

Literature update week 10 (2020)

[1] *Saavedra A, Rodrigues E, Carvalho D. [Dyslipidemia Secondary to Hypothyroidism and Cholestasis]. Acta medica portuguesa 2020; 33:204-207.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32130100>

ABSTRACT

In about 28% of patients, dyslipidemia has a secondary cause. Many times, the treatment of these causes can lead to the total correction of dyslipidemia. We describe the case of a 50-year-old female patient with class II obesity and primary biliary cirrhosis, evaluated for mixed dyslipidemia with poor control (statins and fibrates were being administered) as well as abnormal liver tests. The investigation carried out revealed primary auto-immune hypothyroidism. After normalisation of thyroid function by treatment with levothyroxine, as well as suspending the administration of statins and fibrates, there was an improvement in the lipid profile, although hypercholesterolemia continued. During this time, the patient was diagnosed with diabetes and she re-commenced statin therapy (atorvastatin 10 mg), which resulted in a normal lipid profile being achieved. In this case, the authors set out to highlight the importance of excluding secondary causes of dyslipidemia - including hypothyroidism, and then go on to discuss particular aspects of statin therapy for liver disease.

[2] *Ishay Y, Nachman D, Khoury T, Ilan Y. The Role of Sphingolipid Pathway in Liver Fibrosis: An Emerging New Potential Target for Novel Therapies. Am J Physiol Cell Physiol 2020.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32130072>

ABSTRACT

Sphingolipids (SL) are a family of bioactive lipids and a major cellular membrane structural component. SLs include three main compounds; Ceramide (Cer), Sphingosine (Sp) and Sphingosine 1 phosphate (S-1P), all of which have emerging roles in biological functions in cells, especially in the liver. They are under investigation in various liver diseases, including cirrhosis and end stage liver disease. In this review, we provide an overview on the role of SLs in liver pathobiology and focus on their potential role in the development of hepatic fibrosis. We describe recent evidence and suggest SLs are a promising potential therapeutic target for the treatment of liver disease and fibrosis.

[3] *Navdaev AV, Sborgi L, Wright SD, Didichenko SA. Nascent HDL (High-Density Lipoprotein) Discs Carry Cholesterol to HDL Spheres: Effects of HDL Particle Remodeling on Cholesterol Efflux.*

Arteriosclerosis, thrombosis, and vascular biology 2020:Atvbaha120313906.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32131613>

ABSTRACT

OBJECTIVE: To characterize the fate of protein and lipid in nascent HDL (high-density lipoprotein) in plasma and explore the role of interaction between nascent HDL and mature HDL in promoting ABCA1 (ATP-binding cassette transporter 1)-dependent cholesterol efflux. Approach and Results: Two discoidal species, nascent HDL produced by RAW264.7 cells expressing ABCA1 (LpA-I [apo AI containing particles formed by incubating ABCA1-expressing cells with apo AI]), and CSL112, human apo AI (apolipoprotein AI) reconstituted with phospholipids, were used for in vitro incubations with human plasma or purified spherical plasma HDL. Fluorescent labeling and biotinylation of HDL were employed to follow the redistribution of cholesterol and apo AI, cholesterol efflux was measured using cholesterol-loaded cells. We show that both nascent LpA-I and CSL112 can rapidly fuse with

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spherical HDL. Redistribution of the apo AI molecules and cholesterol after particle fusion leads to the formation of (1) enlarged, remodeled, lipid-rich HDL particles carrying lipid and apo AI from LpA-I and (2) lipid-poor apo AI particles carrying apo AI from both discs and spheres. The interaction of discs and spheres led to a greater than additive elevation of ABCA1-dependent cholesterol efflux. CONCLUSIONS: These data demonstrate that although newly formed discs are relatively poor substrates for ABCA1, they can interact with spheres to produce lipid-poor apo AI, a much better substrate for ABCA1. Because the lipid-poor apo AI generated in this interaction can itself become discoid by the action of ABCA1, cycles of cholesterol efflux and disc-sphere fusion may result in net ABCA1-dependent transfer of cholesterol from cells to HDL spheres. This process may be of particular importance in atherosclerotic plaque where cholesterol acceptors may be limiting.

[4] Zijlstra LE, Trompet S, Mooijart SP et al. **The association of kidney function and cognitive decline in older patients at risk of cardiovascular disease: a longitudinal data analysis.** *BMC Nephrol* 2020; 21:81.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32138689>

ABSTRACT

BACKGROUND: Chronic kidney disease (CKD) has been identified as a significant direct marker for cognitive decline, but controversy exists regarding the magnitude of the association of kidney function with cognitive decline across the different CKD stages. Therefore, the aim of this study was to investigate the association of kidney function with cognitive decline in older patients at high risk of cardiovascular disease, using data from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). **METHODS:** Data of 5796 patients of PROSPER were used. Strata were made according to clinical stages of CKD based on estimated glomerular filtration rate; < 30 ml/min/1.73m² (stage 4), 30-45 ml/min/1.73m² (stage 3b), 45-60 ml/min/1.73m² (stage 3a) and ≥ 60 ml/min/1.73m² (stage 1-2). Cognitive function and functional status was assessed at six different time points and means were compared at baseline and over time, adjusted for multiple prespecified variables. Stratified analyses for history of vascular disease were executed. **RESULTS:** Mean age was 75.3 years and 48.3% participants were male. Mean follow-up was 3.2 years. For all cognitive function tests CKD stage 4 compared to the other stages had the worst outcome at baseline and a trend for faster cognitive decline over time. When comparing stage 4 versus stage 1-2 over time the estimates (95% CI) were 2.23 (0.60-3.85; p = 0.009) for the Stroop-Colour-Word test, - 0.33 (- 0.66-0.001; p = 0.051) for the Letter-Digit-Coding test, 0.08 (- 0.06-0.21; p = 0.275) for the Picture-Word-Learning test with immediate recall and - 0.07 (- 0.02-0.05; p = 0.509) for delayed recall. This association was most present in patients with a history of vascular disease. No differences were found in functional status. **CONCLUSION:** In older people with vascular burden, only severe kidney disease (CKD stage 4), but not mild to modest kidney disease (CKD stage 3a and b), seem to be associated with cognitive impairment at baseline and cognitive decline over time. The association of severe kidney failure with cognitive impairment and decline over time was more outspoken in patients with a history of vascular disease, possibly due to a higher probability of polyvascular damage, in both kidney and brain, in patients with proven cardiovascular disease.

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[5] Li ZH, Zhong WF, Liu S et al. **Associations of habitual fish oil supplementation with cardiovascular outcomes and all cause mortality: evidence from a large population based cohort study.** *Bmj* 2020; 368:m456.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32131999>

ABSTRACT

OBJECTIVES: To evaluate the associations of habitual fish oil supplementation with cardiovascular disease (CVD) and mortality in a large prospective cohort. DESIGN: Population based, prospective cohort study. SETTING: UK Biobank. PARTICIPANTS: A total of 427 678 men and women aged between 40 and 69 who had no CVD or cancer at baseline were enrolled between 2006 and 2010 and followed up to the end of 2018. MAIN EXPOSURE: All participants answered questions on the habitual use of supplements, including fish oil. MAIN OUTCOME MEASURES: All cause mortality, CVD mortality, and CVD events. RESULTS: At baseline, 133 438 (31.2%) of the 427 678 participants reported habitual use of fish oil supplements. The multivariable adjusted hazard ratios for habitual users of fish oil versus non-users were 0.87 (95% confidence interval 0.83 to 0.90) for all cause mortality, 0.84 (0.78 to 0.91) for CVD mortality, and 0.93 (0.90 to 0.96) for incident CVD events. For CVD events, the association seemed to be stronger among those with prevalent hypertension (P for interaction=0.005). CONCLUSIONS: Habitual use of fish oil seems to be associated with a lower risk of all cause and CVD mortality and to provide a marginal benefit against CVD events among the general population.

[6] Abacioglu OO. **Monocyte to high-density lipoprotein ratio: a prognostic factor for mitral valve prolapse?** *Bratislavske lekarske listy* 2020; 121:151-153.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32115969>

ABSTRACT

BACKGROUND: Mitral valve prolapse (MVP) is a common disorder, afflicting 2 % to 3 % of the general population. Despite the general belief of a benign disorder, there is an increasing awareness of an association between mitral valve prolapse and sudden cardiac death from arrhythmia and also atherosclerosis. Monocyte to high density lipoprotein ratio (MHR) is a new tool for predicting inflammation, which plays a major role in atherosclerosis. OBJECTIVE: To evaluate the relationship between MHR and the presence of MVP. METHODS: The study population consisted of 82 patients with MVP and the control group of 78 normal individuals. Transthoracic echocardiography was performed for all of the study population and peripheral venous blood samples were drawn for measuring MHR and other haematological parameters. RESULTS: The patients with MVP were more likely to have higher MHR values (15.82+/-6.01 in MVP patients and 13.30 +/- 6.43 in controls; p=0.011). Monocyte counts and MHR of the MVP group were significantly higher than the control group and MHR values were directly proportional with the regurgitation area. CONCLUSION: The MHR is strongly associated with MVP and regurgitation area and might be a prognostic factor for patients with MVP (Tab. 3, Fig. 1, Ref. 15).

[7] Kaplan IG, Kaplan M, Abacioglu OO et al. **Monocyte/HDL ratio predicts hypertensive complications.** *Bratislavske lekarske listy* 2020; 121:133-136.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32115966>

ABSTRACT

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OBJECTIVE: We aimed to investigate whether a simple and easily calculated parameter such as monocyte/ HDL ratio (MHR) may be used in predicting non-dipper (NDHT)-dipper HT (DHT) end organ damage. **METHODS:** 70 NDHT and 73 DHT patient groups were included in the study according to ambulatory blood pressure screening results. Basic laboratory parameters and spot urine samples were evaluated. Transthoracic echocardiography and ophthalmological examination were performed for end-organ damages. **RESULTS:** The MHR among the groups was higher in the NDHT group; which was statistically significant ($p \leq 0.001$). In the NDHT group, albumin, creatinine, protein values, protein/creatinine ratio in the spot urine were significantly higher than in the DHT group ($p \leq 0.05$). Left ventricular hypertrophy (LVH) and retinopathy were also more frequently observed in the NDHT group ($p \leq 0.001$ and $p = 0.001$, respectively). MHR in patients with LVH and retinopathy was significantly higher than in those without these complications ($p = 0.001$). **CONCLUSION:** Easy to use, non-invasive and simple calculation, MHR can be used to predict end organ damage in hypertensive cases, and can be also used to distinguish between DHT/NDHT groups. This data supports the role of inflammation (Tab. 7, Ref. 14).

[8] *Zhu L, Hayen A, Bell KJL. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. Cardiovascular diabetology 2020; 19:28.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32138746>

ABSTRACT

BACKGROUND: The Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid study found no evidence of a beneficial effect of statin-fibrate combined treatment, compared to statins alone, on cardiovascular outcomes and mortality in type 2 diabetes mellitus after 5 years of active treatment. However, a beneficial reduction in major CVD events was shown in a pre-specified subgroup of participants with dyslipidemia. The extended follow-up of this trial provides the opportunity to further investigate possible beneficial effects of fibrates in this group of patients. We aimed to evaluate possible "legacy effects" of fibrate add-on therapy on mortality and major cardiovascular outcomes in patients with dyslipidemia. **METHODS:** The ACCORD-lipid study was a randomized controlled trial of 5518 participants assigned to receive simvastatin plus fenofibrate vs simvastatin plus placebo. After randomized treatment allocation had finished at the end of the trial, all surviving participants were invited to attend an extended follow-up study (ACCORDION) to continue prospective collection of clinical outcomes. We undertook a secondary analysis of trial and post-trial data in patients who had dyslipidemia. The primary outcome was all-cause and cardiovascular mortality, and secondary outcomes were nonfatal myocardial infarction, stroke, congestive heart failure and major coronary heart disease. We used an intention-to-treat approach to analysis to make comparisons between the original randomized treatment groups. **RESULTS:** 853 participants with dyslipidemia had survived at the end of the trial. Most participants continued to use statins, but few used fibrates in either group during the post-trial period. The incidence rates in the fenofibrate group were lower with respect to all-cause mortality, CVD mortality, nonfatal myocardial infarction, congestive heart failure and major coronary heart disease than those in the placebo group over a post-trial follow-up. Allocation to the combined fibrate-statin treatment arm during the trial period had a beneficial legacy effect on all-cause mortality (adjusted HR = 0.65, 95% CI 0.45-0.94; $P = 0.02$). **CONCLUSIONS:** Fibrate treatment during the initial trial period was associated with a legacy benefit of improved survival over a post-trial follow-up. These findings

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support re-evaluation of fibrates as an add-on strategy to statins in order to reduce cardiovascular risk in diabetic patients with dyslipidemia. Trial registration clinicaltrials.gov, Identifier: NCT00000620.

[9] *Sujanani SM, Elfishawi MM, Zarghamravanbaksh P et al. Dapagliflozin-Induced Acute Pancreatitis: A Case Report and Review of Literature. Case reports in endocrinology 2020; 2020:6724504.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32123591>

ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are increasingly used as add-on therapy in patients with poorly controlled type 2 diabetes mellitus (T2DM). Although pancreatitis is not a known side effect of SGLT-2 inhibitors, there have been case reports of SGLT-2 inhibitor use being associated with pancreatitis. Case Presentation. A 51-year-old male with a history of type 2 diabetes, dyslipidemia, and status-post cholecystectomy presented to the emergency room with a four-day history of periumbilical pain radiating to the back. He denied any history of recent alcohol intake or prior episodes of pancreatitis. On physical examination, his abdomen was diffusely tender to palpation without guarding or rebound. Initial labs were notable for a leukocyte count of $9.3 \times 10^9/L$, creatinine level of 0.72 mg/dL, calcium level of 9.5 mg/dL, lipase level of 262 U/L, and triglyceride level of 203 mg/dL. His last HbA1c was 8.5%. CT scan of his abdomen and pelvis showed findings consistent with acute pancreatitis with no biliary ductal dilatation. Careful review of his medications revealed the patient was recently started on dapagliflozin five days prior to admission in addition to his longstanding regimen of insulin detemir, sitagliptin, metformin, and rosuvastatin. His symptoms resolved after discontinuation of sitagliptin and dapagliflozin. A year later, due to increasing HbA1c levels, a decision was made to rechallenge the patient with dapagliflozin, after which he developed another episode of acute pancreatitis. His symptoms resolved upon cessation of dapagliflozin. Conclusion. This case highlights the possible association of SGLT-2 inhibitors and pancreatitis. Patients should be informed about the symptoms of acute pancreatitis and advised to discontinue SGLT-2 inhibitors in case such symptoms occur.

[10] *Turner RM, Fontana V, Zhang JE et al. A genome-wide association study of circulating levels of atorvastatin and its major metabolites. Clinical pharmacology and therapeutics 2020.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32128760>

ABSTRACT

Atorvastatin (ATV) is frequently prescribed and generally well tolerated, but can lead to myotoxicity, especially at higher doses. A genome-wide association study of circulating levels of ATV, 2-hydroxy (2-OH) ATV, ATV lactone (ATV L) and 2-OH ATV L was performed in 590 patients that had been hospitalised with a non-ST elevation acute coronary syndrome one month earlier and were on high dose ATV (80mg or 40mg daily). The UGT1A locus (lead SNP, rs887829) was strongly associated with both increased 2-OH ATV/ATV ($p=7.25 \times 10^{-16}$) and 2-OH ATV L/ATV L ($p=3.95 \times 10^{-15}$) metabolic ratios. Moreover, rs45446698, which tags CYP3A7*1C, was nominally associated with increased 2-OH ATV/ATV ($p=6.18 \times 10^{-7}$), and SLCO1B1 rs4149056 with increased ATV ($p=2.21 \times 10^{-6}$) and 2-OH ATV ($p=1.09 \times 10^{-6}$) levels. In a subset of these patients whose levels of ATV and metabolites had also been measured at 12 months after hospitalisation ($n=149$), all of these associations remained, except for 2-OH ATV and rs4149056 ($p=0.057$). Clinically,

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rs4149056 was associated with increased muscular symptoms (OR 3.97, 95% CI 1.29-12.27, $p=0.016$) and ATV intolerance (OR 1.55, 95% CI 1.09-2.19, $p=0.014$) in patients ($n=870$) primarily discharged on high dose ATV. In summary, both novel and recognised genetic associations have been identified with circulating levels of ATV and its major metabolites. Further study is warranted to determine the clinical utility of genotyping rs4149056 in patients on high dose ATV.

[11] *Ballout RA, Bianconi S, Livinski A et al. Statins for Smith-Lemli-Opitz syndrome. Cochrane Libr* 2020; 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32132878>

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: 1. To evaluate the efficacy of statin therapy in reducing the frequency or severity of the neurobehavioral abnormalities seen in people with SLOS (e.g. aggression, anxiety, irritability, self-mutilation, autistic behaviors, sleep disturbances, etc.) (Wassif 2017). 2. To evaluate the potential effects of statin therapy on survival.

[12] *Schwartz GG, Leiter LA, Ballantyne CM et al. Dalcetrapib Reduces Risk of New-Onset Diabetes in Patients With Coronary Heart Disease. Diabetes Care* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32144166>

ABSTRACT

OBJECTIVE: Incident type 2 diabetes is common among patients with recent acute coronary syndrome and is associated with an adverse prognosis. Some data suggest that cholesteryl ester transfer protein (CETP) inhibitors reduce incident type 2 diabetes. We compared the effect of treatment with the CETP inhibitor dalcetrapib or placebo on incident diabetes in patients with recent acute coronary syndrome. **RESEARCH DESIGN AND METHODS:** In the dal-OUTCOMES trial, 15,871 patients were randomly assigned to treatment with dalcetrapib, 600 mg daily, or placebo, beginning 4-12 weeks after an acute coronary syndrome. Absence of diabetes at baseline was based on medical history, no use of antihyperglycemic medication, and hemoglobin A1c and serum glucose levels below diagnostic thresholds. Among these patients, incident diabetes after randomization was defined by any diabetes-related adverse event, new use of antihyperglycemic medication, hemoglobin A1c $\geq 6.5\%$, serum glucose ≥ 7.0 mmol/L (fasting) or ≥ 11.1 mmol/L (random). **RESULTS:** At baseline, 10,645 patients (67% of the trial cohort) did not have diabetes. During a median follow-up of 30 months, incident diabetes was identified in 403 of 5,326 patients (7.6%) assigned to dalcetrapib and in 516 of 5,319 (9.7%) assigned to placebo, corresponding to absolute risk reduction of 2.1%, hazard ratio of 0.77 (95% CI 0.68-0.88; $P < 0.001$), and a need to treat 40 patients for 3 years to prevent 1 incident case of diabetes. Considering only those with prediabetes at baseline, the number needed to treat for 3 years to prevent 1 incident case of diabetes was 25. Dalcetrapib also decreased the number of patients who progressed from normoglycemia to prediabetes and increased the number who regressed from diabetes to no diabetes. **CONCLUSIONS:** In patients with a recent acute coronary syndrome, incident diabetes is common, and is reduced substantially by treatment with dalcetrapib.

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[13] *Tamburrino D, Crippa S, Partelli S et al. Statin use improves survival in patients with pancreatic ductal adenocarcinoma: A meta-analysis. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32113888>

ABSTRACT

BACKGROUND: Previous studies on statins' effect on survival of patients with pancreatic ductal adenocarcinoma (PDAC) report conflicting results. AIMS: To evaluate the association between statin use and PDAC patients' survival. METHODS: A systematic review and meta-analysis was performed including case-control, cohort studies and randomized controlled trials assessing the association between statin use and survival in PDAC patients. Pooled HRs with 95%CIs were calculated using random effects model; publication bias was assessed through Begg and Mazumdar test and heterogeneity by I(2) value. RESULTS: 14 studies with 33,137 PDAC patients, 40% under statins, were included. Statins use was associated to a reduced death risk (HR 0.871; 95%CI: 0.819; 0.927; p=0.0001) suggesting a protective effect, homogeneous for different geographic areas. This effect was significant in surgically resected patients (HR 0.50; 95%CI: 0.32; 0.76; p=0.001) but not in those with advanced disease (HR 0.78; 95%CI: 0.59; 1.02; p=0.07). In studies providing information on statin type, only rosuvastatin resulted associated to a reduced risk of death (HR 0.88; 95%CI: 0.81; 0.96; p=0.004). CONCLUSIONS: Statins use is significantly associated with a reduced risk of death in resected PDAC patients. This finding has to be considered with caution due to publication bias and the availability of only few studies for sensitivity analyses.

[14] *He W, Cao M, Li Z. Effects of different doses of atorvastatin, rosuvastatin, and simvastatin on elderly patients with ST-elevation acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI). Drug development research* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32142170>

ABSTRACT

OBJECTIVE: To conduct a randomized double-blind prospective study to investigate effect of different doses of atorvastatin, rosuvastatin, and simvastatin on elderly patients with ST-elevation AMI after PCI. METHODS: One hundred and ninety-two AMI patients over 60 years old who underwent PCI were randomly divided into six groups: the low atorvastatin group, high atorvastatin group; low rosuvastatin group; high rosuvastatin group; low simvastatin group; high simvastatin group. Demographic data and clinical information as well as coronary angiography parameters were recorded. Plasma levels of CK-MB, BNP, ALT, and TnI were measured at 12 hr, 24 hr, and 1 week after PCI. Major cardiovascular events (MACE) were recorded and analyzed using Kaplan-Meier (K-M) curve. RESULTS: No significant differences were observed in angiographic and procedural characteristics. In all high dose groups, all levels of CK-MB, BNP, ALT, and TnI were significantly lower. However, after 1 week of PCI, only CK-MB, BNP, and TnI showed significant difference between high and low dose groups. Patients in high dose groups had significantly lower rates for surgical or percutaneous intervention, recurrence of angina, and rehospitalization. K-M curve analysis also showed cumulative incidence freedom time of overall MACE in high dose groups was significantly longer. No significant differences were found among different drugs with the same doses. CONCLUSION: Patients with higher doses had lower level of CK-MB, BNP, ALT, and TnI and lower occurrence of MACE after PCI.

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[15] *Chen M, Hu S, Li Y et al. Role of OATP2B1 in drug absorption and drug-drug interactions. Drug metabolism and disposition: the biological fate of chemicals* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32114507>

ABSTRACT

The organic anion transporting polypeptide OATP2B1 is localized on the basolateral membrane of hepatocytes and is expressed in enterocytes. Based on its distribution pattern and functional similarity to OATP1B-type transporters, OATP2B1 might have a role in the absorption and disposition of a range of xenobiotics. Although several prescription drugs, including HMG-CoA inhibitors (statins) such as fluvastatin, are OATP2B1 substrates *in vitro*, evidence supporting the *in vivo* relevance of this transporter remains limited, and most has relied on substrate-inhibitor interactions resulting in altered pharmacokinetic properties of the victim drugs. In order to address this knowledge deficit, we developed and characterized an OATP2B1-deficient mouse model and evaluated the impact of this transporter on the absorption and disposition of fluvastatin. Consistent with the intestinal localization of OATP2B1, we found that the genetic or pharmacological inhibition of OATP2B1 was associated with decreased absorption of fluvastatin by 2- to 3-fold. The availability of a viable OATP2B1-deficient mouse model provides an opportunity to unequivocally determine the contribution of this transporter to the absorption and drug-drug interaction potential of drugs. SIGNIFICANCE STATEMENT: The current investigation suggests that OATP2B1-deficient mice provide a valuable tool to study the *in vivo* importance of this transporter. In addition, our studies have identified novel potent inhibitors of OATP2B1 among the class of tyrosine kinase inhibitors, a rapidly expanding class of drugs used in various therapeutic areas that may cause drug-drug interactions with OATP2B1 substrates.

[16] *Littmann K, Szummer K, Hagstrom H et al. Lomitapide treatment in a female with homozygous familial hypercholesterolaemia: a case report. European heart journal. Case reports* 2020; 4:1-6.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32128483>

ABSTRACT

Background: Homozygous familial hypercholesterolaemia (FH) is an autosomal-dominant inherited disease presenting with highly elevated low-density lipoprotein cholesterol (LDL-C) levels. Untreated, the patient can develop atherosclerosis and cardiovascular disease already in adolescence. Treatment with statins and ezetimibe is usually not sufficient and LDL apheresis is often required. Lomitapide, an inhibitor of the microsomal triglyceride transfer protein, reduces LDL-C and triglyceride levels and can be used alone or in combination with other therapies in homozygous FH. However, experience with this agent is still limited. Case summary: We present a young female who was diagnosed with homozygous FH at 6 years of age. She shows a complete lack of normal LDL receptor activity and no cholesterol-lowering effect from statins. The patient was treated with LDL apheresis from 7 years of age. When LDL apheresis treatment extended to twice a week, she began to experience adverse effects, including catheter-related complications, infections, and hospital admissions. When lomitapide treatment was initiated, the frequency of apheresis reduced, the LDL-C levels improved and she has not had any further hospital admissions since. Initially, she suffered from gastrointestinal disturbances. However, after 3 years of treatment with lomitapide 20 mg/day, the patient has not experienced any adverse effects. Discussion: In this female with homozygous FH adding lomitapide treatment to LDL apheresis has contributed to

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improved LDL-C levels, a reduction in LDL apheresis sessions and enhanced quality of life. No adverse effects have been reported. These findings suggest that lomitapide can be a drug of choice in patients with homozygous FH.

[17] *Allahyari A, Jernberg T, Lautsch D et al. LDL-cholesterol target attainment according to the 2011 and 2016 ESC/EAS dyslipidaemia guidelines in patients with a recent myocardial infarction - nationwide cohort study, 2013-2017. European heart journal. Quality of care & clinical outcomes 2020.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32142112>

ABSTRACT

AIMS: To assess low-density lipoprotein cholesterol (LDL-C) treatment target attainment among myocardial infarction (MI) patients according to the ESC/EAS dyslipidaemia guidelines from 2011 (LDL-C <1.8 mmol/L or \geq 50% LDL-C reduction) and 2016 (LDL-C <1.8 mmol/L and \geq 50% LDL-C reduction). METHODS AND RESULTS: Using nationwide registers, we identified 44,890 patients aged 21-74 admitted for MI, 2013-2017. We included those attending follow-up visits at 6-10 weeks (n = 25,466) and 12-14 months (n = 17,117) after the event. Most patients received high-intensity statin monotherapy (84.3% [6-10 weeks] and 69.0% [12-14 months]) or statins with ezetimibe (2.7% and 10.2%). The proportion of patients attaining the 2011 LDL-C target was 63.8% (6-10 weeks) and 63.5% (12-14 months). The corresponding numbers for the 2016 LDL-C target was 31.6% (6-10 weeks) and 31.5% (12-14 months). At the 6-10-week follow-up, 37% of those not attaining the 2011 LDL-C target and 48% of those not attaining the 2016 target had an LDL-C level that was \geq 0.5 mmol/L from the target. When comparing LDL-C measurements performed before vs. after the release of the 2016 guidelines, attainment of the 2016 LDL-C target increased from 30.2% to 35.0% (6-10 weeks) and from 27.6% to 37.6% (12-14 months). CONCLUSIONS: In a nationwide register, one out of three patients with a recent MI had not attained the LDL-C target of the 2011 ESC/EAS guidelines and two out of three patients had not attained the LDL-C target of the 2016 guidelines.

[18] *Katsanos AH, Lioutas VA, Charidimou A et al. Statin treatment and accrual of covert cerebral ischaemia on neuroimaging: a systematic review and meta-analysis of randomized trials. European journal of neurology : the official journal of the European Federation of Neurological Societies 2020.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32133735>

ABSTRACT

BACKGROUND AND PURPOSE: Prevention of ischaemic stroke and cardiovascular events is an established benefit of statin therapy, but the effects of statin treatment on the accrual of magnetic resonance imaging (MRI) markers of ischaemic cerebral injury remain unknown. A systematic review was performed to identify all studies that randomized patients with cardiovascular risk factors to statin treatment and assessed the effect of statin treatment on covert infarcts (asymptomatic, evident only on neuroimaging) and white matter hyperintensity (WMH) accrual on MRI. METHODS: A systematic review in MEDLINE and Scopus from inception to 23 October 2019 was performed. A random-effects model was used to calculate the pooled estimates of the crude risk ratios and standardized mean differences. RESULTS: Data from three randomized controlled trials (1430 participants) were included evaluating the effect of rosuvastatin (10 mg/day) in 668

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hypertensive patients older than 60 years of age over 5 years, pravastatin (40 mg/day) in 554 elderly people more than 70 years of age over 3 years and simvastatin (20 mg/day) in 208 patients with asymptomatic middle cerebral artery stenosis over 2 years. Patients randomized to statin treatment had decreased accrual of new covert infarcts (risk ratio 0.63, 95% confidence interval 0.46-0.88) during a mean follow-up of 2-6 years. Only one study reported WMH decreased volume change in patients randomized to statin treatment compared to patients randomized to non-statin treatment (standardized mean difference -1.17; 95% confidence interval -1.33, -1.00).
CONCLUSION: Our findings suggest that, in addition to stroke prevention, statin treatment can reduce the accrual of covert MRI markers of ischaemic cerebral injury.

[19] *Drosos GC, Konstantonis G, Sfikakis PP, Tektonidou MG. Underperformance of clinical risk scores in identifying vascular ultrasound-based high cardiovascular risk in systemic lupus erythematosus. European journal of preventive cardiology 2020:2047487320906650.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32122200>

ABSTRACT

AIMS: The aim of this study was to assess the performance of eight clinical risk prediction scores to identify individuals with systemic lupus erythematosus (SLE) at high cardiovascular disease (CVD) risk, as defined by the presence of atherosclerotic plaques. METHODS: CVD risk was estimated in 210 eligible SLE patients without prior CVD or diabetes mellitus (female: 93.3%, mean age: 44.8 +/- 12 years) using five generic (Systematic Coronary Risk Evaluation (SCORE), Framingham Risk Score (FRS), Pooled Cohort Risk Equations (ASCVD), Globorisk, Prospective Cardiovascular Munster Study risk calculator (PROCAM)) and three 'SLE-adapted' (modified-SCORE, modified-FRS, QRESEARCH risk estimator, version 3 (QRISK3)) CVD risk scores, as well as ultrasound examination of the carotid and femoral arteries. Calibration, discrimination and classification measures to identify high CVD risk based on the presence of atherosclerotic plaques were assessed for all risk models. CVD risk reclassification was applied for all scores by incorporating ultrasound results. RESULTS: Moderate calibration (p-value range from 0.38 to 0.63) and discrimination (area under the curve 0.73-0.84), and low-to-moderate sensitivity (8.3-71.4%) and classification ability (Matthews correlation coefficient (MCC) 0.25-0.47) were observed for all risk models to identify patients with plaques at any arterial site as high-risk. MCC was improved for modified-FRS versus FRS (0.43 vs 0.36), but not for modified-SCORE versus SCORE (0.25 vs 0.25). Based on plaque presence, CVD risk was upgraded to high-risk in 10%, 16.1%, 20.5%, 21.5%, 24%, 28.2% and 28.6% of cases classified as non-high-risk by QRISK3, modified-FRS, Globorisk, FRS/PROCAM, ASCVD, modified-SCORE and SCORE, respectively. CONCLUSIONS: Most of the five generic and three 'SLE-adapted' clinical risk scores underestimated high CVD risk defined by atherosclerotic plaque presence in patients with SLE.

[20] *Toyoda Y, Takada T, Umezawa M et al. Identification of hepatic NPC1L1 as an NAFLD risk factor evidenced by ezetimibe-mediated steatosis prevention and recovery. FASEB Bioadv 2019; 1:283-295.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32123832>

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a serious global public health concern. Nevertheless, there are no specific medications for treating the associated abnormal accumulation of hepatic lipids such as cholesterol and triglycerides. While seminal findings suggest a link between hepatic

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cholesterol accumulation and NAFLD progression, the molecular bases of these associations are not well understood. Here, we experimentally demonstrate that hepatic Niemann-Pick C1-Like 1 (NPC1L1), a cholesterol re-absorber from bile to the liver, can cause steatosis, an early stage of NAFLD using genetically engineered L1-Tg mice characterized by hepatic expression of NPC1L1 under the control of ApoE promoter. Contrary to wild-type mice that have little expression of hepatic Npc1l1, the livers of L1-Tg mice fed a high-fat diet became steatotic within only a few weeks. Moreover, hepatic NPC1L1-mediated steatosis was not only prevented, but completely rescued, by orally administered ezetimibe, a well-used lipid-lowering drug on the global market, even under high-fat diet feedings. These results indicate that hepatic NPC1L1 is an NAFLD-exacerbating factor amendable to therapeutic intervention and would extend our understanding of the vital role of cholesterol uptake from bile in the development of NAFLD. Furthermore, administration of a TLR4 inhibitor also prevented the hepatic NPC1L1-mediated steatosis formation, suggesting a latent link between physiological roles of hepatic NPC1L1 and regulation of innate immune system. Our results revealed that hepatic NPC1L1 is a novel NAFLD risk factor contributing to steatosis formation that is rescued by ezetimibe; additionally, our findings uncover feasible opportunities for repositioning drugs to treat NAFLD in the near future.

[21] *Liu G, Gibson RA, Callahan D et al. Pure omega 3 polyunsaturated fatty acids (EPA, DPA or DHA) are associated with increased plasma levels of 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) in a short-term study in women. Food & function 2020; 11:2058-2066.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32142084>

ABSTRACT

3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) is a metabolite of furan fatty acids found in plasma and urine of humans after consumption of foods containing these fatty acids. Recently, CMPF has been identified as a prominent metabolite following the consumption of either fish oil, fish oil fatty acid-ethyl esters or diets rich in fish. As furan fatty acids are known to occur in fish and fish oils (at a low level), it is possible that in these studies the CMPF in plasma originated from furan fatty acids. We report the plasma CMPF levels in 10 healthy women who consumed 1 gram of pure eicosapentaenoic acid (EPA), or docosapentaenoic acid (DPA) or docosahexaenoic acid (DHA), or olive oil daily for 6 days, in a cross-over study. The supplemented omega 3 fatty acids contained no detectable levels of furan fatty acids. The plasma CMPF and omega 3 fatty acid levels were measured by LC-MS/MS. Consumption of pure omega 3 fatty acids led to a significant increase in the plasma CMPF levels, but not with olive oil (from 1.6 to 2.5-fold compared with baseline). The plasma free fatty acid levels of EPA, DPA and DHA also increased significantly when they were supplemented ($p < 0.05$). Significant positive correlations existed between the plasma free fatty acid DPA and DHA levels ($p < 0.05$ and $r = +0.49$ to $+0.81$), but not between the EPA and CMPF levels. These data suggest that purified long chain omega 3 fatty acids may be precursors of CMPF; however the metabolic pathway(s) from omega 3 fatty acids to CMPF remain to be elucidated.

[22] *Shi X, Gao J, Lv Q et al. Calcification in Atherosclerotic Plaque Vulnerability: Friend or Foe? Front Physiol 2020; 11:56.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32116766>

ABSTRACT

Calcification is a clinical marker of atherosclerosis. This review focuses on recent findings on the association between calcification and plaque vulnerability. Calcified plaques have traditionally been regarded as stable atheromas, those causing stenosis may be more stable than non-calcified plaques. With the advances in intravascular imaging technology, the detection of the calcification and its surrounding plaque components have evolved. Microcalcifications and spotty calcifications represent an active stage of vascular calcification correlated with inflammation, whereas the degree of plaque calcification is strongly inversely related to macrophage infiltration. Asymptomatic patients have a higher content of plaque calcification than that in symptomatic patients. The effect of calcification might be biphasic. Plaque rupture has been shown to correlate positively with the number of spotty calcifications, and inversely with the number of large calcifications. There may be certain stages of calcium deposition that may be more atherogenic. Moreover, superficial calcifications are independently associated with plaque rupture and intraplaque hemorrhage, which may be due to the concentrated and asymmetrical distribution of biological stress in plaques. Conclusively, calcification of differential amounts, sizes, shapes, and positions may play differential roles in plaque homeostasis. The surrounding environments around the calcification within plaques also have impacts on plaque homeostasis. The interactive effects of these important factors of calcifications and plaques still await further study.

[23] Lander M, Abedin Y, Gabrilovich S, Marcus JZ. **Severe hypertriglyceridemia during treatment with intraperitoneal cisplatin and paclitaxel for advanced stage fallopian tube carcinoma.**

Gynecol Oncol Rep 2020; 32:100552.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32140531>

ABSTRACT

This case report describes a patient who developed severe hypertriglyceridemia (1871 mg/dL) and hyperlipidemia (LDL 132 mg/dL) during intraperitoneal (IP) administration of cisplatin and paclitaxel as adjuvant treatment for stage IIIC fallopian tube carcinoma. After an evaluation with her primary care physician, she was treated with gemfibrozil and rosuvastatin for the duration of her treatment. There was complete resolution of hypertriglyceridemia after completion of chemotherapy. This adverse event is rare and has not been reported in the literature with this chemotherapeutic regimen. A pre-chemotherapy evaluation for dyslipidemia may be beneficial in the detection and monitoring of this condition.

[24] A OK, Lusebrink E, Lahrmann C et al. **Toll-Like Receptor 7 Stimulation Promotes the Development of Atherosclerosis in Apolipoprotein E-Deficient Mice.** Int Heart J 2020; 61:364-372.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32132319>

ABSTRACT

Atherosclerosis is a chronic inflammatory disease with multiple characteristic facets, including vascular inflammation, endothelial dysfunction, plaque development, impaired blood flow, and cholesterol deposition through dyslipidemia. Toll-like receptors (TLRs) of the innate immune system have been closely linked to the development of atherosclerotic lesions. TLR7 recognizes viral or endogenous single-stranded RNA, which is released during vascular apoptosis and necrosis. The role of TLR7 in vascular disease remains controversial, and therefore, we sought to investigate the effects of TLR7 stimulation in mice. Intravenous injection of a ligand for TLR7 (R848) induced a

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significant pro-inflammatory cytokine response in mice. This was associated with impaired reendothelialization upon acute denudation of the carotid artery, as measured by Evan's blue staining, and increased numbers of circulating endothelial microparticles (EMPs) and circulating Sca1/Flk1 positive cells as a marker for increased endothelial damage. Chronic subcutaneous stimulation of TLR7 in apolipoprotein E-deficient (ApoE(-/-)) mice increased aortic production of reactive oxygen species (ROS), the number of circulating EMPs, and most importantly, augmented the formation of atherosclerotic plaque when compared with vehicle-treated animals. Systemic stimulation of TLR7 leads to impaired reendothelialization upon acute vascular injury and is associated with the production of pro-inflammatory cytokines and increased levels of circulating EMPs and Sca1/Flk1 positive cells. Importantly, ApoE(-/-) mice chronically treated with R848 displayed increased atherosclerotic plaque development and elevated levels of ROS in the aortic tissue. In addition, TLR7-activation-induced apoptosis and impaired migration in human coronary artery endothelial cells and showed significant upregulation of the signaling cascade of IL-1 receptor-associated kinase (IRAK) 2 and IRAK4. Our data highlight the importance of fully understanding the pathomechanisms involved in atherogenesis, and further studies are necessary to identify the ligand-specific effects of TLR7 for possible therapeutic targeting.

[25] Pradhan A, Bhandari M, Vishwakarma P, Sethi R. **Triglycerides and Cardiovascular Outcomes- Can We REDUCE-IT ?** *Int J Angiol* 2020; 29:2-11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32132810>

ABSTRACT

The causal linkage between triglycerides and coronary artery disease has been controversial. Most of the trials hitherto have shown marginal or no beneficial effects of reduction of triglycerides (with fibrates) on top of low-density lipoprotein (LDL) reduction. But a significant residual cardiovascular risk remains even after use of high dose of statins. Omega-3 fatty acids have been shown to reduce triglyceride levels and some old trials have shown the benefits of fish oils in reducing cardiovascular events. However, barring a few trials most of the large trials of omega-3 fatty acids are negative. Recently, few large trials have been conducted to see the effects of high dose omega-3 fatty acids on cardiovascular outcomes and some of them have shown promising results on top of LDL reduction.

[26] Liberale L, Carbone F, Montecucco F, Sahebkar A. **Statins reduce vascular inflammation in atherogenesis: A review of underlying molecular mechanisms.** *The international journal of biochemistry & cell biology* 2020; 122:105735.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32126319>

ABSTRACT

Chronic inflammation enhances the detrimental role of dyslipidaemia during atherogenesis. Statins are among the most effective anti-atherosclerotic medications, being able to impact on both cardiovascular morbidity and mortality. Although these molecules have been first described as lipid-lowering medications, several lines of evidence suggest additional benefits through their "pleiotropic" anti-atherosclerotic activities. Specifically, statins can modulate vascular atherosclerotic inflammation by directly improving functions of endothelial cells, vascular smooth muscle cells, platelets, and immune cells. Here, we discuss basic and clinical evidence to provide an

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update on the molecular mechanisms underlying the protective anti-inflammatory role of statins in atherogenesis.

[27] *Toth PP, Jones SR, Monsalvo ML et al. Effect of Evolocumab on Non-High-Density Lipoprotein Cholesterol, Apolipoprotein B, and Lipoprotein(a): A Pooled Analysis of Phase 2 and Phase 3 Studies. Journal of the American Heart Association* 2020; 9:e014129.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32114889>

ABSTRACT

Background Dyslipidemia guidelines recommend non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (ApoB) as additional targets of therapy and consider lipoprotein(a) a significant cardiovascular risk marker. The current analysis evaluates the effects of evolocumab on these parameters in various patient populations over time. Methods and Results Data from 7690 patients, 4943 of whom received at least 1 dose of evolocumab, in 15 phase 2 and phase 3 studies with a duration ranging from 12 weeks to 5 years were pooled based on study length, patient population, and ezetimibe or placebo comparator groups. Patients could receive intensive statin therapy but not in the statin intolerance and monotherapy studies. The effects of evolocumab on percent change from baseline for non-HDL-C, ApoB, and lipoprotein(a) and achievement of treatment goals for non-HDL-C and ApoB were examined. Compared with placebo, evolocumab at both approved dosing regimens substantially reduced mean non-HDL-C (Q2W dose: -49% to -56%, monthly dose: -48% to -52%), mean ApoB (Q2W dose: -46% to -52%, monthly dose: -40% to -48%), and median lipoprotein(a) (Q2W dose: -22% to -38%, monthly dose: -20% to -33%) at 12 weeks. Effects on all 3 parameters persisted over 5 years. Lipid-lowering effects were consistent among the patient populations examined (hypercholesterolemia/mixed dyslipidemia, statin intolerance, heterozygous familial hypercholesterolemia, and type 2 diabetes mellitus). Conclusions In this pooled analysis, evolocumab substantially reduced non-HDL-C, ApoB, and lipoprotein(a) compared with placebo. The effect was consistent and maintained in various patient populations over 5 years.

[28] *Cecconi A, Vilchez-Tschischke JP, Mateo J et al. Effects of Colchicine on Atherosclerotic Plaque Stabilization: a Multimodality Imaging Study in an Animal Model. Journal of cardiovascular translational research* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32140929>

ABSTRACT

Colchicine demonstrated clinical benefits in the treatment of stable coronary artery disease. Our aim was to evaluate the effects of colchicine on atherosclerotic plaque stabilization. Atherosclerosis was induced in the abdominal aorta of 20 rabbits with high-cholesterol diet and balloon endothelial denudation. Rabbits were randomized to receive either colchicine or placebo. All animals underwent MRI, (18)F-FDG PET/CT, optical coherence tomography (OCT), and histology. Similar progression of atherosclerotic burden was observed in the two groups as relative increase of normalized wall index (NWI). Maximum (18)F-FDG standardized uptake value (meanSUVmax) decreased after colchicine treatment, while it increased in the placebo group with a trend toward significance. Animals with higher levels of cholesterol showed significant differences in favor to colchicine group, both as NWI at the end of the protocol and as relative increase in meanSUVmax. Colchicine may stabilize atherosclerotic plaque by reducing inflammatory activity and plaque burden, without altering macrophage infiltration or plaque typology.

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[29] *Gidding SS, Sheldon A, Neben CL et al. Patient acceptance of genetic testing for familial hypercholesterolemia in the CASCADE FH Registry. Journal of clinical lipidology* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32143996>

ABSTRACT

BACKGROUND: Barriers to genetic testing and subsequent family cascade screening for familial hypercholesterolemia (FH) include cost, patient and provider awareness, privacy and discrimination concerns, need for a physician order, underutilization of genetic counselors, and family concerns about the implications of genetic testing for care. OBJECTIVES: The objective of the study was to determine the uptake of genetic testing with cost and privacy removed. METHODS: The FH Foundation offered free genetic testing and counseling to patients in the patient portal of the CASCADE FH Registry, who had not previously undergone genetic testing for 3 genes associated with FH (LDLR, APOB, and PCSK9). The free testing offer was extended to first-degree relatives of participants who had a positive genetic test result for cascade screening. RESULTS: Of 435 eligible patients, 147 opted in to participate, 122 consented, and 110 (68.2% female, median age: 52 years) received genetic testing. Of the participants, 64 had a positive genetic test result for a pathogenic variant in LDLR (59) or APOB (5); 11 had a variant of uncertain significance. Only 3 first-degree relatives underwent genetic testing. CONCLUSIONS: Although there was substantial interest in genetic testing, uptake of family cascade screening was poor. Innovative approaches to increase family cascade screening should be explored.

[30] *Madan S, Mehra MR. Rhabdomyolysis with the combined use of danazol and rosuvastatin in left ventricular assist devices. J Heart Lung Transplant* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32122697>

ABSTRACT

[31] *Wenning C, Vrachimis A, Pavenstadt HJ et al. Coronary artery calcium burden, carotid atherosclerotic plaque burden, and myocardial blood flow in patients with end-stage renal disease: A non-invasive imaging study combining PET/CT and 3D ultrasound. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32140994>

ABSTRACT

BACKGROUND: Imaging-based measures of atherosclerosis such as coronary artery calcium score (CACS) and coronary flow reserve (CFR) as well as carotid atherosclerotic plaque burden (cPB) are predictors of cardiovascular events in the general population. The objective of this study was to correlate CACS, cPB, myocardial blood flow (MBF), and CFR in patients with end-stage renal disease (ESRD). METHODS AND RESULTS: 39 patients (mean age 53 +/- 12 years) with ESRD prior to kidney transplantation were enrolled. MBF and CFR were quantified at baseline and under hyperemia by (13)N-NH3-PET/CT. CACS was calculated from low-dose CT scans acquired for PET attenuation correction. cPB was assessed by 3D ultrasound. Uni- and multivariate regression analyses between these and clinical parameters were performed. Median follow-up time for clinical events was 4.4 years. Kaplan-Meier survival estimates with log-rank test were performed with regards to cardiovascular (CV) events and death of any cause. CACS and cPB were associated in ESRD patients ($r = 0.48$; $p \leq 0.01$). While cPB correlated with age ($r = 0.43$; $p < 0.01$), CACS did not. MBFstress

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was negatively associated with age ($r = 0.44$; $p < 0.01$) and time on dialysis ($r = 0.42$; $p < 0.01$). There were negative correlations between MBFstress and CACS ($r = -0.62$; $p < 0.001$) and between MBFstress and cPB ($r = -0.43$; $p < 0.01$). Age and CACS were the strongest predictors for MBFstress. CFR was impaired (< 2.0) in eight patients who also presented with higher cPB and higher CACS compared to those with a CFR > 2.0 ($p = 0.06$ and $p = 0.4$). In contrast to MBFstress, there was neither a significant correlation between CFR and CACS ($r = -0.2$; $p = 0.91$) nor between CFR and cPB ($r = -0.1$; $p = 0.55$). CV event-free survival was associated with reduced CFR and MBFstress ($p = 0.001$ and $p < 0.001$) but not with cPB or CACS. CONCLUSIONS: CACS, cPB, and MBFstress are associated in patients with ESRD. Atherosclerosis is earlier detected by MBFstress than by CFR. CV event-free survival is associated with impaired CFR and MBFstress.

[32] Liu H, Deng Y, Wu L et al. **Interleukin-1beta Regulates Lipid Homeostasis in Human Glomerular Mesangial Cells.** *The journal of nutrition, health & aging* 2020; 24:246-250.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32115603>

ABSTRACT

BACKGROUND: Recent studies have shown that hyperlipidemia is closely related to the progression of kidney disease and glomerulosclerosis has similar pathophysiological mechanisms with atherosclerosis. Atherosclerosis is essentially a chronic inflammatory process and various kidney diseases are characterized by a micro-inflammatory state. Hyperlipidemia levels are not parallel to the degree of glomerulosclerosis, inflammatory factors together with lipids may contribute to the pathogenesis of glomerulosclerosis. Therefore, it is key to clarify lipid-mediated renal injury through studying the mechanism by which inflammation affects cholesterol homeostasis at the cellular level. Intracellular lipid homeostasis involves both lipid uptake and excretion, therefore in this study, we aimed to explore whether interleukin-1beta (IL-1beta) promotes the uptake of oxidized low-density lipoprotein (Ox-LDL) to increase in intracellular lipid levels, and to clarify the effect of IL-1beta on the expression of lectin-like oxidized LDL receptor 1 (LOX-1) and ATP-binding cassette transporter A1 (ABCA1), which may regulate cholesterol homeostasis in human mesangial cells (HMCs). **METHODS:** The effect of IL-1beta on uptake of Ox-LDL labeled with fluorescent Dil (Dil-Ox-LDL) by HMCs was observed using laser confocal microscopy. The effect of IL-1beta on LOX-1 and ABCA1 expression in HMCs was detected by polymerase chain reaction and western blotting. **RESULTS:** Laser confocal microscopy revealed that HMCs took up Dil-Ox-LDL. Treatment of HMCs with 5 ng/ml IL-1beta for 24 h significantly increased uptake of Dil-Ox-LDL. IL-1beta also promoted LOX-1 mRNA and protein expression in a dose-dependent manner. Moreover, ABCA1 mRNA and protein expression were reduced by IL-1beta in lipid-loaded HMCs in a dose-dependent manner. **CONCLUSIONS:** IL-1beta promotes the uptake of Ox-LDL and expression of LOX-1 in HMCs, whereas it inhibits expression of ABCA1 under lipid load. The imbalance in intracellular cholesterol resulted by IL-1beta can in turn transform HMCs into foam cells and aggravate glomerulosclerosis.

[33] Bal Topcu D, Tugcu G, Ozcan F et al. **Plasma Ceramides and Sphingomyelins of Pediatric Patients Increase in Primary Ciliary Dyskinesia but Decrease in Cystic Fibrosis.** *Lipids* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32120452>

ABSTRACT

We investigated plasma sphingomyelin (CerPCho) and ceramide (Cer) levels in pediatric patients with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD). Plasma samples were obtained from CF

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(n = 19) and PCD (n = 7) patients at exacerbation, discharge, and stable periods. Healthy children (n = 17) of similar age served as control. Levels of 16-24 CerPCho and 16-24 Cer were measured by LC-MS/MS. Concentrations of all CerPCho and Cer species measured at exacerbation were significantly lower in patients with CF than PCD. 16, 18, 24 CerPCho, and 22, 24 Cer in exacerbation; 18, 24 CerPCho, and 18, 20, 22, 24 Cer at discharge; 18, 24 CerPCho and 24 Cer at stable period were significantly lower in CF patients than healthy children ($p < 0.001$ and $p < 0.05$). All CerPCho and Cer levels of PCD patients were significantly higher except 24 CerPCho and 24 Cer during exacerbation, 24 CerPCho at discharge, and 18, 22 CerPCho levels at stable period ($p < 0.001$ and $p < 0.05$) compared with healthy children. There was no significant difference among exacerbation, discharge, and stable periods in each group for Cer and CerPCho levels. This is the first study measuring plasma Cer and CerPCho levels in PCD and third study in CF patients. The dramatic difference in plasma levels of most CerPCho and Cer species found between two diseases suggest that cilia pathology in PCD and CFTR mutation in CF seem to alter sphingolipid metabolism possibly in opposite directions.

[34] *Eser Faki H, Tras B, Uney K. Alpha lipoic acid and vitamin E improve atorvastatin-induced mitochondrial dysfunctions in rats. Mitochondrion* 2020; 52:83-88.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32119925>

ABSTRACT

To determine the effects of alpha lipoic acid (ALA) and vitamin E (Vit E) on mitochondrial dysfunction caused by statins. A total of 38 Wistar Albino rats were used in this study. The control group received dimethyl sulfoxide. The atorvastatin (A) group received atorvastatin (10 mg/kg). The A + ALA group received atorvastatin (10 mg/kg) and ALA (100 mg/kg). The A + Vit E group was administered atorvastatin (10 mg/kg) and Vit E (100 mg/kg). The A + ALA + Vit E group was administered atorvastatin (10 mg/kg), ALA (100 mg/kg) and Vit E (100 mg/kg). All applications were administered simultaneously by gavage for 20 days. ATP level and complex I activity were measured from liver, muscle, heart, kidney and brain. Atorvastatin significantly decreased the ATP levels in heart and kidney, while a slight decrease was seen in liver, muscle and brain. Atorvastatin caused an insignificant decrease in the complex I activity in all tissues examined. ALA administration significantly improved the ATP levels in the liver, heart and kidney, while Vit E improved the ATP levels in all tissues except the muscle compared to Atorvastatin group. Single administration of both ALA and vit E ameliorated complex I activity in the muscle, heart, kidney and brain. The combination of ALA and Vit E significantly improved the ATP levels in the liver, heart, kidney and brain and also provided significant improvements the complex I activity in all tissues. The undesirable effects of Atorvastatin on mitochondrial functions in this study ameliorated by using ALA and/or Vit E alone and in combination.

[35] *Kutryb-Zajac B, Jablonska P, Hebanowska A et al. Statin treatment of patients with calcific aortic valve disease modulates extracellular adenosine metabolism on the cell surface of the aortic valve. Nucleosides Nucleotides Nucleic Acids* 2020:1-11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32126886>

ABSTRACT

Statins efficiently prevent cardiovascular events by lipid-dependent and independent mechanisms. We hypothesize that part of these protective effects could be associated with an increased

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extracellular adenosine signaling. We demonstrated previously that aortic valves obtained from patients with calcific aortic valve disease (CAVD) disclosed disturbances in extracellular adenosine metabolism. This study aimed to analyze the impact of statin treatment on extracellular nucleotides and adenosine metabolism in aortic valves originated from CAVD patients and to elucidate potential mechanisms that are involved in the regulation of ecto-enzyme activities by statins. Aortic valves of CAVD patients treated with statins (n = 45) revealed higher adenosine production and its lower degradation than in non-treated patients (n = 28). Statin treatment was also related to the improvement in pre-operative echocardiographic data indicating milder aortic valve stenosis and a better function of the left ventricle. The rates of aortic valve adenosine conversions correlated with plasma lipid profile parameters, within both statin-treated and non-treated groups. Valvular extracellular AMP hydrolysis correlated negatively, while adenosine deamination positively with plasma total and LDL cholesterol. Atorvastatin treatment of murine heart endothelial cells led to the enhanced ecto-5'-nucleotidase (CD73) and decreased ecto-adenosine deaminase (eADA) activity. When endothelial cells were stimulated with thrombin that induces endothelial cell exocytosis, activities of both cell-surface CD73 and eADA were increased, while co-treatment with atorvastatin reversed only thrombin-induced eADA activity. In conclusion, early intervention with statins may provide beneficial effects for CAVD therapy. Here, we presented results showing that these protective outcomes could be mediated via the regulation of extracellular adenosine metabolism pathways.

[36] *Kuszewski JC, Wong RHX, Wood LG, Howe PRC. Effects of fish oil and curcumin supplementation on cerebrovascular function in older adults: A randomized controlled trial. Nutrition, metabolism, and cardiovascular diseases : NMCD 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32127335>

ABSTRACT

BACKGROUND AND AIMS: Chronic conditions such as obesity, which contribute to endothelial dysfunction in older adults, can cause impairments in cerebrovascular perfusion, which is associated with accelerated cognitive decline. Supplementing the diet with bioactive nutrients that can enhance endothelial function, such as fish oil or curcumin, may help to counteract cerebrovascular dysfunction. **METHODS AND RESULTS:** A 16-week double-blind, randomized placebo-controlled trial was undertaken in 152 older sedentary overweight/obese adults (50-80 years, body mass index: 25-40 kg/m²) to investigate effects of fish oil (2000 mg docosahexaenoic acid + 400 mg eicosapentaenoic acid/day), curcumin (160 mg/day) or a combination of both on cerebrovascular function (measured by Transcranial Doppler ultrasound), systemic vascular function (blood pressure, heart rate and arterial compliance) and cardiometabolic (fasting glucose and blood lipids) and inflammatory (C-reactive protein) biomarkers. The primary outcome, cerebrovascular responsiveness to hypercapnia, was not affected by the interventions. However, cerebral artery stiffness was significantly reduced in males following fish oil supplementation (P = 0.007). Furthermore, fish oil reduced heart rate (P = 0.038) and serum triglycerides (P = 0.006) and increased HDL cholesterol (P = 0.002). Curcumin did not significantly affect these outcomes either alone or in combination with fish oil. **CONCLUSION:** Regular supplementation with fish oil but not curcumin improved biomarkers of cardiovascular and cerebrovascular function. The combined supplementation did not result in additional benefits. Further studies are warranted to identify an efficacious curcumin dose and to characterize (in terms of sex, BMI, cardiovascular and metabolic

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risk factors) populations whose cerebrovascular and cognitive functions might benefit from either intervention. CLINICAL TRIAL REGISTRATION: ACTRN12616000732482p.

[37] *Li D, Wu T, Wang T et al. Effects of sodium glucose cotransporter 2 inhibitors on risk of dyslipidemia among patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Pharmacoeconomics and drug safety 2020.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32124527>

ABSTRACT

PURPOSE: Sodium glucose cotransporter 2 (SGLT2) inhibitors are shown to cause small, but significant changes of lipid profiles, we aim to investigate whether such altered lipid profiles can be translated into clinically meaningful changes in dyslipidemia. **METHODS:** PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized controlled trials (RCTs) that compared SGLT2 inhibitors with placebo or other oral glucose-lowering drugs in patients with type 2 diabetes mellitus and reported the events of dyslipidemia. A random-effect meta-analysis was performed to calculate the pooled estimates with risk ratio (RR) for dyslipidemia risk and weighted mean difference for lipid profiles with their 95% confidential intervals (CIs). **RESULTS:** Of 2427 studies identified, 15 RCTs involving 7578 patients were included. This meta-analysis found no association between SGLT2 inhibitors and risk of dyslipidemia (RR: 1.13; 95% CI: 0.91-1.40). However, SGLT2 inhibitors were significantly associated with increases in total cholesterol by 0.15 mmol/L, low-density lipoprotein cholesterol by 0.12 mmol/L, and high-density lipoprotein cholesterol by 0.07 mmol/L while they can significantly decrease triglycerides by -0.12 mmol/L compared to controls. **CONCLUSIONS:** SGLT2 inhibitors were not associated with increased risk of dyslipidemia. Further trials with longitudinal assessment are needed to assess the effect of SGLT2 inhibitors on trajectories of changes of lipid metabolism.

[38] *Siwek M, Woron J, Gorostowicz A, Wordliczek J. Adverse effects of interactions between antipsychotics and medications used in the treatment of cardiovascular disorders.*

Pharmacological reports : PR 2020; 72:350-359.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32124390>

ABSTRACT

BACKGROUND: High level of comorbidity between bipolar disorder or schizophrenia and cardiovascular diseases (CVD) in clinical practice may contribute to drug-drug interactions between medications used in these conditions. The aim of this study was to evaluate harmful interactions between antipsychotics and medications used in treatment of CVD. **METHODS:** The analysis of 52 cases of adverse reactions with a clinical picture indicates that they were the result of the combination of antipsychotic with cardiovascular medications. **RESULTS:** The highest number of interactions with antipsychotics was recorded among beta-blockers (n = 13, 25% of all cases), including cardiac arrhythmias [atrial fibrillation (n = 1): risperidone plus atenolol; bradycardia (n = 1): perphenazine with metoprolol; ventricular arrhythmias: sertindole with metoprolol (n = 1) and ziprasidone with sotalol (n = 3)] and hypotension [chlorprothixene with nebivolol or metoprolol (n = 2)]. 12 cases concerned statins-myalgia, myopathy, or creatine kinase elevation appeared after combination of atorvastatin with haloperidol (n = 1), quetiapine (n = 3) or risperidone (n = 1), and simvastatin with quetiapine (n = 5) or risperidone (n = 2). There were also cases of interactions observed for the use of antipsychotics with anti-arrhythmic drugs (amiodarone, flecainide,

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propafenone) (n = 11), calcium channel blockers (n = 6), and other cardiac medications: clonidine, dabigatran, doxazosin, ivabradine, and losartan (n = 10). CONCLUSIONS: Due to a high risk of interactions and related adverse effects, particular attention should be paid while using cardiovascular medications with antipsychotics. Clinical decisions should be preceded by a detailed analysis of safety, risk-benefit ratio to search for, as safe as possible, drug combinations.

[39] Sun D, Zhang F, Ma T et al. **Atorvastatin alleviates left ventricular remodeling in isoproterenol-induced chronic heart failure in rats by regulating the RhoA/Rho kinase signaling pathway.** *Pharmacological reports* : PR 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32144744>

ABSTRACT

BACKGROUND: Chronic heart failure (CHF) is characterized by left ventricular dysfunction and altered autonomic control of cardiac function. This study aimed to investigate the effects of atorvastatin on left ventricular remodeling (LVR) and cardiac function in rats with isoproterenol-induced CHF and the possible mechanism. METHODS: An isoproterenol-induced CHF model was established in rats, which were subsequently treated with atorvastatin. Echocardiography, hemodynamic, and left ventricular mass indexes were assessed. The mRNA expression of RhoA, Rho kinase, and endothelial nitric oxide synthase (eNOS) was determined by RT-qPCR. The protein expression of myosin-binding subunit (MBS), MBS-P, eNOS, phosphorylated-eNOS, RhoA, and Rho kinase was measured by Western blot analysis. The relative activity of NADPH oxidase, ROS, and NO was assessed by ELISA. RESULTS: Isoproterenol-induced CHF rats treated with atorvastatin exhibited decreased left ventricular end-systolic dimension, left ventricular end-diastolic dimension, left ventricular end-diastolic pressure, left ventricular mass index, maximum fall rate of change in left ventricular pressure, heart rate ($p < 0.001$), expression of RhoA, Rho kinase, MBS and MBS-P ($p < 0.01$), and relative activity of NADPH oxidase, ROS and NO ($p < 0.05$) and increased left ventricular short axis fractional shortening, left ventricular end-systolic pressure, maximum rise rate of change in left ventricular pressure ($p < 0.001$) and expression of eNOS, and phosphorylated-eNOS ser1177 (all $p < 0.05$) compared with those of rats with isoproterenol-induced CHF. CONCLUSION: We demonstrated that atorvastatin inhibits LVR and improves cardiac function in rats with isoproterenol-induced CHF through inhibition of the RhoA/Rho kinase signaling pathway.

[40] Reynolds AN, Akerman AP, Mann J. **Dietary fibre and whole grains in diabetes management: Systematic review and meta-analyses.** *PLoS medicine* 2020; 17:e1003053.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32142510>

ABSTRACT

BACKGROUND: Fibre is promoted as part of a healthy dietary pattern and in diabetes management. We have considered the role of high-fibre diets on mortality and increasing fibre intake on glycaemic control and other cardiometabolic risk factors of adults with prediabetes or diabetes. METHODS AND FINDINGS: We conducted a systematic review of published literature to identify prospective studies or controlled trials that have examined the effects of a higher fibre intake without additional dietary or other lifestyle modification in adults with prediabetes, gestational diabetes, type 1 diabetes, and type 2 diabetes. Meta-analyses were undertaken to determine the effects of higher fibre intake on all-cause and cardiovascular mortality and increasing fibre intake on glycaemic control and a range of cardiometabolic risk factors. For trials, meta regression

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analyses identified further variables that influenced the pooled findings. Dose response testing was undertaken; Grading of Recommendations Assessment, Development and Evaluation (GRADE) protocols were followed to assess the quality of evidence. Two multicountry cohorts of 8,300 adults with type 1 or type 2 diabetes followed on average for 8.8 years and 42 trials including 1,789 adults with prediabetes, type 1, or type 2 diabetes were identified. Prospective cohort data indicate an absolute reduction of 14 fewer deaths (95% confidence interval (CI) 4-19) per 1,000 participants over the study duration, when comparing a daily dietary fibre intake of 35 g with the average intake of 19 g, with a clear dose response relationship apparent. Increased fibre intakes reduced glycated haemoglobin (HbA1c; mean difference [MD] -2.00 mmol/mol, 95% CI -3.30 to -0.71 from 33 trials), fasting plasma glucose (MD -0.56 mmol/L, 95% CI -0.73 to -0.38 from 34 trials), insulin (standardised mean difference [SMD] -2.03, 95% CI -2.92 to -1.13 from 19 trials), homeostatic model assessment of insulin resistance (HOMA IR; MD -1.24 mg/dL, 95% CI -1.72 to -0.76 from 9 trials), total cholesterol (MD -0.34 mmol/L, 95% CI -0.46 to -0.22 from 27 trials), low-density lipoprotein (LDL) cholesterol (MD -0.17 mmol/L, 95% CI -0.27 to -0.08 from 21 trials), triglycerides (MD -0.16 mmol/L, 95% CI -0.23 to -0.09 from 28 trials), body weight (MD -0.56 kg, 95% CI -0.98 to -0.13 from 18 trials), Body Mass Index (BMI; MD -0.36, 95% CI -0.55 to -0.16 from 14 trials), and C-reactive protein (SMD -2.80, 95% CI -4.52 to -1.09 from 7 trials) when compared with lower fibre diets. All trial analyses were subject to high heterogeneity. Key variables beyond increasing fibre intake were the fibre intake at baseline, the global region where the trials were conducted, and participant inclusion criteria other than diabetes type. Potential limitations were the lack of prospective cohort data in non-European countries and the lack of long-term (12 months or greater) controlled trials of increasing fibre intakes in adults with diabetes. CONCLUSIONS: Higher-fibre diets are an important component of diabetes management, resulting in improvements in measures of glycaemic control, blood lipids, body weight, and inflammation, as well as a reduction in premature mortality. These benefits were not confined to any fibre type or to any type of diabetes and were apparent across the range of intakes, although greater improvements in glycaemic control were observed for those moving from low to moderate or high intakes. Based on these findings, increasing daily fibre intake by 15 g or to 35 g might be a reasonable target that would be expected to reduce risk of premature mortality in adults with diabetes.

[41] *Barthold D, Joyce G, Diaz Brinton R et al. Association of combination statin and antihypertensive therapy with reduced Alzheimer's disease and related dementia risk. PLoS one* 2020; 15:e0229541.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32130251>

ABSTRACT

BACKGROUND: Hyperlipidemia and hypertension are modifiable risk factors for Alzheimer's disease and related dementias (ADRD). Approximately 25% of adults over age 65 use both antihypertensives (AHTs) and statins for these conditions. While a growing body of evidence found statins and AHTs are independently associated with lower ADRD risk, no evidence exists on simultaneous use for different drug class combinations and ADRD risk. Our primary objective was to compare ADRD risk associated with concurrent use of different combinations of statins and antihypertensives. METHODS: In a retrospective cohort study (2007-2014), we analyzed 694,672 Medicare beneficiaries in the United States (2,017,786 person-years) who concurrently used both

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statins and AHTs. Using logistic regression adjusting for age, socioeconomic status and comorbidities, we quantified incident ADRD diagnosis associated with concurrent use of different statin molecules (atorvastatin, pravastatin, rosuvastatin, and simvastatin) and AHT drug classes (two renin-angiotensin system (RAS)-acting AHTs, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs), vs non-RAS-acting AHTs). FINDINGS: Pravastatin or rosuvastatin combined with RAS-acting AHTs reduce risk of ADRD relative to any statin combined with non-RAS-acting AHTs: ACEI+pravastatin odds ratio (OR) = 0.942 (CI: 0.899-0.986, $p = 0.011$), ACEI+rosuvastatin OR = 0.841 (CI: 0.794-0.892, $p < 0.001$), ARB+pravastatin OR = 0.794 (CI: 0.748-0.843, $p < 0.001$), ARB+rosuvastatin OR = 0.818 (CI: 0.765-0.874, $p < 0.001$). ARBs combined with atorvastatin and simvastatin are associated with smaller reductions in risk, and ACEI with no risk reduction, compared to when combined with pravastatin or rosuvastatin. Among Hispanics, no combination of statins and RAS-acting AHTs reduces risk relative to combinations of statins and non-RAS-acting AHTs. Among blacks using ACEI+rosuvastatin, ADRD odds were 33% lower compared to blacks using other statins combined with non-RAS-acting AHTs (OR = 0.672 (CI: 0.548-0.825, $p < 0.001$)). CONCLUSION: Among older Americans, use of pravastatin and rosuvastatin to treat hyperlipidemia is less common than use of simvastatin and atorvastatin, however, in combination with RAS-acting AHTs, particularly ARBs, they may be more effective at reducing risk of ADRD. The number of Americans with ADRD may be reduced with drug treatments for vascular health that also confer effects on ADRD.

[42] *Eckardstein AV*. [CME-Laboratory 61: New European Consensus Recommendations on Dyslipidemia]. *Praxis* 2020; 109:215-220.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32126909>

ABSTRACT

CME-Laboratory 61: New European Consensus Recommendations on Dyslipidemia Abstract. The lipid status primarily serves to estimate the risk of atherosclerotic cardiovascular diseases (ASCVD). LDL cholesterol (LDL-C) is the primary target of lipid-lowering therapies. NonHDL cholesterol and apolipoprotein B are secondary targets. The European Cardiology and Atherosclerosis Societies have lowered their treatment targets for all risk groups. Triglycerides and HDL cholesterol are also recommended for risk assessment, but are not therapeutic goals. Lipoprotein (a) is a strongly genetically determined ASCVD risk factor and contains a statin-resistant part of LDL-C. The quality of laboratory diagnostics for all lipid risk factors is in need of improvement due to the fact that it is too dependent on methods and in view of the indication of new and expensive lipid-modifying therapies.

[43] *Limwattananon C, Soontornpas C, Waleekhachonloet O et al*. Effects of restrictive reimbursement on the prescription of and expenditure on non-essential lipid-lowering drugs. *Res Social Adm Pharm* 2020.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32144087>

ABSTRACT

BACKGROUND: The rapid cost escalation of the government employee scheme in Thailand was driven by the overprescription of non-essential drugs (NEDs), which were not listed in the National Lists of Essential Medicines. A restrictive reimbursement policy implemented in October 2012 required prescribers to base the prescription of NEDs on six criteria, including A and B for safety, C

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for effectiveness, D for availability, and E and F for costs, hence known as the A-F policy.

OBJECTIVE: The A-F policy was examined in terms of its outcomes regarding the prescription volume and reimbursement expenditure for lipid-lowering drugs (LLDs). **METHODS:** Data on LLD prescription in 2012-2015 from outpatient settings in 29 public hospitals were standardized using quantities based on the World Health Organization's Anatomical, Therapeutic and Chemical (ATC) classification and the defined daily dose (DDD) system. The policy effects were estimated using an interrupted time-series analysis. **RESULTS:** The restrictive reimbursement policy decreased both the prescription volume and the reimbursement value of non-essential LLDs. Within the first month of policy implementation, the percentage of NEDs, as defined by DDDs and reimbursement expenditure, immediately decreased by 15.1 and 15.2% points in provincial hospitals and by 8.3 and 4.4% points in military hospitals, respectively. The prescription of NEDs continued to decrease thereafter, despite there being no statistically significant changes in the trend of decreased prescribing compared with the prepolicy period. The decrease in the prescription of NEDs resulted in the declining reimbursed amount per day and stable expenditure of LLDs as a whole. **CONCLUSION:** The effectiveness on the A-F restrictive reimbursement on NED prescribing helped stabilize the expenditure on LLDs.

[44] *Bretagne L, Aubert C, Nanchen D, Rodondi N.* **[Controversies concerning screening and treatment of primary dyslipidemias in 2020].** *Revue medicale suisse* 2020; 16:433-437.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32134221>

ABSTRACT

Familial dyslipidemia is rare compared to polygenetic causes. Nevertheless, it is important not to miss this diagnosis, as it is more strongly associated with an increased risk of early cardiovascular disease and scores for calculating cardiovascular risk are not valid in this population. Early detection and management based on lifestyle optimization and treatment of cardiovascular risk factors can delay the onset of cardiovascular complications and thus improve patients' quality of life. A LDL-Cholesterol of 4,9 mmol/l has recently been suggested as the cut-off for starting lipid lowering therapy, but remains controversial because the majority of people above this threshold do not have primary monogenic dyslipidemia. The age at which therapy should be initiated as well as the targets for treatment are also controversial.

[45] *Butty A, Rodondi N, Nanchen D.* **[New European and American guidelines on the management of blood cholesterol : similarities and differences].** *Revue medicale suisse* 2020; 16:438-443.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32134222>

ABSTRACT

Experts' guidelines for the management of dyslipidemias differ from country to country, with important differences between medical societies of Europe and the United States. Recently, new American and European guidelines have been established. These guidelines mainly differ for cardiovascular risk stratification in secondary prevention, and for LDL-cholesterol (LDL-c) goals to achieve. Similarities between guidelines include the global strategy to initiate lipid-lowering drugs, which is based first on the global cardiovascular risk, then on the LDL-c level. We are here presenting a comparison and an interpretation of these guidelines.

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[46] Garelli V, Pauchet A, Kissling S *et al.* **[The management of hypertriglyceridemia and the risk of pancreatitis]**. Revue medicale suisse 2020; 16:451-454.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32134224>

ABSTRACT

In the face of hypertriglyceridemia, the potential causes must be assessed to choose the best medical therapeutic option. In cases of secondary hypertriglyceridemia, physicians should use treatments targeting the pathophysiological mechanisms underlying the lipid disorder. Lifestyle interventions are the cornerstone of an effective treatment, to achieve controlled glycemia, blood pressure and weight loss. Only in cases where these measures are insufficient, fibrates can be trialed although their clinical benefit is controversial, with special caution when combined with statins (risk of rhabdomyolysis). Plasmapheresis or intravenous insulin therapy are only used in severe situations after a multidisciplinary decision process in the hospital setting. The clinical case presented here reminds us to assess hypertriglyceridemia in the face of any acute pancreatitis.

[47] Li S, Petraskova T, Stys N *et al.* **Dietary Supplement Use in Patients with Cardiovascular Disease.** S D Med 2020; 73:72-76.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32135055>

ABSTRACT

IMPORTANCE AND OBJECTIVE: Dietary supplements and herbs (called naturoceuticals) are commonly used by Americans, but little is known about their use in cardiovascular disease patient populations. The objective was to evaluate naturoceutical use in a sample population of cardiovascular disease patients in the U.S. DESIGN, SETTING and PARTICIPANTS: A non-blinded, single medical center clinic open questionnaire was delivered to cardiovascular clinic patients with known cardiovascular diseases. MAIN OUTCOMES AND MEASURES, AND RESULTS: Estimation of naturoceutical usage prevalence and frequency in the sample population of cardiovascular disease patients. A total of 163 patients (n = 99 males, 64 females) participated (mean age: males, 66 years; females, 64 years). Overall, 76.7 percent of participants reported using naturoceuticals. Of them, about 63.2 percent took more than one type, and 90.3 percent reported daily usage. Of the naturoceuticals reportedly being taken, multivitamins containing vitamin K were the most commonly consumed (32.3 percent male, 29.7 percent female), followed by vitamin D (23.2 percent male, 31.3 percent female) and fish oil (24.2 percent male, 15.6 percent female). CONCLUSIONS AND RELEVANCE: The present study revealed that naturoceutical use was very popular in cardiovascular disease patients, largely due to the belief that they could reduce and/or prevent symptoms and disease in general. The benefits and hazards of those naturoceuticals being used concurrent with other prescription medications were discussed.

[48] Patnode CD, Perdue LA, Rossom RC *et al.* U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. In: Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.

[49] Abbas Z, Saad M, Asim M *et al.* **The effect of twelve weeks of treatment with ezetimibe on HDV RNA level in patients with chronic hepatitis D.** The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology 2020; 31:136-141.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32141822>

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ABSTRACT

BACKGROUND/AIMS: Sodium taurocholate co-transporting polypeptide (NTCP) is the receptor for the hepatitis B virus (HBV) and hepatitis D virus (HDV) entry into hepatocytes. Ezetimibe is a cholesterol-lowering drug that possesses the pharmacophore features to inhibit NTCP. This study evaluates the efficacy of ezetimibe in patients with chronic HDV infection in a nonrandomized trial. **MATERIALS AND METHODS:** This proof of concept phase 2 trial evaluated the efficacy and safety of ezetimibe 10 mg daily in (interferon treatment-experienced or interferon ineligible) patients with chronic hepatitis D (CHD). Forty-four patients with CHD were recruited, 38 male and 6 female patients, mean age 35.2+/-8.7 (range 19-64). Fifteen (34%) patients were on concomitant nucleoside therapy, and cirrhosis was present in 14 subjects. The primary therapeutic endpoint was a decline in HDV RNA at one log or more from the baseline at week 12. **RESULTS:** The mean HDV RNA level was 5.4+/-1.3 log₁₀ IU/mL. HBeAg was non-reactive in 43 (98%). HBV DNA was undetectable in 28 (64%). One patient stopped treatment at week 4, and one patient did not follow-up. One log or more reduction in the HDV RNA levels was observed in 18/44 (41%) patients. No log reduction occurred in 16 patients, and 8 experienced a log increase. No adverse effects from the concomitant nucleoside analogue use or clinical cirrhosis were observed. The drug exhibited a positive safety profile. **CONCLUSION:** Treatment of CHD patients with ezetimibe resulted in a one log reduction of viral load in 43% (18/42) of the patients who completed the 12 weeks of therapy.

[50] *Doshi JA, Li P, Puckett JT et al. Trends and Factors Associated With Insurer Approval of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Prescriptions. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2020; 23:209-216.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=32113626>

ABSTRACT

OBJECTIVES: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is)-innovative yet costly cholesterol-lowering agents-have been subject to substantial prior authorization (PA) requirements and low approval rates. We aimed to investigate trends in insurer approval and reasons for rejection for PCSK9i prescriptions as well as associations between patients' demographic, clinical, pharmacy, payer, and PCSK9i-specific plan/coverage factors and approval. **METHODS:** We examined trends in PCSK9i approval rates and reasons for rejection using medical and prescription claims from 2015 to 2017 for individuals who received a PCSK9i prescription. We used multinomial logistic regression to estimate quarterly risk-adjusted approval rates for initial PCSK9i prescriptions and approval for any PCSK9i prescription within 30, 90, and 180 days of the initial PCSK9i prescription. For a 2016 subsample for whom we had PCSK9i-specific plan policy data, we examined factors associated with approval including PCSK9i-specific plan formulary coverage, step therapy requirements, and number of PA criteria. **RESULTS:** The main sample included 12 309 patients (mean age 64.8 years [SD = 10.8], 52.1% female, 51.5% receiving Medicare) and was similar in characteristics to the 2016 subsample (n = 6091). Approval rates varied across quarters but remained low (initial prescription, 13%-23%; within 90 days, 28%-44%). Over time, rejections owing to a lack of formulary coverage decreased and rejections owing to PA requirements increased. Lack of formulary coverage and having >=11 PA criteria in the plan policy were associated with lower odds of PCSK9i prescription approval. **CONCLUSIONS:** These findings confirm ongoing PCSK9i access issues and offer a baseline for comparison in future studies examining the impact of recent efforts to improve PCSK9i access.

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