVD. Epidemiological and retrospective studies have long shown the inverse relationship of omega-3 PUFA consumption and ASCVD event but results of previous large randomized controlled trials have not consistently shown the same effect. Meta-analysis and a recent clinical trial using a high dose of eicosapentaenoic acid showed convincing protective effects of omega-3 PUFAs on ASCVD. Emerging evidence shows that both chronic inflammation and hypertriglyceridemia increase the risk of atherosclerosis. Amelioration of the inflammatory process and reduction of hypertriglyceridemia provide two mechanisms on the prevention and management of ASCVD, and agents with both of these effects are more potent and desirable. Omega-3 PUFAs exert anti-hypertriglyceridemia effect, ameliorate inflammation, and maintain the resolution of inflammation homeostasis pleiotropically through multiple molecular and cellular mechanisms. This review presents the pathophysiology of atherosclerosis, the mechanisms of omega-3 PUFAs on the reduction of the atherosclerotic risk, and the current clinical utilities of omega-3 PUFAs on the prevention of ASCVD.

[24] *Rubino J, MacDougall DE, Sterling LR et al.* **Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/kexin type 9 inhibitor therapy: A randomized, controlled trial**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34172394
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) lower low-density lipoprotein cholesterol (LDL-C) in patients with hypercholesterolemia. However, some patients receiving PCSK9i therapy might require additional lipid-lowering therapy (LLT) to reach LDL-C goals. Bempedoic acid is an oral, once-daily, ATP-citrate lyase inhibitor that significantly lowers LDL-C in patients with hypercholesterolemia when given alone or as add-on therapy to statins and/or ezetimibe. OBJECTIVE: Assess safety and efficacy of bempedoic acid added to PCSK9i (evolocumab) background therapy in patients with hypercholesterolemia. METHODS: This phase 2, randomized, double-blind, placebo-controlled study was conducted in three phases: 1.5-month screening/washout period including discontinuation of all LLTs, a 3-month period wherein patients initiated background PCSK9i therapy, and a 2-month treatment period in which patients were randomized 1:1 to receive bempedoic acid 180 mg or placebo once daily while continuing PCSK9i therapy. RESULTS: Of 59 patients randomized, 57 completed the study. Mean baseline LDL-C after 3 months of PCSK9i background therapy was 103.1 ± ±30.4 mg/dL. Bempedoic acid added to background PCSK9i therapy significantly lowered LDL-C by 30.3% ($P < .001$) vs placebo. Compared

with placebo, bempedoic acid significantly lowered apolipoprotein B, non-high-density lipoprotein cholesterol, and total cholesterol (nominal P < .001 for all), and high-sensitivity C-reactive protein (P = .029). When added to background PCSK9i therapy, the safety profile of bempedoic acid was comparable to that observed for placebo. CONCLUSIONS: When added to a background of PCSK9i therapy, bempedoic acid significantly lowered LDL-C levels with a safety profile comparable to placebo in patients with hypercholesterolemia.

[25] *Abdulfattah SY, Al-Awadi SJ*. **ApoB gene polymorphism (rs676210) and its pharmacogenetics impact on atorvastatin response among Iraqi population with coronary artery disease**. J Genet Eng Biotechnol 2021; 19:95.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34156559

ABSTRACT

BACKGROUND: Drug response is below genetic influence, proven by the genetic variants. Pharmacogenetics trials are performed in many diseases, including coronary artery disease. This study was designed to determine the genetic polymorphism (rs676210) Pro2739leu G > A in the lipid metabolism-related gene (ApoB gene) and its pharmacogenetic role in the response to atorvastatin drug in a sample of Iraqi population with coronary artery disease (CAD). RESULTS: Significant differences of genotype distribution in CAD patients and controls were observed in ApoB(+8216) in Iraqi population from Hardy Weinberg Analysis. It also found that dramatic difference of low-density lipoprotein (LDL-C) level in response to 40 mg/day of atorvastatin therapy, the minor allele (A) observed a greater LDL-C lowering than the wild type allele (G). In ANOVA analysis, the result showed that the rs676210, Pro2739Leu, in ApoB gene increased non significantly, but gradually in plasma level of total cholesterol (TC), triglyceride (TG), very low-density lipoprotein (VLDL), and oxidize low-density lipoprotein (oxLDL) in the order of genotype AA, GA, and GG in response to 40 mg atorvastatin. CONCLUSION: We found the results highlighted the function of the rs676210, Pro2739Leu, in the ApoB gene in CAD etiology, and the findings support this variant's impact in predicting the response of (LDL-C) to 40 mg of atorvastatin therapy. ApoB gene polymorphism (rs676210, Pro2739Leu), specifically the AA genotype, may help to identify individuals who will profit from atorvastatin's lowering effects.

[26] *Kupferminc MJ, Kliger C, Rimon E et al.* **Pravastatin is useful for prevention of recurrent severe placenta-mediated complications - a pilot study**. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2021:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34154497

ABSTRACT

BACKGROUND: Preeclampsia with severe features and other severe placenta-mediated complications may be life threatening to mother and fetus, especially when they are recurrent. Recurrence of pregnancy complications is common, however, when combined treatment with low molecular weight heparin and low dose aspirin fails, there are not any proven therapeutic options for prevention of recurrence of obstetrical complications. OBJECTIVE: We aimed to determine the impact of adding pravastatin to low molecular weight heparin and low dose aspirin for improving pregnancy outcome in women with severe recurrent placenta-mediated complications. DESIGN: A retrospective study of 32 women with severe recurrent placenta-mediated complications

(preeclampsia with severe features, placental abruption, severe intrauterine growth retardation or intra uterine fetal death) in spite of treatment with low molecular weight heparin and low dose aspirin in previous pregnancy. All women were treated in the index pregnancy with 20 mg pravastatin starting at 12 weeks, with low molecular weight heparin and low dose aspirin. Antiphospholipid syndrome was evident for 10 of the 32 women. RESULTS: In the index pregnancy, only one woman had recurrence of severe placenta-mediated complications. Gestational age at delivery in the index pregnancy compared to previous pregnancy when women were treated with low molecular weight heparin and low dose aspirin was 36.5 ± 1.7 vs. 32 ± 3.6 weeks, and mean birth weight 2691 ± 462 vs. 1436 ± 559 grams, compared to previous pregnancy when women were treated with low molecular weight heparin and low dose aspirin ($p < .001$ for both). Of the 17 women with previous preeclampsia with severe features, 15 had no recurrence of preeclampsia and 2 women had mild preeclampsia at term. Of the 8 women with previous severe intrauterine growth retardation, all delivered at significant higher gestational age compare to previous pregnancy, [37.0 ± 1 vs. 34 ± 3 weeks, ($p < .05$)] with higher mean birth-weight [2648 ± 212 vs. 1347 ± 465 grams, ($p = .05$)]. Of the 3 women with previous placental abruption, one delivered at 32 weeks due to non-reassuring fetal heart monitoring, one woman was delivered at 36 weeks due to mild preeclampsia, and one woman underwent elective induction of labor at 37 weeks with no intrauterine growth retardation. Of the 4 women with previous recurrent intrauterine fetal death, 3 women delivered at 37 weeks after elective induction, and one woman at 30 weeks with a birthweight of 960 grams due to severe intrauterine growth retardation. CONCLUSIONS: Additive treatment with pravastatin to low molecular weight heparin and low dose aspirin may be a promising option in cases of previous severe recurrent placenta-mediated complications.

[27] *Morin R, Mauger JF, Amaratunga R, Imbeault P*. **The effect of acute intermittent hypoxia on postprandial triglyceride levels in humans: a randomized crossover trial**. Journal of translational medicine 2021; 19:268.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34158069

ABSTRACT

BACKGROUND: Obstructive sleep apnea (OSA), a sleep disorder frequently observed in individuals living with obesity, consists of repeated involuntary breathing obstructions during sleep, leading to intermittent hypoxia (IH). In humans, acute continuous hypoxia slightly increases plasma triglycerides (TG). However, no study yet compared the postprandial TG response of individuals with or without OSA under intermittent hypoxia. METHODS: Using a randomized crossover design, seven individuals diagnosed with moderate OSA and eight healthy individuals without OSA were given a meal after which they were exposed for 6 h to normoxia or intermittent hypoxia (e.g., 15 hypoxic events per hour). Blood lipid levels were measured hourly during each session. RESULTS: Peak postprandial TG concentrations tended to be 22% higher under IH irrespective of group (IH × time interaction, $p = 0.068$). This trend toward higher total plasma TG was attributable to increased levels of denser TG-rich lipoproteins such as very low-density lipoproteins (VLDL) and chylomicrons (CM) remnants. Irrespective of group, the postprandial TG concentrations in denser TG-rich lipoproteins was 20% higher under IH (IH × time interaction, $p = 0.036$), although IH had virtually no impact on denser TG-rich lipoprotein concentrations in the OSA group. CONCLUSION: Acute intermittent hypoxia tends to negatively affect postprandial TG levels in healthy individuals, which is attributable to an increase in

denser TG-carrying lipoprotein levels such as VLDL and CM remnants. This altered postprandial TG response to acute intermittent hypoxia was not observed in individuals with OSA.

[28] *Li K, Fan F, Zheng B et al.* **Associations between remnant lipoprotein cholesterol and central systolic blood pressure in a Chinese community-based population: a cross-sectional study**. Lipids in health and disease 2021; 20:60.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34174876

ABSTRACT

BACKGROUND: The lipid profile is reportedly related to peripheral blood pressure or pulse wave velocity. However, no studies have investigated the associations between lipid parameters, especially remnant lipoprotein cholesterol (RLP-C), and central systolic blood pressure (cSBP). METHODS: This study used baseline data of a community-based cohort in Beijing, China. Participants who had been treated with anti-hypertensive or lipid-lowering agents were excluded. RLP-C is equal to total cholesterol (TC) minus the sum of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). An Omron HEM-9000AI device was used to measure non-invasive cSBP. The associations between blood lipid profile and non-invasive cSBP were evaluated using multivariable regression models. RESULTS: The 5173 included participants were 55.0 ± 8.5 years old; 35.7% (1845) of participants were men. Increased cSBP was significantly associated with increased TC, LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), triglyceride (TG), and RLP-C but with decreased HDL-C, even after adjusting for possible covariates. When simultaneously entering individual pairs of RLP-C and other blood lipid parameters into the multivariable regression model, RLP-C remained significantly associated with cSBP, even after adjusting for other lipids. Compared with participants who had RLP-C levels in the first quartile (Q1), cSBP for those with RLP-C in Q4 was increased to 4.57 (95% confidence interval [CI]: 3.08-6.06) mmHg after adjusting for LDL-C, 4.50 (95%CI: 2.98-6.02) mmHg after adjusting for TC, 3.91 (95%CI: 1.92-5.89) mmHg after adjusting for TG, 5.15 (95%CI: 3.67-6.63) mmHg after adjusting for HDL-C, and 4.10 (95%CI: 2.36-5.84) mmHg after adjusting for non-HDL-C. CONCLUSIONS: Increased blood RLP-C level was significantly associated with higher cSBP in a Chinese population, independently of other lipids, which indicates its importance in individual cardiovascular risk assessment.

[29] *Jacome Sanz D, Saralahti AK, Pekkarinen M et al.* **Proprotein convertase subtilisin/kexin type 9 regulates the production of acute-phase reactants from the liver**. Liver international : official journal of the International Association for the Study of the Liver 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34174143

ABSTRACT

BACKGROUND & AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) controls blood cholesterol levels by fostering the LDL receptor (LDLR) degradation in hepatocytes. Additionally, PCSK9 has been suggested to participate in immunoregulation by modulating cytokine production. We studied the immunological role of PCSK9 in Streptococcus pneumoniae bacteraemia in vivo and in a human hepatocyte cell line. METHODS: CRISPR/Cas9 mutagenesis was utilized to create pcsk9 knock-out (KO) zebrafish, which were infected with S pneumoniae to assess the role of PCSK9 for the survival of the fish and in the transcriptomic response of the liver. The direct effects of PCSK9 on the expression of acute-phase reaction (APR) genes were studied in HepG2 cells. RESULTS: The pcsk9 KO zebrafish lines (pcsk9(tpu-13) and pcsk9(tpu-2,+15)) did not show developmental defects

or gross phenotypical differences. In the S pneumoniae infected zebrafish, the mortality of pcsk9 KOs was similar to the controls. A liver-specific gene expression analysis revealed that a pneumococcal challenge upregulated pcsk9, and that the pcsk9 deletion reduced the expression of APR genes, including hepcidin antimicrobial peptide (hamp) and complement component 7b (c7b). Accordingly, silencing PCSK9 in vitro in HepG2 cells using small interfering RNAs (siRNAs) decreased HAMP expression. CONCLUSIONS: We demonstrate that PCSK9 is not critical for zebrafish survival in a systemic pneumococcal infection. However, PCSK9 deficiency was associated with the lower expression of APR genes in zebrafish and altered the expression of innate immunity genes in a human hepatocyte cell line. Overall, our data suggest an evolutionarily conserved function for PCSK9 in APR in the liver.

[30] *DiNicolantonio J, O'Keefe JH*. **Does Fish Oil Reduce the Risk of Cardiovascular Events and Death? Recent Level 1 Evidence Says Yes: PRO: Fish Oil is Useful to Prevent or Treat Cardiovascular Disease**. Missouri medicine 2021; 118:214-218.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34149080
ABSTRACT
Over the past decade there has been a considerable debate whether fish oil supplementation works to prevent and/or treat cardiovascular disease. This is due to the fact that previous studies testing fish oil in Italy and Japan found significant reductions in all-cause mortality, sudden cardiac death, and cardiovascular events, whereas more recent studies have in general been considered negative. We will discuss the reasons for these discrepancies and pave a better path forward when it comes to interpreting studies testing fish oil for the prevention or treatment of cardiovascular disease.

[31] *Khoukaz HB, Fay WP*. **Fish Oil Supplements for Prevention of Cardiovascular Disease: The Jury Is Still Out: CON: Fish Oil is Useful to Prevent or Treat Cardiovascular Disease**. Missouri medicine 2021; 118:219-225.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34149081
ABSTRACT
Consumption of oily fish high in omega-3 fatty acids (n-3FAs) is strongly associated with reduced risk of adverse cardiovascular events. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the n-3FAs in fish oil believed to confer its beneficial effects. Over the past two decades, multiple clinical trials have been conducted to test the hypothesis that encapsulated EPA and DHA supplements improve cardiovascular outcomes in patients with established cardiovascular disease or at risk of developing it. Over the same time period, over-the-counter fish oil supplements have become a multi-billion-dollar industry. In this article, we briefly review available clinical trial data involving EPA and DHA supplementation. Based on currently available information, we conclude that combination capsules containing EPA and DHA should not be used to reduce cardiovascular risk. Some studies suggest that EPA as stand-alone therapy decreases cardiovascular risk. Nevertheless, we advocate a restrictive approach to using EPA to improve cardiovascular outcomes.

[32] *Xiao J, Song SS, Schlick KH et al.* **Disparate trends of atherosclerotic plaque evolution in stroke patients under 18-month follow-up: a 3D whole-brain magnetic resonance vessel wall imaging study**. Neuroradiol J 2021:19714009211026920.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34159814

ABSTRACT
PURPOSE: The trend of atherosclerotic plaque feature evolution is unclear in stroke patients with and without recurrence. We aimed to use three-dimensional whole-brain magnetic resonance vessel wall imaging to quantify the morphological changes of causative lesions during medical therapy in patients with symptomatic intracranial atherosclerotic disease. METHODS: Patients with acute ischemic stroke attributed to intracranial atherosclerotic disease were retrospectively enrolled if they underwent both baseline and follow-up magnetic resonance vessel wall imaging. The morphological features of the causative plaque, including plaque volume, peak normalized wall index, maximum wall thickness, degree of stenosis, pre-contrast plaque-wall contrast ratio, and post-contrast plaque enhancement ratio, were quantified and compared between the non-recurrent and recurrent groups (defined as the recurrence of a vascular event within 18 months of stroke). RESULTS: Twenty-nine patients were included in the final analysis. No significant differences were found in plaque features in the baseline scan between the non-recurrent (n = 22) and recurrent groups (n = 7). The changes in maximum wall thickness (-13.32% vs. 8.93%, P = 0.026), plaque-wall contrast ratio (-0.82% vs. 3.42%, P = 0.005) and plaque enhancement ratio (-11.03% vs. 9.75%, P = 0.019) were significantly different between the non-recurrent and recurrent groups. Univariable logistic regression showed that the increase in plaque-wall contrast ratio (odds ratio 3.22, 95% confidence interval 1.55-9.98, P = 0.003) was related to stroke recurrence. CONCLUSION: Morphological changes of plaque features on magnetic resonance vessel wall imaging demonstrated distinct trends in symptomatic intracranial atherosclerotic disease patients with and without stroke recurrence.

[33] *Sałacka A, Boroń A, Gorący I et al.* **An association of ABCG8: rs11887534 polymorphism and HDL-cholesterol response to statin treatment in the Polish population**. Pharmacological reports : PR 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34173968

ABSTRACT
BACKGROUND: Variation in lipid changes in response to statin treatment is associated with genetic polymorphism. Sterolin-1, encoded by ABCG5, and sterolin-2, encoded by ABCG8, together form a sterol transporter. There are some reports indicating association of rs11887534 (ABCG8:c.55G>C) polymorphism with lipid concentrations, both prior to and after statin treatment. The aim of this study was to analyze both baseline plasma lipids and their concentrations in response to statin treatment with regard to ABCG8: rs11887534 polymorphism in Caucasian patients of Polish origin. METHODS: The study group consisted of 170 consecutive adult out-patients treated with atorvastatin or simvastatin for a minimum of 2 months. Concentrations of triglycerides (TG), total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) were measured before and after statin treatment. The ABCG8 polymorphism was identified by mini-sequencing genomic DNA extracted from peripheral blood leukocytes. RESULTS: There were no significant differences in regard to ABCG8 variants for baseline TG, TC, LDL-C and HDL-C as well as for TG, TC or LDL-C concentrations after statin treatment. However, patients carrying at least one C allele showed a decrease in post-statin HDL-C concentrations and the absolute and relative changes between post- and pre-statin HDL-C concentrations were negative in contrast to positive values in wild-type homozygotes. CONCLUSIONS: Our results suggest that the c.55C allele of the ABCG8: rs11887534 polymorphism might be associated with decrease in HDL-cholesterol in response to statin treatment in Polish patients.

[34] *Pawar A, Pal A, Goswami K et al.* **Molecular basis of quercetin as a plausible common denominator of macrophage-cholesterol-fenofibrate dependent potential COVID-19 treatment axis**. Results Chem 2021; 3:100148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34150487
ABSTRACT
The world's largest randomized control trial against COVID-19 using remdesivir, hydroxychloroquine, lopinavir and interferon-β1a appeared to have little or no effect on hospitalized COVID-19 patients. This has again led to search for alternate re-purposed drugs and/or effective "add-on" nutritional supplementation, which can complement or enhance the therapeutic effect of re-purposed drug. Focus has been shifted to therapeutic targets of severe acute respiratory syndrome coronavirus (SARS-CoV-2), which includes specific enzymes and regulators of lipid metabolism. Very recently, fenofibrate (cholesterol-lowering drug), suppressed the SARS-CoV-2 replication and pathogenesis by affecting the pathways of lipid metabolism in lung cells of COVID-19 patients. A preclinical study has shown synergistic effect of quercetin (a flavonoid) and fenofibrate in reducing the cholesterol content, which might be useful in COVID-19 treatment. Based on the scientific literature, use of quercetin and fenofibrate in COVID-19 seems meaningful in pharmaceutical and biomedical research, and warrants basic, experimental and clinical studies. In this article, we have summarized the contemporary findings about drug fenofibrate and its effect on membrane synthesis of COVID-19 virus along with emphasizing on possible synergistic effects of quercetin with fenofibrate.

[35] *Bivanco-Lima D, de Souza Santos I, Wang YP et al.* **Cardiovascular risk factors and major depressive disorder: a cross-sectional study in São Paulo, Brazil**. Sao Paulo medical journal = Revista paulista de medicina 2021; 139:364-371.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34161521
ABSTRACT
BACKGROUND: Cardiovascular risk factors can mediate the association between depression and cardiovascular diseases. OBJECTIVE: To evaluate cardiovascular risk factors in adult individuals with and without histories of major depression in the metropolitan region of São Paulo, Brazil. DESIGN AND SETTING: Cross-sectional study in São Paulo (SP), Brazil. METHODS: This study evaluated 423 individuals without any lifetime diagnosis of major depression and 203 individuals with a previous diagnosis of major depression (n = 626). The participants underwent a psychiatric evaluation using a structured clinical interview (SCID-1), an anthropometric evaluation and a clinical evaluation that included blood pressure measurement and assessment of fasting blood glucose, lipid profile and physical activity levels. RESULTS: Individuals with histories of major depression were more likely to be female ($P < 0.0001$). Individuals with lifetime diagnoses of major depression were more likely to be current smokers (odds ratio, OR 1.61; 95% confidence interval, CI 1.01-2.59) and to have diabetes (OR 1.79; 95% CI 1.01-3.21); and less likely to be obese (OR 0.58; 95% CI 0.35-0.94). CONCLUSION: Individuals with major depression had higher odds of presenting tobacco smoking and diabetes, and lower odds of being obese. Healthcare professionals need to be aware of this, so as to increase the rates of diagnosis and treatment in this population.

[36] *Sanz-Cuesta BE, Saver JL*. **Lipid-Lowering Therapy and Hemorrhagic Stroke Risk: Comparative Meta-Analysis of Statins and PCSK9 Inhibitors**. Stroke 2021:Strokeaha121034576.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34154390

ABSTRACT

BACKGROUND AND PURPOSE: Statins were shown to increase hemorrhagic stroke (HS) in patients with a first cerebrovascular event in 2006 (SPARCL), likely due to off-target antithrombotic effects, but continued to sometimes be used in patients with elevated HS risk due to absence of alternative medications. Recently, the PCSK9Is (proprotein convertase subtilisin kexin 9 inhibitors) have become available as a potent lipid-lowering class with potentially less hemorrhagic propensity. METHODS: We performed a systematic comparative meta-analysis assessing HS rates across all completed statin and PCSK9I randomized clinical trials with treatment >3 months, following PRISMA guidelines. In addition to HS rates across all trials, causal relation was probed by evaluating for dose-response relationships by medication (low versus high medication dose/potency) and by presence and type of preceding brain vascular events at inception (none versus ischemic stroke/transient ischemic attack versus HS). RESULTS: The systematic review identified 36 statin randomized clinical trials (204 918 patients) and 5 PCSK9I randomized clinical trials (76 140 patients). Across all patient types and all medication doses/potencies, statins were associated with increased HS: relative risk 1.15, P=0.04; PCSK9Is were not (P=0.77). In the medication dose/potency analysis, higher dose/potency statins (7 trials, 62 204 patients) were associated with magnified HS risk: relative risk, 1.53; P=0.002; higher dose/potency PCSK9Is (1 trial, 27 564 patients) were not (P=0.99). In the type of index brain vascular injury analysis for statins (5 trials, 9772 patients), prior ischemic stroke/transient ischemic attack was associated with a magnified risk of HS: relative risk, 1.43; P=0.04; and index intracerebral hemorrhage was associated with an extremely high effect estimate of risk of recurrent HS: hazard ratio, 4.06. For PCSK9Is, prior ischemic stroke/transient ischemic attack (1 trial, 5337 patients) was not associated with increased HS risk (P=0.97). CONCLUSIONS: Statins increase the risk of HS in a medication dose- and type of index brain vascular injury-dependent manner; PCSK9Is do not increase HS risk. PCSK9Is may be a preferred lipid-lowering medication class in patients with elevated HS risk, including patients with prior HS.

[37] *Soška V, Kyselák O*. **Don't we forget about biological therapy of hypercholesterolemia with PCSK9-inhibitors?** Vnitr Lek 2021; 67:138-142.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34171952

ABSTRACT

In many patients it is difficult to achieve the current very low target LDL-cholesterol levels, recommended for the prevention of atherosclerotic cardiovascular events. If statin therapy or statins in combination with ezetimibe are not sufficient, addition of PCSK9 inhibitors should be considered. PCSK9 inhibitors reduce LDL-CH by an average of 50-60 % and reduce the risk of atherosclerotic cardiovascular events. They are currently reserved for patients with atherosclerotic cardiovascular disease and for patients with familial hypercholesterolaemia, in whom despite intensive hypolipidemic therapy statins with ezetimibe the target LDL-cholesterol value is not reached. In these patients, PCSK9 inhibitors may also be indicated in case of statin intolerance.

[38] *Feysa SV, Rudakova SO*. **INFLUENCE OF COMPLEX TREATMENT ON BIOCHEMICAL BLOOD PARAMETERS OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND CONCOMITANT PRE-DIABETES**. Wiadomosci lekarskie (Warsaw, Poland : 1960) 2021; 74:986-991.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34156017

ABSTRACT

OBJECTIVE: The aim: Of this research is to evaluate laboratory changes in the liver blood tests, carbohydrate and lipid metabolism in NAFLD patients with concomitant pre-diabetes, and to study the feasibility of their complex treatment with the inclusion of omega-3 polyunsaturated fatty acids and essential phospholipids. PATIENTS AND METHODS: Materials and methods: We have examined 55 patients with non-alcoholic fatty liver disease on the background of pre-diabetes aged 40 to 75 years. Modification of lifestyle was recommended to all patients as a basic treatment. In addition, the patients were prescribed essential phospholipids in 2 capsules 3 times a day and omega-3 polyunsaturated fatty acids 1000 mg per day for 28 patients (group 1) or rosuvastatin 10 mg per day for 27 persons (group 2). The effectiveness of the treatment was evaluated in 3 months, and the long-term outcomes were evaluated in 12 months. RESULTS: Results: Under the influence of the prescribed treatment, a hypolipidemic effect was observed in both groups, but a significant decline in the activity of alanine aminotransferase and aspartate aminotransferase occurred only under the influence of a combination of essential phospholipids and omega-3 polyunsaturated fatty acids. CONCLUSION: Conclusions: Thus, the described results allow to recommend this combination of medicines to patients with non-alcoholic fatty liver disease and concomitant pre-diabetes.

[39] *Ivachevska VV*. **THE EFFECT OF COMPREHENSIVE TREATMENT OF PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN COMBINATION WITH PREDIABETES ON THE LIPID PROFILE**. Wiadomosci lekarskie (Warsaw, Poland : 1960) 2021; 74:957-760.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34156011

ABSTRACT

OBJECTIVE: The aim: To evaluate the efficiency of the proposed therapy, which included recommendations for nutrition, physical activity and treatment with rosuvastatin, omega-3 PUFA and ursodeoxycholic acid, on the indicators of the lipid profile in patients with NAFLD and prediabetes. PATIENTS AND METHODS: Materials and methods: 78 patients with impaired glucose tolerance were examined. According to the inclusion and exclusion criteria, 55 patients with prediabetes and concomitant NAFLD were included in the study. All patients underwent a comprehensive clinical examination, which included anthropometric data collection, objective examination, and venous blood sampling for laboratory tests. RESULTS: Results: The data obtained after 12 months of proposed treatment revealed a statistically significant improvement of indicators lipid profile in patients with prediabetes and NAFLD. Moreover, no significant difference between mean values of HDLC, LDLC, TG and atherogenic coefficient of almost healthy individuals and the corresponding indicators of treated patients detected. CONCLUSION: Conclusions: therapy which included recommendations for nutrition, physical activity and treatment with rosuvastatin, omega-3 PUFA and ursodeoxycholic acid significantly improved lipid metabolism in patients with prediabetes and NAFLD.

[40] *de Beer R, Outhoff K, Phulukdaree A, Soma P*. **Prevalence of SLCO1B1 single nucleotide variations and their association with hypercholesterolaemia in hypercholesterolemic patients in Gauteng, South Africa**. Xenobiotica 2021; 51:949-959.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34154510

ABSTRACT

Literature update week 25 (2021)

Statins, the standard treatment for hypercholesterolaemia, among the most widely prescribed, have been associated with side effects, including statin intolerance. The aim of this study was to determine the background prevalence of SLCO1B1 SNVs in a randomly selected sample and to investigate if there are associations between SLCO1B1 SNVs and hypercholesterolaemia patients on statin therapy.Using Polymerase Chain Reaction - Restriction Fragment Length Polymorphism, the presence of SLCO1B1 SNVs (rs4149056, rs2306283 and rs4363657) was identified, while ELISA was used to quantify serum CK levels. Statin intolerance risk was calculated using a quantitative questionnaire.The risk of developing statin intolerance was found to be low (in 36%), moderate (in 49%), or high (in 15%) in the statin-treated group. The prevalence of the rs4149056 variant was 16% in (controls) and 20% in (statin) group; rs2306283 variant was present in 31.5% (controls), 10.5% in (statin) group; while the prevalence of the rs4363657 variant was similar in each. No association between the presence of any one of the SNVs and the statin intolerance severity risk score or CK elevation was found.These findings will facilitate a more personalized approach to statin therapy, especially relevant within the diverse South African population.