[1] *Huang S, Zhou C, Yuan Z et al.* **The clinical value of high-density lipoprotein in the evaluation of new coronavirus pneumonia**. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 2021; 30:153-156.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33571404

ABSTRACT
BACKGROUND: The new coronavirus pneumonia (NCP, COVID-19) outbreak began in Wuhan in December 2019. The new coronavirus (2019 novel coronavirus (2019-nCoV)) can cause multiple organ damage, mainly to lung tissue, and induce inflammation in the body. OBJECTIVES: To investigate the changes of high-density lipoprotein (HDL) level in patients with COVID-19 and assess its value in the evaluation and prognosis of this disease. MATERIAL AND METHODS: This paper is a cross-sectional retrospective study. Eighty-six severe COVID-19 patients, 132 non-severe COVID-19 patients and 76 healthy individuals (control group) were recruited to measure triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) using enzyme-coupled colorimetry. RESULTS: The serum HDL-C level in COVID-19 group was 1.02 ±0.28 mmol/L which was significantly lower than in control group (1.52 ±0.55 mmol/L) ($p < 0.05$). In addition, the serum HDL-C level in severe COVID-19 group was 0.83 ±1.67 mmol/L, which was significantly lower than that in non-severe COVID-19 group (1.15 ±0.27 mmol/L) ($p < 0.05$). CONCLUSIONS: Changes in HDL levels in patients with COVID-19 can reflect the severity of the disease and have a clinical significance in establishing the prognosis.

[2] *Galappatthy P, Ranasinghe P, Liyanage CK et al.* **Core Prescribing Indicators and the Most Commonly Prescribed Medicines in a Tertiary Health Care Setting in a Developing Country**. Adv Pharmacol Pharm Sci 2021; 2021:6625377.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33564747

ABSTRACT
Irrational prescribing is common, especially in developing countries. It is important to identify the magnitude of irrational use, to take necessary steps to promote rational prescribing. We identified core prescribing indicators and commonly prescribed medicines at ward settings (IW) and outpatients' clinics (OPC) in a tertiary care hospital in Sri Lanka. A descriptive cross-sectional study was carried out at IW and OPC settings. Prescriptions were obtained from 5 major specialties (Clinical Medicine (CM), Gynaecology and Obstetrics (GO), Paediatrics, Psychiatry, and Surgery). The WHO core prescribing indicators were used to describe the pattern of prescribing, and the most commonly prescribed medicines were identified. A total of 1,318 prescriptions were analyzed. The five most commonly prescribed medicines were paracetamol (31.0%), omeprazole (20.6%), folic acid (18.3%), atorvastatin (16.2%), and salbutamol (15.3%). The average number of medicines per encounter was 4.8 ± 3.6 (IW: 5.7 ± 4; OPC: 3.8 ± 2.8; $p < 0.001$), with the highest IW (7.8 ± 4.2) and OPC (7.8 ± 2.7) values were from CM, being significantly higher than all other disciplines ($p < 0.05$). Percentage encounters with an antibiotic or an injection was 26.4% and 30.1%, respectively, with IW being significantly higher than OPC ($p < 0.001$). Percentage of medicines prescribed by generic name and from the essential medicine list (EML) was 90.1% and 91.1%, respectively, with no significant IW and OPC difference. In conclusion, a high degree of polypharmacy was noted. The use of injectable medicines, prescribing from the EML, and generic name prescribing was satisfactory; however, overall rational prescribing needs further improvement. Further investigation into the degree of rational prescribing associating it with clinical information will be important.

[3] *Jiang Y, Liu J, Chen X et al.* **Efficacy and Safety of Glucagon-Like Peptide 1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus: A Network Meta-analysis**. Adv Ther 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33582976

ABSTRACT

INTRODUCTION: The present study aimed to evaluate the effects of glucagon-like peptide 1 receptor agonists (GLP-1RAs) on clinical and safety outcomes including glycemic control and cardiometabolic indicators using network meta-analysis. METHODS: MEDLINE, Embase, and Cochrane Library Central Register of Controlled Trials were searched from inception through June 30, 2019. Randomized clinical trials comparing one or more of six eligible GLP-1RAs with placebo or another eligible GLP-1RA were identified. We further screened studies that had 24-30 week follow-up periods and target endpoints. The primary outcome was change in hemoglobin A(1c) (HbA(1c)). Secondary outcomes included additional glycemic control indicators, cardiometabolic measures, and adverse events. Frequentist random-effect network meta-analyses were conducted for effect comparison. RESULTS: The NMA synthesized evidence from 54 studies covering 23,209 patients and 18 GLP-1RA regimens. All included GLP-1RA regimens except liraglutide 0.3 mg once weekly (QW) significantly lowered HbA(1c) after 24-30 weeks compared with placebo. The pairwise comparison of HbA(1c)-lowering effect showed that dulaglutide 0.75 mg QW, dulaglutide 1.5 mg QW, exenatide 2 mg QW, liraglutide 0.9 mg QW, liraglutide 1.2 mg QW, liraglutide 1.8 mg QW, loxenatide 100 μg QW, and loxenatide 200 μg QW were not significantly outperformed by any of the other regimens. The effects on blood pressure, weight, and lipids were relatively mixed. The GLP-1RA regimens had comparable safety profiles with regard to hypoglycemia and adverse events. CONCLUSION: Regimens of GLP-1RAs had differential glycemic control and cardiometabolic effectiveness. Policymaking and patient-centric clinical decisions should take into consideration the comparative effectiveness profiles.

[4] *Díaz-López A, Becerra-Tomás N, Ruiz V et al.* **Effect of an Intensive Weight-Loss Lifestyle Intervention on Kidney Function: A Randomized Controlled Trial**. American journal of nephrology 2021:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33556935

ABSTRACT

INTRODUCTION: Large randomized trials testing the effect of a multifactorial weight-loss lifestyle intervention including Mediterranean diet (MedDiet) on renal function are lacking. Here, we evaluated the 1-year efficacy of an intensive weight-loss intervention with an energy-reduced MedDiet (erMedDiet) plus increased physical activity (PA) on renal function. METHODS: Randomized controlled "PREvención con DIeta MEDiterránea-Plus" (PREDIMED-Plus) trial is conducted in 23 Spanish centers comprising 208 primary care clinics. Overweight/obese (n = 6,719) adults aged 55-75 years with metabolic syndrome were randomly assigned (1:1) to an intensive weight-loss lifestyle intervention with an erMedDiet, PA promotion, and behavioral support (intervention) or usual-care advice to adhere to an energy-unrestricted MedDiet (control) between September 2013 and December 2016. The primary outcome was 1-year change in estimated glomerular filtration rate (eGFR). Secondary outcomes were changes in urine albumin-to-creatinine ratio (UACR), incidence of moderately/severely impaired eGFR (<60 mL/min/1.73 m2) and micro- to macroalbuminuria (UACR

≥30 mg/g), and reversion of moderately (45 to <60 mL/min/1.73 m2) to mildly impaired GFR (60 to <90 mL/min/1.73 m2) or micro- to macroalbuminuria. RESULTS: After 1 year, eGFR declined by 0.66 and 1.25 mL/min/1.73 m2 in the intervention and control groups, respectively (mean difference, 0.58 mL/min/1.73 m2; 95% CI: 0.15-1.02). There were no between-group differences in mean UACR or micro- to macroalbuminuria changes. Moderately/severely impaired eGFR incidence and reversion of moderately to mildly impaired GFR were 40% lower (HR 0.60; 0.44-0.82) and 92% higher (HR 1.92; 1.35-2.73), respectively, in the intervention group. CONCLUSIONS: The PREDIMED-Plus lifestyle intervention approach may preserve renal function and delay CKD progression in overweight/obese adults.

[5] *Dagli-Hernandez C, de Freitas RCC, Marçal E et al.* **Late response to rosuvastatin and statin-related myalgia due to SLCO1B1, SLCO1B3, ABCB11, and CYP3A5 variants in a patient with Familial Hypercholesterolemia: a case report**. Annals of translational medicine 2021; 9:76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33553369

ABSTRACT

Statins are the most widely used cholesterol-lowering drugs for cardiovascular diseases prevention. However, some patients are refractory to treatment, whereas others experience statin-related adverse events (SRAE). It has been increasingly important to identify pharmacogenetic biomarkers for predicting statin response and adverse events. This case report describes a female patient with familial hypercholesterolemia (FH) who showed late response to rosuvastatin and experienced myalgia on statin treatment. In the first visit (V1), the patient reported myalgia to rosuvastatin 40 mg, which was interrupted for a 6-week wash-out period. In V2, rosuvastatin 20 mg was reintroduced, but her lipid profile did not show any changes after 6 weeks (V3) (LDL-c: 402 vs. 407 mg/dL). Her lipid profile markedly improved after 12 weeks of treatment (V4) (LDL-c: 208 mg/dL), suggesting a late rosuvastatin response. Her adherence to treatment was similar in V1 and V3 and no drug interactions were detected. Pharmacogenetic analysis revealed that the patient carries low-activity variants in SLCO1B1*1B and*5, SLCO1B3 (rs4149117 and rs7311358), and ABCB11 rs2287622, and the non-functional variant in CYP3A5*3. The combined effect of variants in pharmacokinetics-related genes may have contributed to the late response to rosuvastatin and statin-related myalgia. Therefore, they should be considered when assessing a patient's response to statin treatment. To the best of our knowledge, this is the first report of a pharmacogenetic analysis on a case of late rosuvastatin response.

[6] *Ji XW, Feng GS, Li HL et al.* **Gender differences of relationship between serum lipid indices and type 2 diabetes mellitus: a cross-sectional survey in Chinese elderly adults**. Annals of translational medicine 2021; 9:115.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33569417

ABSTRACT

BACKGROUND: To investigate the gender differences of the relationships between clinical serum lipid indices and type 2 diabetes mellitus (T2DM) in Chinese elderly adults. METHODS: Between 2014 and 2016, participants selected from three communities in an urban district of Shanghai were measured for serum lipid indices of low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol (TC), and triglyceride (TG). Age and multivariate adjusted logistic regression models were utilized to estimate the odds ratios (ORs) and 95%

confidence intervals (CIs) of serum lipid indices on T2DM prevalence. RESULTS: In total, 4,023 male and 3,862 female participants were included in this study, with the T2DM prevalence proportions of 13.03% and 11.73%, respectively. In association analysis, the serum levels of LDL-c, HDL-c, TC were significant between non-T2DM individuals and T2DM patients in men, but the HDL-c and TG in women. LDL-c/HDL-c, TG/HDL-c, and TC/HDL-c ratios were associated with the T2DM prevalence only in women. In the multivariate analysis, a higher serum LDL-c level was positively associated with a reduced risk of T2DM prevalence in men with OR (95% CI) of 0.57 (0.39-0.85) (P=0.006). Higher ratios of LDL-c/HDL-c, TG/HDL-c, and TC/HDL-c were all more likely associated with the decreased risks of T2DM prevalence with the ORs ranging from 0.45 to 0.62 in men (all P<0.05), but not in women. CONCLUSIONS: High LDL-c concentration was significantly associated with a lower T2DM prevalence in men. A gender difference of the associations between the lipid ratios and T2DM prevalence was observed for LDL-c/HDL-c and TC/HDL-c ratios, which might be validated in female T2DM prevalence in the future.

[7] *Yuan Y, Zhao X, Teng X, Zhang Y*. **Identifying familial hypercholesterolemia in an early onset ischemic cerebrovascular disease patient and the cascade screening in the pedigree: a case report**. Annals of translational medicine 2021; 9:180.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33569482
ABSTRACT
Familial hypercholesterolemia (FH) is one of the most common inherited metabolic disorders characterized by elevated low-density lipid cholesterol (LDL-C) levels that lead to coronary artery disease at an early age and a low occurrence of cerebrovascular disease. Low-density lipoprotein receptor (LDLR) gene mutation is the most common cause of FH. Here, we report a case of a 47-year-old woman who had multiple carotid artery stenosis and brain ischemic foci, an elevated level of LDL-C, underwent eyelid xanthoma excision, and a family history of hyperlipidemia. Thereafter, she was diagnosed with FH according to the Dutch Lipid Clinical Network criteria and whole genome sequencing revealed compound heterozygous LDLR mutations. However, she denied a history of coronary heart disease (CAD). The patient underwent stenting of the right subclavicular artery and right internal carotid artery in our hospital. Lipid-lowering drugs were also administered to prevent stroke recurrence. During a 3-year follow-up, the blood lipid level of the patient reduced, and the condition of intracranial and extracranial vascular stenosis improved. Furthermore, a cascade screening was performed in her pedigree, and 7/9 family members were found to have elevated LDL-C, 6/7 were found to carry one of the two LDLR variants detected in the proband, and in 4/6, the carotid intima-media thickness was ≥1 mm, which was predicted as a high risk factor of cerebrovascular disease. Her relatives with high risks of cardiovascular or cerebrovascular diseases have been under lipid monitoring and management of risk factors since then. To date, no cardiovascular or cerebrovascular event has been reported. In conclusion, this case reminds us to consider FH screening in early-onset stroke or transient ischemic attack patients with elevated LDL-C level. Our report also demonstrates the beneficial role of genetic testing and cascade screening in the relatives of FH patients.

[8] *Gamboa R, Jaramillo-Estrella MJ, Martínez-Alvarado MDR et al.* **Monocyte Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1) Expression Correlates with cIMT in Mexican Hypertensive Patients**. Arquivos brasileiros de cardiologia 2021; 116:56-65.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33566965

ABSTRACT

BACKGROUND: Arterial hypertension (HTA) represents a major risk factor for cardiovascular morbidity and mortality. It is not yet known which specific molecular mechanisms are associated with the development of essential hypertension. OBJECTIVE: In this study, we analyzed the association between LRP1 monocyte mRNA expression, LRP1 protein expression, and carotid intima media thickness (cIMT) of patients with essential hypertension. METHODS: The LRP1 monocyte mRNA expression and protein levels and cIMT were quantified in 200 Mexican subjects, 91 normotensive (NT) and 109 hypertensive (HT). Statistical significance was defined as $p < 0.05$. RESULTS: HT patients group had highly significant greater cIMT as compared to NT patients ($p=0.002$) and this correlated with an increase in the expression of LRP1 mRNA expression (6.54 vs. 2.87) ($p = 0.002$) and LRP1 protein expression (17.83 vs. 6.25), respectively ($p = 0.001$). These differences were maintained even when we divided our study groups, taking into account only those who presented dyslipidemia in both, mRNA ($p = 0.041$) and proteins expression ($p < 0.001$). It was also found that Ang II mediated LRP1 induction on monocytes in a dose and time dependent manner with significant difference in NT vs. HT (0.195 ± 0.09 vs. 0.226 ± 0.12, $p = 0.046$). CONCLUSION: An increase in cIMT was found in subjects with hypertension, associated with higher mRNA and LRP1 protein expressions in monocytes, irrespective of the presence of dyslipidemias in HT patients. These results suggest that LRP1 upregulation in monocytes from Mexican hypertensive patients could be involved in the increased cIMT. (Arq Bras Cardiol. 2021; 116(1):56-65).

[9] *Póvoa R*. **New Markers of Carotid Thickening in Hypertension**. Arquivos brasileiros de cardiologia 2021; 116:66-67.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33566966

ABSTRACT

[10] *Rezano A, Ridhayanti F, Rangkuti AR et al.* **Cytotoxicity of Simvastatin in Human Breast Cancer MCF-7 and MDA-MB-231 Cell Lines**. Asian Pacific journal of cancer prevention : APJCP 2021; 22:33-42.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33576210

ABSTRACT

OBJECTIVE: Statins, 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors, have been shown to be effective in the treatment of cardiovascular disease. Recent reports demonstrate an anticancer effect induced by statins on lung and prostate cancer cells. The present study aimed to investigate the therapeutic potential of Simvastatin can serve as chemotherapeutic agent against human breast cancer MCF-7 and MDA-MB-231 cell lines. METHODS: The cytotoxic effect of simvastatin against breast cancer cells were evaluated using MTT assay. The related mechanism of cell death was further determined by trypan blue staining, morphological changes observation, and drug combination index. RESULTS: The results showed that simvastatin treatment substantially induced cell death in a dose-dependent and time-dependent manner on MCF-7 and MDA-MB-231 cells. Simvastatin exhibited a highly cytotoxic effect on MCF7 and MDA-MB-231 with half-maximal (50%) inhibitory concentration (IC50) 8.9 µM and 4.5 µM respectively. Consistently, we observed antiproliferative effect of Simvastatin was associated with apoptosis on breast cancer cell lines by determination of morphological changes. Moreover, this drug demonstrated a synergistic activity with

doxorubicin on triggering cell death in MCF7 cells, but not in MDA-MB-231. CONCLUSION: Simvastatin has a potent cytotoxic effect resulting in the death of human breast cancer MCF-7 and MDA-MB-231 cell lines, demonstrating its potential as a new candidate for cancer drug.
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[11] *Olaniyi KS, Badejogbin OC, Saliu SB, Olatunji LA*. **Rescue effect of sodium acetate in diabetes mellitus-associated testicular dysfunction is accompanied by PCSK9 modulation**. Biochimie 2021; 184:52-62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33581194
ABSTRACT
Diabetes mellitus (DM) is a global health burden, affecting about 463 million of the adult population worldwide. Approximately 94% of diabetic male individuals develop varying degrees of testicular disorders (TDs), which usually result in hypogonadism, hypotestosteronemia and defective spermatogenesis and steroidogenesis. Short chain fatty acids (SCFAs) have shown potential benefits in metabolic health. However, its effect on TD associated with DM is not clear. Howbeit, the present study investigated the hypothesis that SCFAs, acetate would ameliorate TD accompanying DM, possibly by suppressing proprotein convertase subtilisin/kexin type 9 (PCSK9). Male Wistar rats (210-240 g) were allotted into groups (n = 6/group): control (vehicle; po), DM with/without 200 mg/kg (po) of sodium acetate (SAc). Diabetes was induced by streptozotocin 65 mg/kg (iv) after a dose of nicotinamide (110 mg/kg). Semen/biochemical and histological analyses were performed with appropriate methods. In addition to hyperglycemia, hyperinsulinemia and reduced insulin sensitivity, DM led to increased serum and testicular triglyceride or total cholesterol/high-density lipoprotein cholesterol ratio, low-density lipoprotein cholesterol, malondialdehyde, TNF-α, IL-6 and PCSK9 as well as reduced high-density lipoprotein cholesterol and glutathione. Moreover, DM caused TD which is characterized by altered sperm parameters, disrupted tissue architecture, atrophied seminiferous tubules, deleterious spermatogonia, disappearance of lumen and cellular degeneration as well as decreased luteinizing hormone and testosterone. However, the administration of SAc attenuated these alterations. The study demonstrates that DM-induced TD is accompanied by elevated PCSK9. The results however suggest that SAc rescues testicular disorder/dysfunction associated with DM by suppression of PCSK9 and improvement of insulin sensitivity.

[12] *Nenna A, Nappi F, Lusini M et al.* **Effect of Statins on Platelet Activation and Function: From Molecular Pathways to Clinical Effects**. BioMed research international 2021; 2021:6661847.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33564680
ABSTRACT
PURPOSE: Statins are a class of drugs widely used in clinical practice for their lipid-lowering and pleiotropic effects. In recent years, a correlation between statins and platelet function has been unveiled in the literature that might introduce new therapeutic indications for this class of drugs. This review is aimed at summarizing the mechanisms underlying statin-platelet interaction in the cardiologic scenario and building the basis for future in-depth studies. METHODS: We conducted a literature search through PubMed, Embase, EBSCO, Cochrane Database of Systematic Reviews, and Web of Science from their inception to June 2020. RESULTS: Many pathways could explain the interaction between statins and platelets, but the specific effect depends on the specific compound. Some could be mediated by enzymes that allow the entry of drugs into the cell (OATP2B1) and others by enzymes that mediate their activation (PLA2, MAPK, TAX2, PPARs, AKT, and COX-1),

recruitment and adhesion (LOX-1, CD36, and CD40L), or apoptosis (BCL2). Statins also appear to have a synergistic effect with aspirin and low molecular weight heparins. Surprisingly, they seem to have an antagonistic effect with clopidogrel. CONCLUSION: There are many pathways potentially responsible for the interactions between statins and platelets. Their effect appears to be closely related, and each single effect can be barely measured. Also, the same compound might have complex downstream signaling with potentially opposite effects, i.e., beneficial or deleterious. The multiple clinical implications that can be derived as a result of this interaction, however, represent an excellent reason to develop future in-depth studies.

[13] *Surdu AM, Pînzariu O, Ciobanu DM et al.* **Vitamin D and Its Role in the Lipid Metabolism and the Development of Atherosclerosis**. Biomedicines 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33572397
ABSTRACT
Vitamin D, a crucial hormone in the homeostasis and metabolism of calcium bone, has lately been found to produce effects on other physiological and pathological processes genomically and non-genomically, including the cardiovascular system. While lower baseline vitamin D levels have been correlated with atherogenic blood lipid profiles, 25(OH)D supplementation influences the levels of serum lipids in that it lowers the levels of total cholesterol, triglycerides, and LDL-cholesterol and increases the levels of HDL-cholesterol, all of which are known risk factors for cardiovascular disease. Vitamin D is also involved in the development of atherosclerosis at the site of the blood vessels. Deficiency of this vitamin has been found to increase adhesion molecules or endothelial activation and, at the same time, supplementation is linked to the lowering presence of adhesion surrogates. Vitamin D can also influence the vascular tone by increasing endothelial nitric oxide production, as seen in supplementation studies. Deficiency can lead, at the same time, to oxidative stress and an increase in inflammation as well as the expression of particular immune cells that play a pivotal role in the development of atherosclerosis in the intima of the blood vessels, i.e., monocytes and macrophages. Vitamin D is also involved in atherogenesis through inhibition of vascular smooth muscle cell proliferation. Furthermore, vitamin D deficiency is consistently associated with cardiovascular events, such as myocardial infarction, STEMI, NSTEMI, unstable angina, ischemic stroke, cardiovascular death, and increased mortality after acute stroke. Conversely, vitamin D supplementation does not seem to produce beneficial effects in cohorts with intermediate baseline vitamin D levels.

[14] *Ezhov MV, Tmoyan NA, Afanasieva OI et al.* **Lipoprotein(a) and Cardiovascular Outcomes after Revascularization of Carotid and Lower Limbs Arteries**. Biomolecules 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33578899
ABSTRACT
BACKGROUND: Despite high-intensity lipid-lowering therapy, there is a residual risk of cardiovascular events that could be associated with lipoprotein(a) (Lp(a)). It has been shown that there is an association between elevated Lp(a) level and cardiovascular outcomes in patients with coronary heart disease. Data about the role of Lp(a) in the development of cardiovascular events after peripheral revascularization are scarce. PURPOSE: To evaluate the relationship of Lp(a) level with cardiovascular outcomes after revascularization of carotid and lower limbs arteries. METHODS: The study included 258 patients (209 men, mean age 67 years) with severe carotid and/or lower

extremity artery disease, who underwent successful elective peripheral revascularization. The primary endpoint was the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The secondary endpoint was the composite of primary endpoint and repeated revascularization. RESULTS: For 36-month follow-up, 29 (11%) primary and 128 (50%) secondary endpoints were registered. There was a greater risk of primary (21 (8%) vs. 8 (3%); hazard ratio (HR), 3.0; 95% confidence interval (CI) 1.5-6.3; $p < 0.01$) and secondary endpoints (83 (32%) vs. 45 (17%), HR, 2.8; 95% CI 2.0-4.0; $p < 0.01$) in patients with elevated Lp(a) level (≥30 mg/dL) compared to patients with Lp(a) < 30 mg/dL. Multivariable-adjusted Cox regression analysis revealed that Lp(a) was independently associated with the incidence of cardiovascular outcomes. CONCLUSIONS: Patients with peripheral artery diseases have a high risk of cardiovascular events. Lp(a) level above 30 mg/dL is significantly and independently associated with cardiovascular events during 3-year follow-up after revascularization of carotid and lower limbs arteries.

[15] *Kårhus ML, Brønden A, Lyng Forman J et al.* **Protocol for a randomised, double-blinded, placebo-controlled, double-dummy 6-week clinical trial comparing the treatment effects of the glucagon-like peptide 1 receptor agonist liraglutide versus the bile acid sequestrant colesevelam on bile acid malabsorption**. BMJ open 2021; 11:e044711.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33558360
ABSTRACT
INTRODUCTION: Bile acid malabsorption (BAM) is a socially debilitating disease characterised by high stool frequency and urgency caused by a spillover of bile acids into the colon. Bile acid sequestrants (BASs) have limited therapeutic effect but represent the only available treatment option. Cases reporting total remission of BAM-related symptoms after treatment with liraglutide, a glucagon-like peptide 1 analogue, prompted us to design a clinical trial investigating the therapeutic effect of this compound in patients with BAM. METHODS AND ANALYSIS: Fifty adult individuals with moderate or severe BAM as assessed by the (75)selenium-homotaurocholic acid test (SeHCAT) will, after a run-in period of 10 days with no BAM treatment, be randomised to either treatment with the BAS colesevelam or liraglutide (double blinded) for 6 weeks. Daily symptom diaries and questionnaires will be filled in. Blood and faecal samples will be collected and SeHCAT will be performed at baseline, after week 3 and at end of trial. The primary endpoint is change in daily stool frequency. Secondary endpoints include changes from baseline in questionnaires, biochemistry, SeHCAT and faecal bile acid content and microbial composition. ETHICS AND DISSEMINATION: The study complies with Danish and European Union legislation and is approved by the Danish Medicines Agency, the Regional Scientific Ethics Committee of the Capital Region of Denmark and the Danish Data Protection Agency. The study is monitored by the Capital Region of Denmark's good clinical practice unit. All results, positive, negative and inconclusive, will be disseminated at national and/or international scientific meetings and in peer-reviewed scientific journals. TRIAL REGISTRATION NUMBER: EudraCA: 2018-003575-34; Pre-results.

[16] *García-Ulloa AC, Lechuga-Fonseca C, Del Razo-Olvera FM et al.* **Clinician prescription of lipid-lowering drugs and achievement of treatment goals in patients with newly diagnosed type 2 diabetes mellitus**. BMJ open diabetes research & care 2021; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33568360
ABSTRACT

INTRODUCTION: Lipid control is essential in type 2 diabetes mellitus (T2DM). The aim of this study is to investigate factors associated with lipid therapy adherence and achievement of goals in real-life setting among patients with recently diagnosed T2DM. RESEARCH DESIGN AND METHODS: This is a longitudinal analysis in a center of comprehensive care for patients with diabetes. We include patients with T2DM, <5 years of diagnosis, without disabling complications (eg, amputation, myocardial infarct, stroke, proliferative retinopathy, glomerular filtration rate <60 mL/min/m(2)) and completed 2-year follow-up. The comprehensive diabetes care model includes 9 interventions in 4 initial visits and annual evaluations. Endocrinologists follow the clinic's guideline and adapt therapy to reach risk-based treatment goal. The main outcome measures were the proportion of patients meeting low-density lipoprotein cholesterol (c-LDL) (<100 mg/dL) and triglycerides (<150 mg/dL) and proportion of patients taking statin, fibrate or combination at baseline, 3 months and annual evaluations. RESULTS: We included 288 consecutive patients (54±9 years, 53.8% women), time since T2DM diagnosis 1 (0-5) year. Baseline, 10.8% patients were receiving statin therapy (46.5% moderate-intensity therapy and 4.6% high-intensity therapy), 8.3% fibrates and 4.2% combined treatment. The proportion of patients with combined treatment increased to 41.6% at 3 months, decreased to 20.8% at 1 year and increased to 38.9% at 2 years of evaluation. Patients receiving treatment met LDL and triglycerides goals at 3 months (17% vs 59.7%, relative ratio (RR)=0.89, 95% CI 0.71 to 1.12), at 1 year (17% vs 26.7%, RR=0.62, 95% CI 0.41 to 0.95) and at 2 years (17% vs 29.9%, RR=0.63, 95% CI 0.43 to 0.93). Main reasons for medication suspension: patient considered treatment was not important (37.5%) and other physician suspended treatment (31.3%). CONCLUSION: 88.2% of patients with T2DM required lipid-lowering drugs. Education for patients and physicians is critical to achieve and maintain diabetes goals. TRIAL REGISTRATION NUMBER: NCT02836808.

[17] *Choi T, Choi IY, Han K et al.* **Lipid Level, Lipid Variability, and Risk of Multiple Myeloma: A Nationwide Population-Based Study of 3,527,776 Subjects**. Cancers 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33572660

ABSTRACT

Background: There is evidence that abnormality in lipid metabolism promotes cancer development. This study investigated whether lipid level and its variability are associated with the development of MM at a population level. (2) Methods: A retrospective cohort study included a total of 3,527,776 subjects aged 40 and above who participated in ≥3 health examinations within the previous five years, including the index year (2012-2013). Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) were measured, and visit-to-visit lipid variability were calculated by variability independent of the mean (VIM) method. The study population was followed from the health examination date in the index year until the diagnosis of MM, death, or the last follow-up date (31 December 2017). (3) Results: During a median (5-95%) 5.1 years of follow-up, 969 subjects developed MM. A lower risk of MM was observed with higher quartiles of baseline lipid levels compared to the lowest quartile group (Q4 vs. Q1: adjusted hazard ratios (aHRs) 0.51, 95% confidence interval (CI) (0.42-0.61) for TC; 0.50 (0.41-0.61) for HDL-C; 0.65 (0.54-0.77) for LDL-C; and 0.72 (0.60-0.87) for TG in model (3). Among all lipid measures, only variability in HDL-C was associated with risk of MM: aHRs (95% CI) were 1.12 (0.91-1.38), 1.19 (0.97-1.46), and 1.34 (1.09-1.65) in the Q2, Q3, and Q4, respectively,

compared to the Q1 of VIM of HDL-C. (4) Conclusions: This study shows that patients with lower lipid levels and high HDL-C variability are at increased risk of developing MM.

[18] *Peng J, Zhu CG, Li JJ*. **The predictive utility of circulating PCSK9 levels on diabetes mellitus**. Cardiovascular diabetology 2021; 20:45.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33581713
ABSTRACT
Increasing data including ours have suggested that proprotein convertase subtilisin/kexin type 9 (PCSK9), a novel regulator of cholesterol metabolism, may also play an important role in the development of type 2 diabetes mellitus (T2DM) and is associated with clinical outcomes in diabetic patients. Previous studies revealed that elevated plasma PCSK9 levels had a higher incidence of new-onset T2DM. Moreover, the results of available epidemiological, preclinical, and clinical studies have indicated that plasma PCSK9 concentration is correlated with glycemic parameters and can predict the adverse cardiovascular events in diabetic patients with coronary artery disease. However, there is currently no general agreement about the association of PCSK9 with T2DM. The usefulness of the circulating PCSK9 concentration as a predictor for the risk of new-onset T2DM should be clinically prudential.

[19] *Climent E, Bea AM, Benaiges D et al.* **LDL Cholesterol Reduction Variability with Different Types and Doses of Statins in Monotherapy or Combined with Ezetimibe. Results from the Spanish Arteriosclerosis Society Dyslipidaemia Registry**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33555511
ABSTRACT
PURPOSE: Low-density lipoprotein (LDL) cholesterol reduction by statin therapy is dose-dependent, varies among different statins, and has wide inter-individual variability. The present study aimed to compare mean LDL cholesterol reduction and its variability achieved with different doses of the three statins most frequently used in monotherapy or combined with ezetimibe in a real clinical setting. METHODS: Of 5620 cases with primary hypercholesterolemia on the Spanish Arteriosclerosis Society Registry, 1004 with non-familial hypercholesterolemia and complete information on drug therapy and lipid profile were included. RESULTS: The lowest mean percentage LDL cholesterol reduction was observed with simvastatin 10 mg (32.5 ± 18.5%), while the highest mean percentage LDL reduction was obtained with rosuvastatin 40 mg (58.7 ± 18.8%). As to combined treatment, the lowest and highest mean percentage LDL cholesterol reductions were obtained with simvastatin 10 mg combined with ezetimibe (50.6 ± 24.6%) and rosuvastatin 40 mg combined with ezetimibe (71.6 ± 11.1%), respectively. Factors associated with a suboptimal response were male sex, lower age, body mass index, and baseline LDL cholesterol levels. Combined treatment was associated with less variability in LDL cholesterol reduction (OR 0.603, $p < 0.001$). CONCLUSION: In a real clinical setting, rosuvastatin was superior to the other statins in lowering LDL cholesterol, both as monotherapy or combined with ezetimibe. Factors associated with a suboptimal response in LDL cholesterol decline were male sex, age, body mass index, and baseline LDL cholesterol levels. Combined treatment was associated with less variability in LDL cholesterol improvement.

[20] *Ozturk N, Uslu S, Mercan T et al.* **Rosuvastatin Reduces L-Type Ca(2+) Current and Alters Contractile Function in Cardiac Myocytes via Modulation of β-Adrenergic Receptor Signaling**. Cardiovascular toxicology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33565033

ABSTRACT
Rosuvastatin is one of the most used statins to lower plasma cholesterol levels. Although previous studies have reported remarkable cardiovascular effects of rosuvastatin (RSV), the mechanisms of these effects are largely unknown. In this study, we investigated the acute effects of RSV on L-type Ca(2+) currents and contractile function of ventricular myocytes under basal conditions and during β-adrenergic stimulation. The effects of RSV were investigated in freshly isolated adult rat ventricular myocytes. L-type Ca(+2) currents and myocyte contractility were recorded using patch-clamp amplifier and sarcomere length detection system. All experimental recordings were performed at 36 ± 1 °C. L-type Ca(+2) currents were significantly reduced with the administration of 1 μM RSV (~24%) and this reduction in Ca(2+) currents was observed at almost all potential ranges applied. Suppression of L-type Ca(2+) current by RSV was prevented by adenylyl cyclase (AC) and protein kinase A (PKA) inhibitors SQ 22536 and KT5720, respectively. However, inhibition of Rho-associated kinases (ROCKs) by Y-27632 or nitric oxide synthase (NOS) by L-NAME failed to circumvent the inhibitory effect of RSV. Finally, we examined the effect of RSV during β-adrenergic receptor stimulation by isoproterenol and observed that RSV significantly suppresses the β-adrenergic responses in both L-type Ca(2+) currents and contraction parameters. In conclusion, RSV modulates the β-adrenergic signaling cascade and thereby mimics the impact of β-adrenergic receptor blockers in adult ventricular myocytes through modulation of the AC-cAMP-PKA pathway.

[21] *Florea A, Sigl JP, Morgenroth A et al.* **Sodium [(18)F]Fluoride PET Can Efficiently Monitor In Vivo Atherosclerotic Plaque Calcification Progression and Treatment**. Cells 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33573188

ABSTRACT
Given the high sensitivity and specificity of sodium [(18)F]Fluoride (Na[(18)F]F) for vascular calcifications and positive emerging data of vitamin K on vascular health, the aim of this study is to assess the ability of Na[(18)F]F to monitor therapy and disease progression in a unitary atherosclerotic mouse model. ApoE(-/-) mice were placed on a Western-type diet for 12-weeks and then split into four groups. The early stage atherosclerosis group received a chow diet for an additional 12-weeks, while the advanced atherosclerosis group continued the Western-type diet. The Menaquinone-7 (MK-7) and Warfarin groups received MK-7 or Warfarin supplementation during the additional 12-weeks, respectively. Control wild type mice were fed a chow diet for 24-weeks. All of the mice were scanned with Na[(18)F]F using a small animal positron emission tomography (PET)/computed tomography (CT). The Warfarin group presented spotty calcifications on the CT in the proximal aorta. All of the spots corresponded to dense mineralisations on the von Kossa staining. After the control, the MK-7 group had the lowest Na[(18)F]F uptake. The advanced and Warfarin groups presented the highest uptake in the aortic arch and left ventricle. The advanced stage group did not develop spotty calcifications, however Na[(18)F]F uptake was still observed, suggesting the presence of micro-calcifications. In a newly applied mouse model, developing spotty calcifications on CT exclusively in the proximal aorta, Na[(18)F]F seems to efficiently monitor plaque progression and the beneficial effects of vitamin K on cardiovascular disease.

[22] *Kurilenko N, Fatkhullina AR, Mazitova A, Koltsova EK*. **Act Locally, Act Globally-Microbiota, Barriers, and Cytokines in Atherosclerosis**. Cells 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33562334
ABSTRACT
Atherosclerosis is a lipid-driven chronic inflammatory disease that is characterized by the formation and progressive growth of atherosclerotic plaques in the wall of arteries. Atherosclerosis is a major predisposing factor for stroke and heart attack. Various immune-mediated mechanisms are implicated in the disease initiation and progression. Cytokines are key mediators of the crosstalk between innate and adaptive immune cells as well as non-hematopoietic cells in the aortic wall and are emerging players in the regulation of atherosclerosis. Progression of atherosclerosis is always associated with increased local and systemic levels of pro-inflammatory cytokines. The role of cytokines within atherosclerotic plaque has been extensively investigated; however, the cell-specific role of cytokine signaling, particularly the role of cytokines in the regulation of barrier tissues tightly associated with microbiota in the context of cardiovascular diseases has only recently come to light. Here, we summarize the knowledge about the function of cytokines at mucosal barriers and the interplay between cytokines, barriers, and microbiota and discuss their known and potential implications for atherosclerosis development.

[23] *Ghuman J, Manasewitsch NT, Ghuman J et al.* **Atorvastatin-Induced Refractory Thrombocytopenia**. Cureus 2021; 13:e12502.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33564510
ABSTRACT
Drug-induced thrombocytopenia is rarely associated with statin medications. We describe the case of a 69-year-old woman who developed refractory thrombocytopenia following atorvastatin use. To our knowledge, this is the fourth reported case of atorvastatin-induced thrombocytopenia and the first reported case of atorvastatin-induced refractory thrombocytopenia. Additionally, we summarize the cases of statin-induced thrombocytopenia reported in the medical literature.

[24] *Aguilar-Ramirez D, Alegre-Díaz J, Gnatiuc L et al.* **Changes in the Diagnosis and Management of Diabetes in Mexico City Between 1998-2004 and 2015-2019**. Diabetes Care 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33568401
ABSTRACT
OBJECTIVE: To investigate the trends in diabetes prevalence, diagnosis, and management among Mexican adults who were participants in a long-term prospective study. RESEARCH DESIGN AND METHODS: From 1998 to 2004, 159,755 adults from Mexico City were recruited to a prospective study, and from 2015 to 2019, 10,144 survivors were resurveyed. Diabetes was defined as self-reported diagnosis, glucose-lowering medication use, or HbA(1c) ≥6.5%. Controlled diabetes was defined as HbA(1c) <7%. Prevalence estimates were uniformly standardized for age, sex, and residential district. Cox models explored the relevance of controlled and inadequately controlled diabetes to cause-specific mortality. RESULTS: During 1998-2004 and 2015-2019, 99,623 and 8,986 participants were aged 45-84 years. Diabetes prevalence had increased from 26% in 1998-2004 to 35% by 2015-2019. Of those with diabetes, the proportion previously diagnosed had increased from 76 to 89%, and glucose-lowering medication use among them had increased from 80 to 94%. Median

HbA(1c) among those with diabetes had decreased from 8.2 to 7.3%, and the proportion of participants with controlled diabetes had increased from 16 to 37%. Use of blood pressure-lowering medication among those with previously diagnosed diabetes had increased from 35 to 51%, and their use of lipid-lowering therapy had increased from 1 to 14%. The excess mortality risk associated with diabetes accounted for 34% of deaths at ages 35-74 years, of which 5% were attributable to controlled and 29% to inadequately controlled diabetes. CONCLUSIONS: Inadequately controlled diabetes is a leading cause of premature adult death in Mexico. Improvements in diabetes management have increased diagnosis and control, but substantial opportunities remain to improve treatment, particularly with lipid-lowering therapy.

[25] *Ye S, Ran H, Zhang H et al.* **Elevated Serum Triglycerides are Associated with Ketosis-Prone Type 2 Diabetes in Young Individuals**. Diabetes, metabolic syndrome and obesity : targets and therapy 2021; 14:497-504.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33568926
ABSTRACT
PURPOSE: Ketosis-prone type 2 diabetes (KPT2D) is increasingly recognized in young adults. However, the role of blood lipids in KPT2D, especially serum triglycerides (TGs), is not yet clearly understood. PATIENTS AND METHODS: We retrospectively evaluated 409 young patients diagnosed with KPT2D or classical type 2 diabetes (T2D) attending an academic tertiary hospital. Clinical characteristics and laboratory findings were compared between KPT2D and T2D patients. ANOVA or a non-parametric test analyses were used to evaluate differences in clinical characteristics and laboratory findings. Multivariate regression analyses and stratified analyses were used to further investigate differences in serum TGs levels between KPT2D and T2D individuals. RESULTS: KPT2D is a subtype of T2D with traits of overweight or obesity. However, hyperglycemia and impaired β-cell functions were more severe in KPT2D patients. Serum TGs levels were significantly higher ($P = 0.0003$) in KPT2D individuals. Furthermore, the proportion of very high serum TGs levels was 6-fold higher ($P < 0.0001$) in KPT2D than in T2D patients. Elevated serum TGs were associated with young KPT2D patients. CONCLUSION: Lifestyle changes as well as lipid-lowering treatments might be effective in lowering the incidence of ketosis as well as stabilizing disease progression.

[26] *Si J, Li J, Yu C et al.* **Improved lipidomic profile mediates the effects of adherence to healthy lifestyles on coronary heart disease**. eLife 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33558007
ABSTRACT
Adherence to healthy lifestyles is associated with reduced risk of coronary heart disease (CHD), but uncertainty persists about the underlying lipid pathway. In a case-control study of 4681 participants nested in the prospective China Kadoorie Biobank, 61 lipidomic markers in baseline plasma were measured by targeted nuclear magnetic resonance spectroscopy. Baseline lifestyles included smoking, alcohol consumption, dietary habit, physical activity, and adiposity levels. Genetic instrument was used to mimic the lipid-lowering effect of statins. We found that 35 lipid metabolites showed statistically significant mediation effects in the pathway from healthy lifestyles to CHD reduction, including very low-density lipoprotein (VLDL) particles and their cholesterol, large-sized high-density lipoprotein (HDL) particle and its cholesterol, and triglyceride in almost all lipoprotein subfractions. The statins genetic score was associated with reduced intermediate- and low-density

lipoprotein, but weak or no association with VLDL and HDL. Lifestyle interventions and statins may improve different components of the lipid profile.

[27] *Camacho OFC, Molina GP, Catalá CFM et al.* **Familial Hypercholesterolemia: Update and Review**. Endocrine, metabolic & immune disorders drug targets 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33563162
ABSTRACT
Knowledge of epidemiology, genetic etiopathogenesis, diagnostic criteria, and management of familial hypercholesterolemia have increased in the last two decades. Several population studies have shown that familial hypercholesterolemia is more frequent than previously thought, making this entity the most common metabolic disease with monogenic inheritence in the world. Identification of causal heterozygous pathogenic variants in LDLR, APOB, and PCSK9 genes have increased diagnostic accuracy of classical criteria (extreme hypercholesterolemia, personal / family history of premature coronary artery disease or other cardiovascular disease). Genetic screening has been recently introduced in many European countries to detect patients with familial hypercholesterolemia, mainly affected pediatric subjects, asymptomatic or those at the beggining of their disease, with the purpose of increasing surveillance and avoiding complications such as cardiovascular diseases. Cholesterol-lowering drugs should be started as soon as the diagnosis is made. Various combinations between drugs can be used when the goal is not achieved. New therapies, including small interference ribonucleic acids (siRNA) are being tested in different clinical trials.

[28] *Macchi C, Iodice S, Persico N et al.* **Maternal exposure to air pollutants, PCSK9 levels, fetal growth and gestational age - An Italian cohort**. Environ Int 2021; 149:106163.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33556817
ABSTRACT
OBJECTIVE: Exposure to airborne pollutants during pregnancy appears to be associated with uterine growth restriction and adverse neonatal outcome. Proprotein convertase subtilisin/kexin type (PCSK9), the key modulator of low-density lipoprotein (LDL) metabolism, increases following particulate matter (PM(10)) exposure. Because maternal cholesterol is required for fetal growth, PCSK9 levels could be used to evaluate the potential impact of airborne pollutants on fetal growth. DESIGN: A cohort of 134 healthy women during early pregnancy (11-12 weeks of gestational age) was studied. RESULTS: A significant association between circulating PCSK9 levels and three tested air pollutants (PM(10), PM(2.5), nitric oxide (NO(2))) was found. Of importance, gestational age at birth was reduced by approximately 1 week for each 100 ng/mL rise in circulating PCSK9 levels, an effect that became more significant at the highest quartile of PM(2.5) (with a 1.8 week advance in delivery date for every 100 ng/mL rise in circulating PCSK9; p for interaction = 0.026). This finding was supported by an elevation of the odds ratio for urgent cesarean delivery for each 100 ng/mL rise in PCSK9 (2.99, 95% CI, 1.22-6.57), similar trends being obtained for PM(10) and NO(2). CONCLUSIONS: The association between exposure to air pollutants during pregnancy and elevation in PCSK9 advances our understanding of the unforeseen influences of environmental exposure in terms of pregnancy associated disorders.

[29] *Bizoń A, Franik G, Madej P*. **The role of proprotein convertase subtilisin/kexin type-9 concentration and paraoxonase 1 activities in the blood of women with polycystic ovary syndrome**. Environmental toxicology and pharmacology 2021; 84:103612.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33571670
ABSTRACT
This study aimed to evaluate the concentration of proprotein convertase subtilisin/kexin type-9 (PCSK9) and the activities of paraoxonase 1 in women with and without polycystic ovary syndrome (PCOS). We found significant higher PCSK9, whereas lower high-density lipoprotein concentration in the serum of women with PCOS when compared to the group without PCOS. Also paraoxonase 1 activities were significantly different between women with PCOS than without PCOS. In addition, the women with PCOS and insulin resistance had higher concentrations of PCSK9 than women with PCOS and insulin sensitivity. Higher PCSK9 concentration in the group with PCOS could be also associated with hormones concentrations. Changes in paraoxonase 1 activities and lipid profile parameters as well as higher concentration of PCSK9 in the group of women with PCOS could be associated with metabolism disorders, but due to the small clinical sample size, the study should be continued.

[30] *Dongiovanni P, Paolini E, Corsini A et al.* **Nonalcoholic fatty liver disease or metabolic dysfunction-associated fatty liver disease diagnoses and cardiovascular diseases: From epidemiology to drug approaches**. European journal of clinical investigation 2021:e13519.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33583033
ABSTRACT
BACKGROUND: A consensus of experts has proposed to replace the term nonalcoholic fatty liver disease (NAFLD), whose global prevalence is 25%, with metabolic dysfunction-associated fatty liver disease (MAFLD), to describe more appropriately the liver disease related to metabolic derangements. MAFLD is closely intertwined with type 2 diabetes, obesity, dyslipidaemia, all linked to a rise in the risk of cardiovascular disease (CVDs). Since controversy still stands on whether or not NAFLD/MAFLD raises the odds of CVD, the present review aims to evaluate the impact of NAFLD/MAFLD aetiologies on CV health and the potential correction by dietary and drug approaches. RESULTS: Epidemiological studies indicate that NAFLD raises risk of fatal or non-fatal CVD events. NAFLD patients have a higher prevalence of arterial plaques and stiffness, coronary calcification, and endothelial dysfunction. Although genetic and environmental factors strongly contribute to NAFLD pathogenesis, a Mendelian randomization analysis indicated that the PNPLA3 genetic variant leading to NAFLD may not be causally associated with CVD risk. Among other genetic variants related to NAFLD, TM6SF2 appears to be protective, whereas MBOAT7 may favour venous thromboembolism. CONCLUSIONS: NAFLD is correlated to a higher CVD risk which may be ameliorated by dietary interventions. This is not surprising, since new criteria defining MAFLD include other metabolic risk abnormalities fuelling development of serious adverse extrahepatic outcomes, for example CVD. The present lack of a targeted pharmacological approach makes the identification of patients with liver disease at higher CVD risk (eg diabetes, hypertension, obesity or high levels of C-reactive protein) of major clinical interest.

[31] *Blaum C, Seiffert M, Goßling A et al.* **The need for PCSK9 inhibitors and associated treatment costs according to the 2019 ESC dyslipidaemia guidelines vs. the risk-based**

allocation algorithm of the 2017 ESC consensus statement: a simulation study in a contemporary CAD cohort. European journal of preventive cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33580772

ABSTRACT

BACKGROUND: The recently updated European Society of Cardiology (ESC) dyslipidaemia guidelines recommend a lower low-density lipoprotein cholesterol (LDL-C) goal of <55 mg/dL for patients with atherosclerotic cardiovascular disease (ASCVD), with a concomitant Class IA upgrade for proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) for patients not reaching their LDL-C goal under conventional lipid-lowering therapy. AIMS: We aim to quantify the need for PCSK9i and the related costs to achieve the revised LDL-C goal in ASCVD patients compared to former ESC recommendations, in particular the risk-based 2017 ESC consensus update. METHODS AND RESULTS: We included patients with ASCVD from an observational cohort study ongoing since 2015. A Monte Carlo simulation incorporating a treatment algorithm adding sequentially a statin, ezetimibe, and a PCSK9i was applied with consideration of partial and total statin intolerance. The need for PCSK9i was calculated for three different ESC recommendations (2019 guidelines, 2016 guidelines, 2017 consensus update). Preventable events and treatment costs due to PCSK9i were calculated for a range of annual event rates from 2% to 8% and annual treatment costs of ca. 6050 €. We included 1780 patients (mean age 69.5 years). Median LDL-C at baseline was 85.0 mg/dL, with 61% of patients taking lipid-lowering medication. The need for PCSK9i was simulated to be 42.0% (ESC 2019), 31.9% (ESC 2016), and 5.0% (ESC 2017). The LDL-C goals were achieved in 97.9%, 99.1%, and 60.9% of patients, respectively. Annual treatment cost for PCSK9i per 1 000 000 ASCVD patients would be 2.54 billion € (ESC 2019) compared to 0.30 billion € (ESC 2017). Costs per prevented event due to PCSK9i initiation differed widely, e.g. 887 000 € for an event rate of 3% and a treatment goal of <55 mg/dL compared to 205 000 € for an event rate of 7% and risk-based use of PCSK9i. CONCLUSION: The revised LDL-C treatment goals increase the projected need for PCSK9i with a substantial increase in associated treatment cost. An allocation strategy based on residual LDL-C and clinical or angiographic risk factors leads to a more tailored target population for PCSK9i with a reasonable benefit/cost ratio.

[32] *Hussain A, Sun C, Selvin E et al.* **Triglyceride-rich lipoproteins, apolipoprotein C-III, angiopoietin-like protein 3, and cardiovascular events in older adults: Atherosclerosis Risk in Communities (ARIC) study**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33580780

ABSTRACT

AIMS: Despite statin and antihypertensive therapies, older Americans have high atherosclerotic cardiovascular disease (ASCVD) risk. Novel measures of triglyceride-rich lipoproteins, low-density lipoprotein triglycerides (LDL-TG), and remnant-like particle cholesterol (RLP-C), are associated with ASCVD in middle-aged adults. Polymorphisms in genes encoding angiopoietin-related protein 3 (ANGPTL3) and apolipoprotein C-III (apoC-III), two proteins involved in triglyceride catabolism, are associated with increased risk for hypertriglyceridaemia and ASCVD and are potential therapeutic targets. We examined associations of LDL-TG, RLP-C, apoC-III, and ANGPTL3 levels with ASCVD events in older adults in the Atherosclerosis Risk in Communities (ARIC) study. METHODS AND RESULTS: In 6359 participants (mean age 75.8 ± 5.3 years) followed for ASCVD events [coronary heart disease (CHD) or ischaemic stroke] up to 6 years, associations between LDL-TG, RLP-C, apoC-

III, and ANGPTL3 and ASCVD events were assessed using Cox regression. With adjustment for age, sex, and race, RLP-C, LDL-TG, apoC-III, and ANGPTL3 (as continuous variables) were significantly associated with CHD. However, after adjustment for traditional risk factors and lipid-lowering medications, only LDL-TG and ANGPTL3 were significantly associated with ASCVD events [hazard ratio (HR) 1.72, 95% confidence interval (CI) 1.25-2.37 per log unit increase in LDL-TG; HR 1.63, 95% CI 1.17-2.28 per log unit increase in ANGPTL3]. CONCLUSIONS: In older adults, LDL-TG, RLP-C, apoC-III, and ANGPTL3 were associated with CHD events in minimally adjusted models; LDL-TG and ANGPTL3 remained independent predictors of ASCVD events with further adjustment. Future studies should assess potential benefit of lowering hepatic apoC-III or ANGPTL3 expression in patients with elevated triglyceride-rich lipoproteins.

[33] *Koskinas KC, Catapano AL, Baigent C et al.* **Current perceptions and practices in lipid management: results of a European Society of Cardiology/European Atherosclerosis Society Survey**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33580792
ABSTRACT
AIMS: We sought to evaluate physicians' opinions and practices in lipid management. METHODS AND RESULTS: A web-based survey by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) was distributed to 70 696 individuals at two time points, before and after publication of the 2019 ESC/EAS dyslipidaemia guidelines. Respondents (1271 in the first and 1056 in the second part) were most commonly cardiologists in Europe. More than 90% of participants reported that they regularly measure lipid levels and discuss lipid-lowering treatment with patients. More than 87% found the use of LDL-C goals useful or potentially useful, although it was acknowledged that recommended goals are frequently not achieved. Regarding the LDL-C goal according to the 2019 guidelines (<1.4 mmol/L for very high-risk patients), more than 70% of respondents felt that it is based on solid scientific evidence, but 31% noted that implementation should also consider available local resources and patient preferences. Statin intolerance was perceived as infrequent, affecting 1-5% of patients according to most respondents but was the main reason for not prescribing a statin to secondary-prevention patients, followed by patient non-adherence. Although most respondents reported that 11-20% of secondary-prevention patients have an indication to add a non-statin medication, fewer patients (<10% according to most respondents) receive these medications. CONCLUSIONS: This survey shows a high level of acceptance of the LDL-C treatment goals recommended by current ESC/EAS guidelines. Although patient-related factors were the main reported reasons for suboptimal lipid-lowering therapy, physician inertia to intensify treatment cannot be excluded as an additional contributing factor.

[34] *Mehta S, Zhao J, Poppe K et al.* **Cardiovascular preventive pharmacotherapy stratified by predicted cardiovascular risk: a national data linkage study**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33580793
ABSTRACT
AIMS: Cardiovascular disease (CVD) risk management guided by predicted CVD risk is widely recommended internationally. This is the first study to examine CVD preventive pharmacotherapy in a whole-of-country primary prevention population, stratified by CVD risk. METHODS AND RESULTS:

Anonymized individual-level linkage of New Zealand administrative health and non-health data identified 2250201 individuals without atherosclerotic CVD, alive, and aged 30-74 years on 31 March 2013. We identified individuals with ≥1 dispensing by community pharmacies of blood pressure lowering (BPL) and/or lipid-lowering (LL) medications at baseline (1 October 2012-31 March 2013) and in 6-month periods between 1 April 2013 and 31 March 2016. Individuals were stratified using 5-year CVD risk equations specifically developed for application in administrative datasets. One-quarter of individuals had ≥5% 5-year risk (the current New Zealand guideline threshold for discussing preventive medications) and 5% met the ≥15% risk threshold for recommended dual therapy. By study end, dual therapy was dispensed to 2%, 18%, 34%, and 49% of individuals with <5%, 5-9%, 10-14%, and ≥15% 5-year risk, respectively. Among those dispensed baseline dual therapy, 83-89% across risk strata were still treated after 3 years. Dual therapy initiation during follow-up occurred among only 13% of high-risk individuals untreated at baseline. People without diabetes and those aged ≥65 years were more likely to remain untreated. CONCLUSION: Cardiovascular disease primary preventive pharmacotherapy was strongly associated with predicted CVD risk and, once commenced, was generally continued. However, only half of high-risk individuals received recommended dual therapy and treatment initiation was modest. Individually linked administrative datasets can identify clinically relevant quality improvement opportunities for entire populations.

[35] *Ray KK, Molemans B, Schoonen WM et al.* **EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study**. European journal of preventive cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33580789

ABSTRACT

AIMS: To provide contemporary data on the implementation of European guideline recommendations for lipid-lowering therapies (LLTs) across different settings and populations and how this impacts low-density lipoprotein cholesterol (LDL-C) goal achievement. METHODS AND RESULTS: An 18 country, cross-sectional, observational study of patients prescribed LLT for primary or secondary prevention in primary or secondary care across Europe. Between June 2017 and November 2018, data were collected at a single visit, including LLT in the preceding 12 months and most recent LDL-C. Primary outcome was the achievement of risk-based 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) LDL-C goal while receiving stabilized LLT; 2019 goal achievement was also assessed. Overall, 5888 patients (3000 primary and 2888 secondary prevention patients) were enrolled; 54% [95% confidence interval (CI) 52-56] achieved their risk-based 2016 goal and 33% (95% CI 32-35) achieved their risk-based 2019 goal. High-intensity statin monotherapy was used in 20% and 38% of very high-risk primary and secondary prevention patients, respectively. Corresponding 2016 goal attainment was 22% and 45% (17% and 22% for 2019 goals) for very high-risk primary and secondary prevention patients, respectively. Use of moderate-high-intensity statins in combination with ezetimibe (9%), or any LLT with PCSK9 inhibitors (1%), was low; corresponding 2016 and 2019 goal attainment was 53% and 20% (ezetimibe combination), and 67% and 58% (PCSK9i combination). CONCLUSION: Gaps between clinical guidelines and clinical practice for lipid management across Europe persist, which will be exacerbated by the 2019 guidelines. Even with optimized statins, greater utilization of non-statin LLT is likely needed to reduce these gaps for patients at highest risk.

[36] *Faccinetto-Beltrán P, Gómez-Fernández AR, Orozco-Sánchez NE et al.* **Physicochemical Properties and Sensory Acceptability of a Next-Generation Functional Chocolate Added with Omega-3 Polyunsaturated Fatty Acids and Probiotics**. Foods (Basel, Switzerland) 2021; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33557241
ABSTRACT
In this study, a milk chocolate formulation was developed to serve as vehicle of Omega-3 (ω3) polyunsaturated fatty acids (PUFAs) and probiotics (L. plantarum 299v and L. rhamnosus GG). Fish oil (FO) was incorporated in chocolate as a source of ω3 PUFAs. Probiotics (Prob) and FO were added during tempering, obtaining chocolates with 76.0 ± 5.2 mg (FO1) or 195.8 ± 6.5 mg (FO2) of ω3 PUFAs, and >1 × 10(6) CFU of Prob per chocolate portion (12 g). The physicochemical properties (rheological analysis, texture, surface instrumental color, aw, and fatty acid profile), and sensory acceptability of the formulations were determined. Prob and FO generated a decrease in L* and white index (WI) values. Except for Prob + FO2, all treatments showed a decrease in aw. Rheological parameters of FO1 and Prob + FO1 presented the most similar behavior as compared with the control. Prob or FO1 addition did not affect the overall consumer's acceptability of chocolate; and when both nutraceuticals were combined (Prob + FO1) the product showed adequate overall acceptability. FO2 formulations were not considered adequate to maintain physicochemical properties and sensory acceptability of chocolate. Results indicated that milk chocolate is a suitable vehicle for delivering ω3 PUFAs and Prob, which are essential to enhance cognitive development in children.

[37] *Shi J, Qu Q, Liu H et al.* **Case Report: PNPLA2 Gene Complex Heterozygous Mutation Leading to Neutral Lipid Storage Disease With Myopathy**. Front Integr Neurosci 2020; 14:554724.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33551761
ABSTRACT
Objective: To investigate the clinical features, skeletal muscle imaging, muscle pathology, blood smear and so on of neutral lipid storage disease with myopathy (NLSDM) caused by PNPLA2 gene mutation. Methods: The clinical data, skeletal muscle imaging, pathological data, and genetic test results of a patient with NLSDM treated in our hospital were collected in detail, and the previous literature was reviewed and compared. Results: The main symptoms were muscle weakness and muscular atrophy. Pathological findings of muscle biopsy showed fat deposition in muscle fibers with border cavitation. Fatty droplets were seen in the cytoplasm of neutrophils in peripheral blood. Magnetic resonance imaging of the muscles of both lower extremities showed that muscle in the thigh vastus intermedius, lateral muscles, biceps, and the muscle abdominal area of the middle leg were filled or replaced by fat. Genetic test results suggested mutations in the PNPLA2 gene. Conclusion: NLSDM is a rare clinical myopathy with abnormal lipid metabolism. Characteristic changes can be seen in skeletal muscle imaging and pathology. The detection of PNPLA2 gene mutation is an important basis for diagnosing NLSDM. Asymmetry and progressive limb weakness are the clinical features. Muscle MRI is mainly involved in the posterior group of the lower limbs. Jordans bodies in the peripheral blood smear and a large number of coarse-grained lipid deposits with rimmed vacuoles in muscle fibers are the characteristic pathological changes.

[38] *Hana CA, Klebermass EM, Balber T et al.* **Inhibition of Lipid Accumulation in Skeletal Muscle and Liver Cells: A Protective Mechanism of Bilirubin Against Diabetes Mellitus Type 2**. Frontiers in pharmacology 2020; 11:636533.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33569010

ABSTRACT

Ectopic lipid accumulation in skeletal muscle and liver drives the pathogenesis of diabetes mellitus type 2 (DMT2). Mild hyperbilirubinaemia has been repeatedly suggested to play a role in the prevention of DMT2 and is known for its capacity to shape an improved lipid phenotype in humans and in animals. To date, the effect of bilirubin on lipid accumulation in tissues that are prone to ectopic lipid deposition is unclear. Therefore, we analyzed the effect of bilirubin on lipid accumulation in skeletal muscle and liver cell lines. C2C12 skeletal mouse muscle and HepG2 human liver cells were treated with physiological concentrations of free fatty acids (FFA) (0.5 mM and 1 mM) and unconjugated bilirubin (UCB) (17.1 and 55 μM). The intracellular presence of UCB upon exogenous UCB administration was confirmed by HPLC and the lipid accumulation was assessed by using Nile red. Exposure of both cell lines to UCB significantly reduced lipid accumulation by up to 23% ($p \leq 0.001$) in HepG2 and by up to 17% ($p \leq 0.01$) in C2C12 cells at 0.5 and 5 h under hypoglycaemic conditions. Simultaneously, UCB slightly increased FFA uptake in HepG2 cells after 0.5 and 5 h and in C2C12 cells after 12 h as confirmed by gas chromatographic analyses of the remaining FFA content in the incubation media. The effects of UCB on lipid accumulation and uptake were abolished in the presence of higher glucose concentrations. Monitoring the uptake of a radiolabeled glucose analogue [18F]FDG: (2-deoxy-2-[(18)F]fluoro-D-glucose) into both cell types further indicated higher glucose consumption in the presence of UCB. In conclusion, our findings show that UCB considerably decreases lipid accumulation in skeletal muscle and liver cells within a short incubation time of max. 5 h which suggests that mildly elevated bilirubin levels could lower ectopic lipid deposition, a major key element in the pathogenesis of DMT2.

[39] *Li T, Fang T, Xu L et al.* **Empagliflozin Alleviates Hepatic Steatosis by Activating the AMPK-TET2-Autophagy Pathway in vivo and in vitro**. Frontiers in pharmacology 2020; 11:622153.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33551821

ABSTRACT

Background: Metabolic associated fatty liver disease (MAFLD), characterized by hepatic lipid accumulation and fatty degeneration, is intertwined with obesity and type 2 diabetes mellitus (T2DM). Empagliflozin is a sodium-glucose cotransporter-2 inhibitor that effectively lowers blood glucose, but its effect on MAFLD and associated mechanisms are not fully understood. Methods: Eight-week-old db/db mice, an in vivo model, were administered empagliflozin or saline intragastrically. A hepatocyte steatosis model was established by inducing HL7702 cells with high glucose and palmitic acid and then treated with or without empagliflozin. The autophagy inhibitor (3-methyladenine, 3-MA) and AMP-activated protein kinase (AMPK) activator (AICAR)/inhibitor (Compound C) were used to determine the involvement of AMPK and autophagy in the regulation of lipid accumulation by empagliflozin. Ten-eleven translocation 2 (TET2) knockdown was achieved by siRNA transfection. Hepatic steatosis was evaluated by Oil Red O staining and triglyceride quantification. Immunohistochemistry, immunofluorescence, and western blot were performed to assess protein levels. Results: Empagliflozin alleviated liver steatosis in db/db mice and reduced triglyceride content and lipid accumulation in the hepatocyte steatosis model. Empagliflozin elevated autophagy, accompanied by an increase in p-AMPK and TET2. Both 3-MA and Compound C abolished the ability of empagliflozin to induce autophagy and reduce hepatic steatosis, while these effects could be recapitulated by AICAR treatment. TET2 knockdown resulted in autophagy inhibition and lipid

accumulation despite empagliflozin treatment. Conclusion: Empagliflozin improves hepatic steatosis through the AMPK-TET2-autophagy pathway. The use of empagliflozin as a treatment for preventing and treating MAFLD in patients with T2DM warrants further study.

[40] *Nwadiugwu MC*. **Inflammatory Activities in Type 2 Diabetes Patients With Co-morbid Angiopathies and Exploring Beneficial Interventions: A Systematic Review**. Frontiers in public health 2020; 8:600427.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33569370
ABSTRACT
Background: Diabetes is a long-term condition that can be treated and controlled but do not yet have a cure; it could be induced by inflammation and the goal of managing it is to prevent additional co-morbidities and reduce glycemic fluctuations. There is a need to examine inflammatory activities in diabetes-related angiopathies and explore interventions that could reduce the risk for future outcome or ameliorate its effects to provide insights for improved care and management strategies. Method: The study was conducted in Embase (1946-2020), Ovid Medline (1950-2020), and PubMed databases (1960-2020) using the PICO framework. Primary studies (randomized controlled trials) on type 2 diabetes mellitus and inflammatory activities in diabetes-related angiopathies were included. Terms for the review were retrieved from the Cochrane library and from PROSPERO using its MeSH thesaurus qualifiers. Nine articles out of 454 total hits met the eligibility criteria. The quality assessment for the selected study was done using the Center for Evidence-Based Medicine Critical Appraisal Sheet. Results: Data analysis showed that elevated CRP, TNF-α, and IL-6 were the most commonly found inflammatory indicator in diabetes-related angiopathies, while increased IL-10 and soluble RAGE was an indicator for better outcome. Use of drugs such as salsalate, pioglitazone, simvastatin, and fenofibrate but not glimepiride or benfotiamine reported a significant decrease in inflammatory events. Regular exercise and consumption of dietary supplements such as ginger, hesperidin which have anti-inflammatory properties, and those containing prebiotic fibers (e.g., raspberries) revealed a consistent significant ($p < 0.05$) reduction in inflammatory activities. Conclusion: Inflammatory activities are implicated in diabetes-related angiopathies; regular exercise, the intake of healthy dietary supplements, and medications with anti-inflammatory properties could result in improved protective risk outcome for diabetes patients by suppressing inflammatory activities and elevating anti-inflammatory events.

[41] *Song Y, Dang Y, Wang J et al.* **Carotid Intraplaque Neovascularization Predicts Ischemic Stroke Recurrence in Patients with Carotid Atherosclerosis**. Gerontology 2021:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33582668
ABSTRACT
INTRODUCTION: This study aimed to examine whether intraplaque neovascularization (IPN) of carotid plaques, as characterized by contrast-enhanced ultrasound (CEUS), is associated with ischemic stroke recurrence in patients with carotid atherosclerosis. METHODS: We conducted a prospective study of consecutive patients with a recent stroke and at least one atherosclerotic plaque in the carotid artery on the side consistent with symptoms. All patients underwent CEUS after their first admission. IPN was graded on the basis of the presence and location of microbubbles within each plaque. RESULTS: We eventually included 155 patients, all of whom underwent IPN analysis. After a follow-up of 24 months, we recorded 25 (16.1%) stroke recurrences in the whole population.

All the recurrences occurred in patients presenting IPN. There was significant difference in the IPN between the 2 groups (p = 0.002). In the final Cox proportional-hazards multivariable models, IPN of grade 2 was independently associated with the risk of stroke recurrence (HR = 4.535; 95% CI: 1.892-10.870; p = 0.001). This association remained after adjusting for the degree of carotid stenosis (HR = 3.491; 95% CI: 1.410-8.646; p = 0.007). CONCLUSIONS: IPN was an independent predictor of stroke recurrence in patients with a recent ischemic stroke and carotid atherosclerosis. In predicting stroke recurrence, IPN may be an earlier indicator than carotid stenosis and may help stratify the risk of stroke recurrence.

[42] *Everhart A, Desai NR, Dowd B et al.* **Physician variation in the de-adoption of ineffective statin and fibrate therapy**. Health services research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33569804
ABSTRACT
OBJECTIVE: To describe physicians' variation in de-adopting concurrent statin and fibrate therapy for type 2 diabetic patients following a reversal in clinical evidence. DATA SOURCES: We analyzed 2007-2015 claims data from OptumLabs(®) Data Warehouse, a longitudinal, real-world data asset with de-identified administrative claims and electronic health record data. STUDY DESIGN: We modeled fibrate use among Medicare Advantage and commercially insured type 2 diabetic statin users before and after the publication of the ACCORD lipid trial, which found statins and fibrates were no more effective than statins alone in reducing cardiovascular events among type 2 diabetic patients. We modeled fibrate use trends with physician random effects and physician characteristics such as age and specialty. DATA EXTRACTION: We identified patient-year-quarters with one year of continuous insurance enrollment, type 2 diabetes diagnoses, and fibrate use. We designated the physician most responsible for patients' diabetes care based on evaluation and management visits and prescriptions of glucose-lowering drugs. PRINCIPAL FINDINGS: Fibrate use increased by 0.12 percentage points per quarter among commercial patients (95% CI, 0.10 to 0.14) and 0.17 percentage points per quarter among Medicare Advantage patients (95% CI, 0.13 to 0.20) before the trial and then decreased by 0.16 percentage points per quarter among commercial patients (95% CI, -0.18 to -0.15) and 0.05 percentage points per quarter among Medicare Advantage patients (95% CI, -0.06 to -0.03) after the trial. However, 45% of physicians treating commercial patients and 48% of physicians treating Medicare Advantage patients had positive trends in prescribing following the trial. Physicians' characteristics did not explain their variation (pseudo $R(2) = 0.000$). CONCLUSION: On average, physicians decreased fibrate prescribing following the ACCORD lipid trial. However, many physicians increased prescribing following the trial. Observable physician characteristics did not explain variations in prescribing. Future research should examine whether physicians vary similarly in other de-adoption settings.

[43] *Hasan R, Agarwal K, Podder I et al.* **Simvastatin in vitiligo: an update with recent review of the literature**. International journal of dermatology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33554328
ABSTRACT
Patients with vitiligo often seek medical attention, as it diminishes their quality of life resulting in significant morbidity. Several topical and systemic therapies are in vogue targeting the immunological aspect of this disease, but results are often unsatisfactory, and complete cure remains elusive.

Recently, simvastatin, a 3-hydroxy-3-methylyglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, is being evaluated for vitiligo management because of its multimodal action, easy availability, and low cost. The proposed multimodal actions range from anti-inflammatory, antioxidant, to immunomodulatory properties which may be of therapeutic benefit in vitiligo patients. The authors intend to evaluate the role of simvastatin as a novel therapeutic agent for vitiligo along with relevant review of literature.

[44] *Zeng J, Tao J, Xi L et al.* **PCSK9 mediates the oxidative low-density lipoprotein-induced pyroptosis of vascular endothelial cells via the UQCRC1/ROS pathway**. International journal of molecular medicine 2021; 47:1.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33576442

ABSTRACT

The present study aimed to explore the role and mechanisms of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the oxidized low-density lipoprotein (oxLDL)-induced pyroptosis of vascular endothelial cells. For this purpose, human umbilical vein endothelial cells (HUVECs) were incubated with oxLDL (100 μg/ml) for 24 h to induce pyroptosis, which was detected using PI/hoechst33342 double staining. The expression of pyroptosis-associated molecules was measured by western blot analysis and RT-qPCR. Reactive oxygen species (ROS) and membrane potential were examined through ROS probe and JC-1 staining, respectively. PCSK9 and mitochondrial ubiquinol-cytochrome c reductase core protein 1 (UQCRC1) protein were knocked down by small interfering RNA (siRNA). PCSK9 was overexpressed by lentivirus. The results revealed that oxLDL induced HUVEC injury, pyroptosis and inflammatory factor release, and upregulated the expression of PCSK9 protein in the HUVECs in a concentration-dependent manner. The silencing of PCSK9 expression with siRNA suppressed the oxLDL-induced damage to HUVECs, the release of inflammatory substances and the occurrence of pyroptosis. In addition, oxLDL inhibited UQCRC1 expression, promoted mitochondrial membrane potential collapse and damaged mitochondrial function; however, these processes were reversed by the silencing of PCSK9. PCSK9 overexpression induced the pyroptosis of HUVECs, the generation of ROS and the disorder of mitochondrial function by inhibiting UQCRC1. Therefore, PCSK9 mediates the oxLDL-induced pyroptosis of vascular endothelial cells via the UQCRC1/ROS pathway.

[45] *Harzandi A, Lee S, Bidkhori G et al.* **Acute kidney injury leading to CKD is associated with a persistence of metabolic dysfunction and hypertriglyceridemia**. iScience 2021; 24:102046.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33554059

ABSTRACT

Fibrosis is the pathophysiological hallmark of progressive chronic kidney disease (CKD). The kidney is a highly metabolically active organ, and it has been suggested that disruption in its metabolism leads to renal fibrosis. We developed a longitudinal mouse model of acute kidney injury leading to CKD and an in vitro model of epithelial to mesenchymal transition to study changes in metabolism, inflammation, and fibrosis. Using transcriptomics, metabolic modeling, and serum metabolomics, we observed sustained fatty acid metabolic dysfunction in the mouse model from early to late stages of CKD. Increased fatty acid biosynthesis and downregulation of catabolic pathways for triglycerides and diacylglycerides were associated with a marked increase in these lipids in the serum. We therefore

suggest that the kidney may be the source of the abnormal lipid profile seen in patients with CKD, which may provide insights into the association between CKD and cardiovascular disease.

[46] *Hart RG, Perera KS*. **Intracranial Atherosclerotic Plaque and Embolic Stroke of Undetermined Source: Another Piece of the Puzzle**. Journal of the American College of Cardiology 2021; 77:692-694.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33573738
ABSTRACT

[47] *Tao L, Li XQ, Hou XW et al.* **Intracranial Atherosclerotic Plaque as a Potential Cause of Embolic Stroke of Undetermined Source**. Journal of the American College of Cardiology 2021; 77:680-691.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33573737
ABSTRACT
BACKGROUND: Previous studies investigated the potential mechanism of embolic stroke of undetermined source (ESUS) from extracranial artery plaque, but there has been no study other than a case report on high-risk intracranial plaque in ESUS. OBJECTIVES: The aim of this study was to investigate the issue by evaluating the morphology and composition of intracranial plaque in patients with ESUS and small-vessel disease (SVD) using 3.0-T high-resolution magnetic resonance imaging. METHODS: Two hundred forty-three consecutive patients with ESUS and 160 patients with SVD-associated stroke between January 2015 and December 2019 were retrospectively enrolled. Multidimensional parameters involving the presence of plaque on both sides, including remodeling index (RI), plaque burden, presence of discontinuity of plaque surface, thick fibrous cap, intraplaque hemorrhage, and complicated American Heart Association type VI plaque at the maximal luminal narrowing site, were evaluated using intracranial high-resolution magnetic resonance imaging. RESULTS: Among 243 patients with ESUS, the prevalence of intracranial plaque was much higher in the ipsilateral than the contralateral side (63.8% vs. 42.8%; odds ratio [OR]: 5.25; 95% confidence interval [CI]: 2.83 to 9.73), a finding that was not evident in patients with SVD (35.6% vs. 30.6%; OR: 2.14; 95% CI: 0.87 to 5.26; $p = 0.134$). Logistic analysis showed that RI was independently associated with ESUS in model 1 (OR: 2.329; 95% CI: 1.686 to 3.217; $p < 0.001$) and model 2 (OR: 2.295; 95% CI: 1.661 to 3.172; $p < 0.001$). RI alone with an optimal cutoff of 1.162, corresponding to an area under the curve of 0.740, had good diagnostic efficiency for ESUS. CONCLUSIONS: The present study supports an etiologic role of high-risk nonstenotic intracranial plaque in ESUS.

[48] *Nilsson A, Tsoumani K, Planck T*. **Statins Decrease the Risk of Orbitopathy in Newly Diagnosed Patients with Graves' disease**. The Journal of clinical endocrinology and metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33560351
ABSTRACT
AIM: The aim of this study was to examine the effect of statins and other lipid-lowering agents on the development of Graves´ orbitopathy (GO) in patients with newly diagnosed Graves´ disease (GD). METHODS: Our sample included the full adult population of individuals living in Sweden with newly diagnosed GD between 2005 and 2018 (n=34,894). We compared the GO incidence in statin users (n=5,574) and nonusers (n=34,409) by applying Cox regression with a time-varying exposure

variable. We adjusted for age, sex, and treatment for hyperthyroidism in the multivariate analyses. RESULTS: Periods of nonusage lasted for a median of 4.3 years (IQR 1.2-8.4), whereas periods of usage lasted for a median of 4.7 years (IQR 2.0-8.1). Among statin users, 77.1% had used simvastatin, 28.9% atorvastatin, and 8.2% had used other statins. Statin users were found to be significantly less likely to develop GO. In the main analysis based on the full cohort, the unadjusted HR was 0.74 (CI [0.65-0.84], p<0.001), whereas full adjustment altered the effect to 0.87 (CI [0.76-1.00], p=0.04). The main results were largely driven by men; the fully adjusted HR was 0.78 (CI [0.58-1.04], p=0.09) for men and 0.91 (CI [0.79-1.06], p=0.24) for women. Lipid-lowering agents other than statins did not exhibit a similar protective effect. CONCLUSIONS: In newly diagnosed patients with GD, treatment with statins may protect against the development of GO. Statins should be investigated in a clinical trial as a preventive treatment for GO in newly diagnosed patients with GD.

[49] *Teng F, Qin R, Liu X et al.* **Interaction between the rs9356744 polymorphism and metabolic risk factors in relation to type 2 diabetes mellitus: The Cardiometabolic Risk in Chinese (CRC) Study**. Journal of diabetes and its complications 2021:107855.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33558148

ABSTRACT

The understanding of the genetic basis of type 2 diabetes mellitus (T2DM) has progressed rapidly, but the interactions among common genetic variants and metabolic risk factors have not been systematically investigated in studies with adequate statistical power. Therefore, we aimed to quantify the combined effects of genetic and metabolic environments on the risk of T2DM. Obesity is emerging as an independent risk factor for T2DM and arterial stiffness. Here, we examined the effect of the rs9356744 polymorphism in the body mass index (BMI) gene CDKAL1 on the risk of T2DM in East Asians and particularly assessed the interactions between this polymorphism and other metabolic risk factors. A total of 1975 subjects in whom the rs9356744 polymorphism had been detected in the CDKAL1 gene were enrolled in this study. The height, weight, blood pressure and relevant markers, including glucose, lipids, liver and renal function, of the participants were successfully measured. Pulse wave velocity (PWV) was measured using an automatic wave form analyzer. At baseline, we found a significant association between BMI and rs9356744 genotypes (CC, CT, TT) (P = 0.048). After adjusting for confounding factors, including sex, age and BMI, participants carrying the T allele of rs9356744 showed a lower incidence of T2DM. Further adjustment for blood pressure and lipids did not appreciably change the results (P = 0.019, 0.009, 0.015, respectively). We found significant interactions between the rs9356744 polymorphism and high-density lipoprotein (HDL), serum uric acid (SUA) and carotid-femoral pulse wave velocity (cf-PWV) in relation to T2DM incidence (P for interaction = 0.007, 0.002, 0.004, respectively), especially in the group with the lowest SUA level and the group with the highest HDL and cf-PWV levels (P for trend = 0.006, 0.008, 0.018, respectively). Furthermore, we found a significant interaction between the rs9356744 polymorphism and cf-PWV in relation to the level of 2-h plasma glucose in the oral glucose tolerance test (OGTT) (P for interaction = 0.0341). In summary, the T allele of rs9356744 was an independent protective factor for T2DM. There were significant interactions between rs9356744 and HDL, SUA, and cf-PWV in relation to T2DM risk.

[50] *Bowling CB, Sloane R, Pieper C et al.* **Association of Sustained Blood Pressure Control with Lower Risk for High-Cost Multimorbidities Among Medicare Beneficiaries in ALLHAT**. Journal of general internal medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33564944
ABSTRACT
BACKGROUND: Clustering of chronic conditions is associated with high healthcare costs. Sustaining blood pressure (BP) control could be a strategy to prevent high-cost multimorbidity clusters. OBJECTIVE: To determine the association between sustained systolic BP (SBP) control and incident multimorbidity cluster dyads and triads. DESIGN: Cohort study of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) linked to Medicare claims. PARTICIPANTS: ALLHAT included adults with hypertension and ≥1 coronary heart disease risk factor. This analysis was restricted to 5234 participants with ≥ 8 SBP measurements during a 48-month BP assessment period. MAIN MEASURES: SBP control was defined as <140 mm Hg at <50%, 50 to <75%, 75 to <100%, and 100% of study visits during the BP assessment period. High-cost multimorbidity clusters included dyads (stroke/chronic kidney disease [CKD], stroke/chronic obstructive pulmonary disease [COPD], stroke/heart failure [HF], stroke/asthma, COPD/CKD) and triads (stroke/CKD/asthma, stroke/CKD/COPD, stroke/CKD/depression, stroke/CKD/HF, stroke/HF/asthma) identified during follow-up. KEY RESULTS: Incident dyads occurred in 1334 (26%) participants and triads occurred in 481 (9%) participants over a median follow-up of 9.2 years. Among participants with SBP control at <50%, 50 to <75%, 75 to <100%, and 100% of visits, 32%, 23%, 23%, and 19% of participants developed high-cost dyads, respectively, and 13%, 9%, 8%, and 5% of participants developed high-cost triads, respectively. Compared to those with sustained BP control at <50% of visits, adjusted HRs (95% CI) for incident dyads were 0.66 (0.57, 0.75), 0.67 (0.59, 0.77), and 0.51 (0.42, 0.62) for SBP control at 50 to <75%, 75 to <100%, and 100% of visits, respectively. The corresponding HRs (95% CI) for incident triads were 0.69 (0.55, 0.85), 0.56 (0.44, 0.71), and 0.32 (0.22, 0.47). CONCLUSIONS: Among Medicare beneficiaries in ALLHAT, sustained SBP was associated with a lower risk of developing high-cost multimorbidity dyads and triads.

[51] *Mefford MT, Chen L, Lewis CE et al.* **Long-Term Levels of LDL-C and Cognitive Function: The CARDIA Study**. J Int Neuropsychol Soc 2021:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33563358
ABSTRACT
OBJECTIVES: It is uncertain if long-term levels of low-density lipoprotein-cholesterol (LDL-C) affect cognition in middle age. We examined the association of LDL-C levels over 25 years with cognitive function in a prospective cohort of black and white US adults. METHODS: Lipids were measured at baseline (1985-1986; age: 18-30 years) and at serial examinations conducted over 25 years. Time-averaged cumulative LDL-C was calculated using the area under the curve for 3,328 participants with ≥3 LDL-C measurements and a cognitive function assessment. Cognitive function was assessed at the Year 25 examination with the Digit Symbol Substitution Test [DSST], Rey Auditory Visual Learning Test [RAVLT], and Stroop Test. A brain magnetic resonance imaging (MRI) sub-study (N = 707) was also completed at Year 25 to assess abnormal white matter tissue volume (AWMV) and gray matter cerebral blood flow volume (GM-CBFV) as secondary outcomes. RESULTS: There were 15.6%, 32.9%, 28.9%, and 22.6% participants with time-averaged cumulative LDL-C <100 mg/dL, 101-129 mg/dL, 130-159 mg/dL, and ≥160 mg/dL, respectively. Standardized differences in all

cognitive function test scores ranged from 0.16 SD lower to 0.09 SD higher across time-averaged LDL-C categories in comparison to those with LDL-C < 100 mg/dL. After covariate adjustment, participants with higher versus lower time-averaged LDL-C had a lower RAVLT score (p-trend = 0.02) but no differences were present for DSST, Stroop Test, AWMV, or GM-CBFV. CONCLUSION: Cumulative LDL-C was associated with small differences in memory, as assessed by RAVLT scores, but not other cognitive or brain MRI measures over 25 years of follow-up.

[52] *Busik JV*. **Lipid metabolism dysregulation in diabetic retinopathy**. Journal of lipid research 2021; 62:100017.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33581416
ABSTRACT
Lipid metabolic abnormalities have emerged as potential risk factors for the development and progression of diabetic complications, including diabetic retinopathy (DR). This review article provides an overview of the results of clinical trials evaluating the potential benefits of lipid-lowering drugs, such as fibrates, omega-3 fatty acids, and statins, for the prevention and treatment of DR. Although several clinical trials demonstrated that treatment with fibrates leads to improvement of DR, there is a dissociation between the protective effects of fibrates in the retina, and the intended blood lipid classes, including plasma triglycerides, total cholesterol, or HDL:LDL cholesterol ratio. Guided by these findings, plasma lipid and lipoprotein-independent mechanisms are addressed based on clinical, cell culture, and animal model studies. Potential retinal-specific effects of fatty acid oxidation products, cholesterol, and ceramide, as well as lipid-independent effects of PPAR alpha activation, are summarized based on the current literature. Overall, this review highlights promising potential of lipid-based treatment strategies further enhanced by the new knowledge of intraretinal lipids and lipoproteins in DR.

[53] *Babaniamansour P, Mohammadi M, Babaniamansour S, Aliniagerdroudbari E*. **The Relation between Atherosclerosis Plaque Composition and Plaque Rupture**. J Med Signals Sens 2020; 10:267-273.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33575199
ABSTRACT
BACKGROUND: Intima, media, and adventitia are three layers of arteries. They have different structures and different mechanical properties. Damage to intima layer of arteries leads to an inflammatory response, which is usually the reason for atherosclerosis plaque formation. Atherosclerosis plaques mainly consist of smooth muscle cells and calcium. However, plaque geometry and mechanical properties change during time. Blood flow is the source of biomechanical stress to the plaques. Maximum stress that atherosclerosis plaque can burden before its rupture depends on fibrous cap thickness, lipid core, calcification, and artery stenosis. When atherosclerotic plaque ruptures, the blood would be in contact with coagulation factors. That is why plaque rupture is one of the main causes of fatality. METHOD: In this article, the coronary artery was modeled by ANSYS. First, fibrous cap thickness was increased from 40 μm to 250 μm by keeping other parameters constant. Then, the lipid pool percentage was incremented from 10% to 90% by keeping other parameters unchanged. Furthermore, for investigating the influence of calcium in plaque vulnerability, calcium was modeled in both agglomerated and microcalcium form. RESULTS: It is proved that atherosclerosis plaque stress decreases exponentially as cap thickness increases. Larger

lipid pool leads to more vulnerable plaques. In addition, the analysis showed maximum plaque stress usually increases in calcified plaque as compared with noncalcified plaque. CONCLUSION: The plaque stress is dependent on whether calcium is agglomerated near the lumen or far from it. However, in both cases, the deposition of more calcium in calcified plaque reduces maximum plaque stress.

[54] *Yang WY, Li YF, Wang ZR et al.* **Combined therapy of intensive statin plus intravenous rt-PA in acute ischemic stroke: the INSPIRE randomized clinical trial**. Journal of neurology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33555418

ABSTRACT

OBJECTIVE: To investigate the safety and efficacy of intensive statin in the acute phase of ischemic stroke after intravenous thrombolysis therapy. METHODS: A total of 310 stroke patients treated with rt-PA were randomly scheduled into the intensive statin group (rosuvastatin 20 mg daily × 14 days) and the control group (rosuvastatin 5 mg daily × 14 days). The primary clinical endpoint was excellent functional outcome (mRS ≤ 1) at 3 months, and the primary safety endpoint was symptomatic intracranial hemorrhage (sICH) in 90 days. RESULTS: The intensive statin users did not achieve a favorable outcome in excellent functional outcome (mRS ≤ 1) at 3 months compared with controls (70.3% vs. 66.5%, p = 0.464). Intensive statin also not significantly improved the overall distribution of scores on the modified Rankin scale, as compared with controls (p = 0.82 by the Cochran-Mantel-Haenszel test). The incidence of primary safety endpoint events (sICH) in 90 days did not significantly differ between the intensive statin group and control group (0.6% vs. 1.3%, p > 0.999). CONCLUSION: The INSPIRE study indicated that intensive statin therapy may not improve clinical outcomes compared with the low dose of statin therapy in AIS patients undergoing intravenous thrombolysis, and the two groups had similar safety profile. CLINICAL TRIAL REGISTRATION: URL: http://www.chictr.org . Unique identifier: ChiCTR-IPR-16008642.

[55] *Buzatto AZ, Malkawi A, Sabi EM et al.* **Tissue Lipidomic Alterations Induced by Prolonged Dexamethasone Treatment**. J Proteome Res 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33557525

ABSTRACT

Dexamethasone is a synthetic glucocorticoid medication vastly used to treat abnormal immune responses and inflammation. Although the medication is well-established in the medical community, the prolonged treatment with high dosages of dexamethasone may lead to severe adverse effects through mechanisms that are not yet well-known. Lipids are a large class of hydrophobic molecules involved in energy storage, signaling, modulation of gene expression, and membranes. Hence, untargeted lipidomics may help unravel the biochemical alterations following prolonged treatment with high dosages of dexamethasone. We performed comprehensive lipidomic analyses of brain, heart, kidney, liver, and muscle samples obtained from rats that were treated with intramuscular injections of dexamethasone for 14 weeks compared to healthy controls. The employed methodology and statistical analysis showed that phosphatidic acids, glycerophospholipids, plasmalogens, and fatty acids are deeply affected by prolonged use of the medication. Brain tissue was only mildly affected, but skeletal muscle showed a strong accumulation of lipids that may be correlated with alterations in the energy metabolism, myopathy, and oxidative processes. This work provides new insights into the

mechanisms of action and adverse effects for one of the most commonly prescribed class of drugs in the world.

[56] *Masson W, Lobo M, Siniawski D et al.* **LDL-C Levels Below 55 mg/dl and Risk of Hemorrhagic Stroke: A Meta-Analysis**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2021; 30:105655.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33571878

ABSTRACT

OBJECTIVE: To evaluate the effect of very low levels of LDL-C (< 55 mg/dl) achieved with lipid-lowering therapy on hemorrhagic stroke incidence. METHODS: We performed a meta-analysis including randomized trials that achieved LDL-C levels under 55 mg/dl in more intensive lipid-lowering arms, regardless of the lipid-lowering drug used. A fixed-effects model was used. This meta-analysis was performed according to PRISMA guidelines. RESULTS: Eight eligible trials including 122.802 patients, were identified and considered eligible for the analyses. A total of 62.526 subjects were allocated to receive more intensive lipid-lowering therapy while 60.276 subjects were allocated to the respective control arms. There were no differences in the incidence of hemorrhagic stroke between the group that received a more intensive lipid-lowering therapy (achieved LDL-C level <55 mg/dl), and the group that received a less intense scheme (OR, 1.05; 95%CI, 0.85-1.31). The statistical heterogeneity was low (I(2) = 2%). The sensitivity analysis showed that the results were robust. CONCLUSIONS: The use of more intensive lipid-lowering therapy that achieved an LDL-C level lower than 55 mg/dl in patients with high cardiovascular risk, is not associated with an increased risk of hemorrhagic stroke. Considering the cardiovascular benefit and safety observed with the achievement of very low LDL-C values, the challenging lipid goals recommended by the new guidelines seem consistent.

[57] *Zhang X, Qin Y, Wan X et al.* **Rosuvastatin exerts anti-atherosclerotic effects by improving macrophage-related foam cell formation and polarization conversion via mediating autophagic activities**. Journal of translational medicine 2021; 19:62.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33568202

ABSTRACT

BACKGROUND: Atherosclerosis is a chronic vascular disease posing a great threat to public health. We investigated whether rosuvastatin (RVS) enhanced autophagic activities to inhibit lipid accumulation and polarization conversion of macrophages and then attenuate atherosclerotic lesions. METHODS: All male Apolipoprotein E-deficient (ApoE(-/-)) mice were fed high-fat diet supplemented with RVS (10 mg/kg/day) or the same volume of normal saline gavage for 20 weeks. The burden of plaques in mice were determined by histopathological staining. Biochemical kits were used to examine the levels of lipid profiles and inflammatory cytokines. The potential mechanisms by which RVS mediated atherosclerosis were explored by western blot, real-time PCR assay, and immunofluorescence staining in mice and RAW264.7 macrophages. RESULTS: Our data showed that RVS treatment reduced plaque areas in the aorta inner surface and the aortic sinus of ApoE(-/-) mice with high-fat diet. RVS markedly improved lipid profiles and reduced contents of inflammatory cytokines in the circulation. Then, results of Western blot showed that RVS increased the ratio LC3II/I and level of Beclin 1 and decreased the expression of p62 in aortic tissues, which might be attributed to suppression of PI3K/Akt/mTOR pathway, hinting that autophagy cascades were activated by RVS.

Moreover, RVS raised the contents of ABCA1, ABCG1, Arg-1, CD206 and reduced iNOS expression of arterial wall, indicating that RVS promoted cholesterol efflux and M2 macrophage polarization. Similarly, we observed that RVS decreased lipids contents and inflammatory factors expressions in RAW264.7 cells stimulated by ox-LDL, accompanied by levels elevation of ABCA1, ABCG1, Arg-1, CD206 and content reduction of iNOS. These anti-atherosclerotic effects of RVS were abolished by 3-methyladenine intervention. Moreover, RVS could reverse the impaired autophagy flux in macrophages insulted by chloroquine. We further found that PI3K inhibitor LY294002 enhanced and agonist 740 Y-P weakened the autophagy-promoting roles of RVS, respectively. CONCLUSIONS: Our study indicated that RVS exhibits atheroprotective effects involving regulation lipid accumulation and polarization conversion by improving autophagy initiation and development via suppressing PI3K/Akt/mTOR axis and enhancing autophagic flux in macrophages.

[58] *Chen MB, Wang H, Cui WY et al.* **Effect of SGLT inhibitors on weight and lipid metabolism at 24 weeks of treatment in patients with diabetes mellitus: A systematic review and network meta-analysis**. Medicine (Baltimore) 2021; 100:e24593.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33578559
ABSTRACT
BACKGROUND: The goals of improving quality of life and increasing longevity are receiving growing amounts of attention. Body weight and lipid metabolism are closely related to various complications of diabetes. The aim of this study was to rank SGLT inhibitors according to their efficacy with regard to weight and evaluate the effect of SGLT inhibitors on lipid metabolism at 24weeks of treatment. METHODS: The Web of Science, PubMed, Cochrane Library, Embase, and Clinical Trials databases were electronically searched to collect randomized controlled trials involving patients with type 2 diabetes mellitus through June 2020. Two researchers independently screened and evaluated the selected studies and extracted the outcome indexes. ADDIS 1.16.5 and STATA 16 software were used to perform the network meta-analysis and draw the plots. RESULTS: Ultimately, 36 studies were selected and included in this study. We found that all SGLT inhibitors were effective at reducing weight; canagliflozin was the most effective. SGLT inhibitors and placebo were not associated with significantly different serum cholesterol levels. SGLT inhibitors lowered serum triglyceride levels and increased serum high-density and low-density lipoprotein cholesterol levels. SGLT inhibitors also reduced the level of alanine aminotransferase. CONCLUSIONS: SGLT inhibitors can bring about weight loss in patients with T2DM and can also improve lipid metabolism. Therefore, patients with hyperlipidemia who have been unsuccessful at losing weight should consider taking SGLT inhibitors. In addition, SGLT inhibitors are hepatoprotective and appear to be safe for patients with mild to moderate liver dysfunction. TRIAL REGISTRATION: CRD42020198516.

[59] *Liu N, Su D, Liu K et al.* **The effects of IL-17/IL-17R inhibitors on atherosclerosis in psoriasis and psoriatic arthritis: A protocol for systematic review and meta analysis**. Medicine (Baltimore) 2021; 100:e24549.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33578549
ABSTRACT
BACKGROUND: Psoriasis (PSO) is a systemic inflammatory disorder that presents with erythematous scaling of the skin and is associated with autoimmune dysfunction. Atherosclerosis is one of the major comorbidities of PSO. PSO-associated inflammatory factor IL-17 could lead to

vascular endothelial cell injury and atherosclerosis. While some research results show that IL-17 helps stabilize plaque formation. Efficacy and safety on PSO and psoriatic arthritis (PSA) of existing IL-17/IL-17R biologics (secukinumab, ixekizumab, brodalumab, and bimekizumab) have been clinically validated, but whether they can improve atherosclerotic outcomes in psoriatic patients remains controversial. METHODS: Seven electronic search engines will be searched from inception to December 1, 2020, including PubMed, Embase, Scopus, PsycINFO, Global Health, Web of Science and the Cochrane Library. Clinical trial registries, potential grey literature, relevant conference abstracts, and reference lists of identified studies will also be searched. Literature selection, data extraction, and quality assessment will be done by 2 independent authors. Based on the heterogeneity test, the fixed effect or random effect model will be used for data synthesis. Changes in lung function will be evaluated as the primary outcome. Assessment of symptoms, quality of life, medication use, exacerbations and adverse events will be assessed as secondary outcomes. RevMan V. 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark) will be used for meta-analysis. RESULTS: This study will provide a synthesis of current evidence of IL-17/IL-17R inhibitors on atherosclerosis in PSO and PSA. CONCLUSION: The conclusion of our study will provide updated evidence to judge whether IL-17/IL-17R inhibitors is an effective solution to atherosclerosis as comorbidity of PSO and PSA. PROSPERP REGISTRATION NUMBER: CRD42020209897.

[60] *Liu Y, Liu Y, Yang J et al.* **Chinese herbal medicine for hypertension complicated with hyperlipidemia: A protocol for a systematic review and meta-analysis**. Medicine (Baltimore) 2021; 100:e24345.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33578530

ABSTRACT

BACKGROUND: Hypertension combined with hyperlipidemia (HTN-HLP), as a common clinical chronic disease combination, will increase the incidence of cardiovascular and cerebrovascular diseases, increase the occurrence of sudden death and other adverse events. At present, the commonly used therapeutic drugs are mainly combined with antihypertensive drugs and lipid-lowering drugs, which not only have poor compliance, but also have adverse reactions. Currently, traditional Chinese medicine, as a traditional medicine in China, has been applied in clinical practice for thousands of years and has rich clinical experience in treating HTN-HLP. However, there is no systematic evaluation of the efficacy, safety and improvement of patients' quality of life. This systematic review and meta-analysis will assess studies of the effects and safety of Chinese herbal medicine (CHM) for HTN-HLP patients. METHODS: We will search PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science (ISI), China National Knowledge Infrastructure, Wan fang Database, Chinese Scientific Journals Full-Text Database (VIP) and China Biological Medicine Database from the time when databases were established to 01, February 2021. After a series of screening, randomized controlled trials (RCTs) will be included related to CHM for HTN-HLP. Two researchers will assess the RCTs through the Cochrane bias risk assessment tool. And the evidence grade of the results will be evaluated by GRADEprofiler software. RESULTS: This study will provide a reliable evidence for the efficiency of antihypertensive and reducing blood lipids of CHM for HTN-HLP. CONCLUSION: We will summarize the methods and provide sufficient evidence to confirm the efficacy and safety of CHM for HTN-HLP. INPLASY REGISTRATION NUMBER: INPLASY2020110144.

[61] *Shi GX, Zhao ZH, Yang XY et al.* **Correlation study of CYP2C19 gene polymorphism and clopidogrel resistance in Han Chinese patients with cerebral infarction in Guizhou region**. Medicine (Baltimore) 2021; 100:e24481.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33578542

ABSTRACT
This study conducts a correlation exploration of CYP2C19 gene polymorphism and clopidogrel resistance in Han Chinese patients with cerebral infarction in Guizhou Region.A total of 270 Han Chinese patients with cerebral infarction, who were hospitalized in our hospital from January 2016 to January 2018, are selected. These patients were divided into 2 groups, clopidogrel resistance group (n=60) and clopidogrel sensitive group (n=210). According to the TEG results, the CYP2C19 gene polymorphism detection was carried out by using the PCR-RFLP method, while IL-6 level in the patient's blood was measured by using the ELISA method.The resistance group occupies 22.22%. The platelet inhibition ratio of the resistance group was 23±7%, which was significantly lower than that of the sensitive group (65±13%), and the difference was statistically significant (P<.05). The Logisitic regression analysis revealed that the history of diabetes, history of high blood pressure, increase in low density lipoprotein and CYP2C19 mutant gene were independent risk factors of clopidogrel resistance. After treatment, the serum IL-6 level of patients in the resistance group was 17.21±0.98ng/L, which was significant higher than that of patients in the sensitive group (11.21±0.68ng/L), and the difference was statistically significant (P<.05).Patients with cerebral infarction in Guizhou region have a higher occurrence rate of clopidogrel resistance. Clopidogrel resistance not only will weaken the anti-inflammatory action of the drug, but also correlates with the patient's CYP2C19 mutant gene and blood lipid level.

[62] *Kothawade PB, Thomas AB, Chitlange SS*. **Novel Niacin Receptor Agonists: A Promising Strategy for the Treatment of Dyslipidemia**. Mini reviews in medicinal chemistry 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33550969

ABSTRACT
BACKGROUND: Hyperlipidemia is characterized by high level of cholesterol and triglycerides in blood. Various classes of drugs like statins, fibrates, niacin etc. are used for treatment of hyperlipidaemia. OBJECTIVE: Niacin, which is one of the beneficial anti-hyperlipidemic agents, helps to lower LDL cholesterol by 20 to 40% and causes increase of HDL cholesterol by 20 to 35%. However cutaneous flushing, loss of glucose tolerance, liver toxicity are the reported side effects of niacin therapy responsible for decreased patient compliance. Very recently, the G protein coupled receptor (GPCR); GPR109A located on the adipocytes has been identified as the receptor for activation of niacin. METHOD: In-vitro studies have demonstrated that GPR109A receptor having high affinity for niacin. The present review attempts to provide a systematic presentation of the various chemical classes of compounds that have been reported as novel niacin receptor agonists including pyrazole-3-carboxylic acids, urea derivatives, anthranilic acids, biaryl anthranilides, tetrahydro anthranilic acid, xanthines, barbituric acid, bicyclic pyrazole carboxylic acids, pyrido pyrimidinones, pyrazolyl propionyl cyclohexenamides, pyrazole acids etc. Results: As the design of GPR109A receptor agonists offers a promising solution for treatment of dyslipidemia, this review will be beneficial for medicinal and drug discovery chemists to expediate the process of discovery of new class of antihyperlipidemic agent with favorable lipid lowering profile with increase in HDL levels.

CONCLUSION: This review explains about novel GPR109A receptor agonist for the treatment of dyslipidemia.

[63] *Agirbasli M*. **Evinacumab for Homozygous Familial Hypercholesterolemia**. The New England journal of medicine 2021; 384:e17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33567205
ABSTRACT

[64] *Luo F, Das A, Fang Z*. **Evinacumab for Homozygous Familial Hypercholesterolemia**. The New England journal of medicine 2021; 384:e17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33567206
ABSTRACT

[65] *Raal FJ, Gaudet D, Gusarova V*. **Evinacumab for Homozygous Familial Hypercholesterolemia. Reply**. The New England journal of medicine 2021; 384:e17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33567208
ABSTRACT

[66] *Xu HG*. **Evinacumab for Homozygous Familial Hypercholesterolemia**. The New England journal of medicine 2021; 384:e17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33567207
ABSTRACT

[67] *Roy G, Boucher A, Couture P, Drouin-Chartier JP*. **Impact of Diet on Plasma Lipids in Individuals with Heterozygous Familial Hypercholesterolemia: A Systematic Review of Randomized Controlled Nutritional Studies**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33561083
ABSTRACT
BACKGROUND: Conclusive data on the effectiveness of dietary interventions in heterozygous familial hypercholesterolemia (HeFH) management are unavailable. Whether this is due to a true lack of effects or biases in intervention designs remains unsettled. We systematically assessed the impact on LDL-C of published dietary randomized controlled trials (RCTs) conducted among individuals with HeFH in relation to their design and risk of bias. METHODS: We systematically searched PubMed, Web of Science, and Embase in November 2020 to identify RCTs that assessed the impact of: (1) food-based interventions; (2) dietary counseling interventions; or (3) dietary supplements on LDL-C in individuals with HeFH. We evaluated the risk of bias of each study using the Cochrane Risk of Bias 2 method. RESULTS: A total of 19 RCTs comprising 837 individuals with HeFH were included. Of those, five were food-based interventions, three were dietary counseling interventions and 12 were dietary supplement-based interventions (omega-3, n = 3; phytosterols, n = 7; guar gum, n = 1; policosanol, n = 1). One study qualified both as a food-based intervention and as a dietary supplement intervention due to its factorial design. A significant reduction in LDL-C levels was reported in 10 RCTs, including eight dietary supplement interventions (phytosterols, n = 6, omega-3, n = 1; guar gum, n = 1), one food-based intervention and one dietary counseling intervention. A total of 13 studies were judged to have some methodological biases in a way that substantially lowers

confidence in the results. Studies at low risk of biases were more likely to report significant reductions in LDL-C concentrations, compared with studies at risk of bias (chi-square statistic: 5.49; p = 0.02). CONCLUSION: This systemic review shows that the apparent lack of effectiveness of diet manipulation in modulating plasma levels of LDL-C among individuals with HeFH is likely due to biases in study designs, rather than a true lack of effects. The likelihood of reporting significant reductions in LDL-C was associated with the concurrent risk of bias.

[68] *Żebrowska A, Hall B, Stolecka-Warzecha A et al.* **The Effect of Omega-3 Fatty Acid Supplementation on Serum Adipocytokines, Lipid Profile and Biochemical Markers of Inflammation in Recreational Runners**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33573042
ABSTRACT
BACKGROUND: The study aimed to evaluate the effects of a 3-week ω-3 PUFA supplementation on serum adipocytokines (i.e., adiponectin, leptin), neuregulin-4 (NRG4) and erythrocyte omega-3 (ω-3) fatty acid content, as well as the blood antioxidant defense capacity in non-elite endurance runners. METHODS: Twenty-four runners were randomized into two groups: the supplemented group, who received omega free fatty acids extract containing 142 mg of EPA, 267 mg of DHA, 12 mg of vitamin E and 5 μg of vitamin D, each administrated at a dose of six capsules twice a day for three weeks, or the placebo group. Venous blood samples were withdrawn at the start and at the end of the study protocols to estimate serum biochemical variables. RESULTS: A significantly higher ω-3 index and lower AA/EPA ratio was observed after ω-3 PUFA compared to pre-supplementation levels ($p < 0.001$ and $p < 0.001$, respectively). An increase in baseline adiponectin and NRG4 levels, as well as a decrease of leptin concentration and lipid profile improvement, were observed in subjects after a ω-3 PUFA diet. The increased ω-3 index had a significant effect on TNFα levels and a serum marker of antioxidant defense. CONCLUSIONS: The ω-3 PUFA extract with added vitamin E and D supplementation may have a positive effect on the function of the adipocyte tissue, as well as the ability to prevent cardiovascular complications in athletes.

[69] *Tomlinson B, Lin CH, Chan P, Lam CW*. **Personalized medicine in lipid-modifying therapy**. Personalized medicine 2021; 18:185-203.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33565320
ABSTRACT
The choice of lipid-modifying treatment is largely based on the absolute level of cardiovascular risk and baseline lipid profile. Statins are the first-line treatment for most patients requiring reduction of low-density-lipoprotein cholesterol (LDL-C) and ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors can be added to reach LDL-C targets. Statins have some adverse effects that are somewhat predictable based on phenotypic and genetic factors. Fibrates or omega-3 fatty acids can be added if triglyceride levels remain elevated. The RNA-targeted therapeutics in development offer the possibility of selective liver targeting for specific lipoproteins such as lipoprotein(a) and long-term reduction of LDL-C with infrequent administration of a small-interfering RNA may help to overcome the problem of adherence to therapy.

[70] *Thompson D, Al-Lamee R, Foley M et al.* **Achieving optimal adherence to medical therapy by telehealth: Findings from the ORBITA medication adherence sub-study**. Pharmacol Res Perspect 2021; 9:e00710.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33570248
ABSTRACT
INTRODUCTION: The ORBITA trial of percutaneous coronary intervention (PCI) versus a placebo procedure for patients with stable angina was conducted across six sites in the United Kingdom via home monitoring and telephone consultations. Patients underwent detailed assessment of medication adherence which allowed us to measure the efficacy of the implementation of the optimization protocol and interpretation of the main trial endpoints. METHODS: Prescribing data were collected throughout the trial. Self-reported adherence was assessed, and urine samples collected at pre-randomization and at follow-up for direct assessment of adherence using high-performance liquid chromatography with tandem mass spectrometry (HPLC MS/MS). RESULTS: Self-reported adherence was >96% for all drugs in both treatment groups at both stages. The percentage of samples in which drug was detected at pre-randomization and at follow-up in the PCI versus placebo groups respectively was: clopidogrel, 96% versus 90% and 98% versus 94%; atorvastatin, 95% versus 92% and 92% versus 91%; perindopril, 95% versus 97% and 85% versus 100%; bisoprolol, 98% versus 99% and 96% versus 97%; amlodipine, 99% versus 99% and 94% versus 96%; nicorandil, 98% versus 96% and 94% versus 92%; ivabradine, 100% versus 100% and 100% versus 100%; and ranolazine, 100% versus 100% and 100% versus 100%. CONCLUSIONS: Adherence levels were high throughout the study when quantified by self-reporting methods and similarly high proportions of drug were detected by urinary assay. The results indicate successful implementation of the optimization protocol delivered by telephone, an approach that could serve as a model for treatment of chronic conditions, particularly as consultations are increasingly conducted online.

[71] *Li YY, Zhang S, Wang H et al.* **Identification of Crucial Genes and Pathways Associated with Atherosclerotic Plaque in Diabetic Patients**. Pharmacogenomics and personalized medicine 2021; 14:211-220.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33568933
ABSTRACT
BACKGROUND: Patients with diabetes have more calcification in atherosclerotic plaque and a higher occurrence of secondary cardiovascular events than patients without diabetes. The objective of this study was to identify crucial genes involved in the development of diabetic atherosclerotic plaque using a bioinformatics approach. METHODS: Microarray dataset GSE118481 was downloaded from the Gene Expression Omnibus (GEO) database; the dataset included 6 patients with diabetic atherosclerotic plaque (DBT) and 6 nondiabetic patients with atherosclerotic plaque (Ctrl). Differentially expressed genes (DEG) between the DBT and Ctrl groups were identified and then subjected to functional enrichment analysis. Based on the enriched pathways of DEGs, diabetic atherosclerotic plaque-related pathways were screened using the comparative toxicogenomics database (CTD). We then constructed a protein-protein interaction (PPI) network and transcription factor (TF)-miRNA-mRNA network. RESULTS: A total of 243 DEGs were obtained in the DBT group compared with the Ctrl group, including 85 up-regulated and 158 down-regulated DEGs. Functional enrichment analysis showed that up-regulated DEGs were mainly enriched in isoprenoid metabolic process, DNA-binding TF activity, and response to virus. Additionally, DEGs participating in the toll-

like receptor signaling pathway were closely related to diabetes, carotid stenosis, and insulin resistance. The TF-miRNA-mRNA network showed that toll-like receptor 4 (TLR4), BCL2-like 11 (BCL2L11), and glutamate-cysteine ligase catalytic subunit (GCLC) were hub genes. Furthermore, TLR4 was regulated by TF signal transducer and activator of transcription 6 (STAT6); BCL2L11 was targeted by hsa-miR-24-3p; and GCLC was regulated by nuclear factor, erythroid 2 like 2 (NFE2L2). CONCLUSION: Identification of hub genes and pathways increased our understanding of the molecular mechanisms underlying the atherosclerotic plaque in patients with or without diabetes. These crucial genes (TLR4, BC2L11, and GCLC) might function as molecular biomarkers for diabetic atherosclerotic plaque.

[72] *Blais JE, Tong GKY, Pathadka S et al.* **Comparative efficacy and safety of statin and fibrate monotherapy: A systematic review and meta-analysis of head-to-head randomized controlled trials**. PloS one 2021; 16:e0246480.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33561179
ABSTRACT
OBJECTIVE: To assess whether in adults with dyslipidemia, statins reduce cardiovascular events, mortality, and adverse effects when compared to fibrates. METHODS: Systematic review and meta-analysis of head-to-head randomized trials of statin and fibrate monotherapy. MEDLINE, EMBASE, Cochrane, WHO International Controlled Trials Registry Platform, and ClinicalTrials.gov were searched through October 30, 2019. Trials that had a follow-up of at least 28 days, and reported mortality or a cardiovascular outcome of interest were eligible for inclusion. Efficacy outcomes were cardiovascular mortality and major cardiovascular events. Safety outcomes included myalgia, serious adverse effects, elevated serum creatinine, and elevated serum alanine aminotransferase. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using the Mantel-Haenszel fixed-effect model, and heterogeneity was assessed using the I2 statistic. RESULTS: We included 19 eligible trials that directly compared statin and fibrate monotherapy and reported mortality or a cardiovascular event. Studies had a limited duration of follow-up (range 10 weeks to 2 years). We did not find any evidence of a difference between statins and fibrates for cardiovascular mortality (OR 2.35, 95% CI 0.94-5.86, I2 = 0%; ten studies, n = 2657; low certainty), major cardiovascular events (OR 1.15, 95% CI 0.80-1.65, I2 = 13%; 19 studies, n = 7619; low certainty), and myalgia (OR 1.32, 95% CI 0.95-1.83, I2 = 0%; ten studies, n = 6090; low certainty). Statins had less serious adverse effects (OR 0.57, 95% CI 0.36-0.91, I2 = 0%; nine studies, n = 3749; moderate certainty), less elevations in serum creatinine (OR 0.17, 95% CI 0.08-0.36, I2 = 0%; six studies, n = 2553; high certainty), and more elevations in alanine aminotransferase (OR 1.43, 95% CI 1.03-1.99, I2 = 44%; seven studies, n = 5225; low certainty). CONCLUSIONS: The eligible randomized trials of statins versus fibrates were designed to assess short-term lipid outcomes, making it difficult to have certainty about the direct comparative effect on cardiovascular outcomes and mortality. With the exception of myalgia, use of a statin appeared to have a lower incidence of adverse effects compared to use of a fibrate.

[73] *Shimizu K, Imamura H, Tani S et al.* **Candidate drugs for preventive treatment of unruptured intracranial aneurysms: A cross-sectional study**. PloS one 2021; 16:e0246865.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33577580
ABSTRACT

BACKGROUND AND PURPOSE: Establishment of drug therapy to prevent rupture of unruptured intracranial aneurysms (IAs) is needed. Previous human and animal studies have gradually clarified candidate drugs for preventive treatment of IA rupture. However, because most of these candidates belong to classes of drugs frequently co-administered to prevent cardiovascular diseases, epidemiological studies evaluating these drugs simultaneously should be performed. Furthermore, because drugs included in the same class may have different effects in terms of disease prevention, drug-by-drug assessments are important for planning intervention trials. MATERIALS AND METHODS: We performed a cross-sectional study enrolling patients diagnosed with IAs between July 2011 and June 2019 at our institution. Patients were divided into ruptured or unruptured groups. The drugs investigated were selected according to evidence suggested by either human or animal studies. Univariate and multivariate logistic regression analyses were performed to assess the association of drug treatment with rupture status. We also performed drug-by-drug assessments of the association, including dose-response relationships, with rupture status. RESULTS: In total, 310 patients with ruptured and 887 patients with unruptured IAs were included. Multivariate analysis revealed an inverse association of statins (odds ratio (OR), 0.54; 95% confidence interval (CI) 0.38-0.77), calcium channel blockers (OR, 0.41; 95% CI 0.30-0.58), and angiotensin II receptor blockers (ARBs) (OR, 0.67; 95% CI 0.48-0.93) with ruptured IAs. Moreover, inverse dose-response relationships with rupture status were observed for pitavastatin and rosuvastatin among statins, benidipine, cilnidipine, and amlodipine among calcium channel blockers, and valsartan, azilsartan, candesartan, and olmesartan among ARBs. Only non-aspirin non-steroidal anti-inflammatory drugs were positively associated with ruptured IAs (OR, 3.24; 95% CI 1.71-6.13). CONCLUSIONS: The present analysis suggests that several types of statins, calcium channel blockers, and ARBs are candidate drugs for preventive treatment of unruptured IAs.

[74] *Mishra S, Rizvi A, Pradhan A et al.* **Circulating microRNA-126 &122 in patients with coronary artery disease: Correlation with small dense LDL**. Prostaglandins Other Lipid Mediat 2021; 153:106536.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33556577
ABSTRACT
BACKGROUND: Coronary artery disease (CAD) and stroke are major causes of cardiovascular diseases related deaths. Conventional risk factors cannot explain the changes in atherosclerosis. New and useful diagnostic markers are required. MicroRNAs are small, noncoding RNA that regulate the gene expression implicated in the pathogenesis of various cardiovascular diseases. Endothelial dysfunction is involved in the early event of the atherosclerosis process. AIMS: The current study was designed to evaluate the vascular endothelium-enriched miRNAs would be altered in CAD patients. METHODS: Circulating miR-126 & 122 levels were measured in serum from 78 CAD patients and 60 non CDA patients by qRT-PCR analysis. RESULTS: MiR-122 was significantly down regulated in CAD patients ($p = 0.001$), however the level of miR-126 did not show any change ($p = 0.507$). Remarkably, the level of miR-126 was significantly decreased in patients with CAD and high small dense low density lipoprotein (sdLDL) level. The level of miR-126 was significantly increased when sdLDL was higher in patients with risk factors for CAD but did not have angiographically significant CAD. CONCLUSION: . In CAD patient's, miR-126 level was lowered compared to non CAD patients, however the difference was not significant (0.507). However we found a direct relationship between endothelium-enriched miR-126 and sdLDL in patients with or without CAD. Our finding suggests that

miR-126 may have a potential role in sdLDL cholesterol metabolism. Mir-122 plays a role in cholesterol biosynthesis and deteriorates the cardiovascular system through the process of inflammation, apoptosis, oxidative stress and ECM deposition in a number of cardiovascular diseases.

[75] *Nambiar S, Tan DBA, Clynick B et al.* **Untargeted metabolomics of human plasma reveal lipid markers unique to chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis**. Proteomics. Clinical applications 2021:e2000039.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33580915
ABSTRACT
Chronic obstructive pulmonary disease (COPD) is characterised by airway inflammation and progressive airflow limitation, whereas idiopathic pulmonary fibrosis (IPF) is characterised by a restrictive pattern due to fibrosis and impaired gas exchange. We undertook metabolomic analysis of blood samples in IPF, COPD and healthy controls (HC) to determine differences in circulating molecules and identify novel pathogenic pathways. An untargeted metabolomics using an ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometer (UHPLC-QTOF-MS) was performed to profile plasma of patients with COPD (n = 21), and IPF (n = 24) in comparison to plasma from healthy controls (HC; n = 20). The most significant features were identified using multiple database matching. One-way ANOVA and variable importance in projection (VIP) scores were also used to highlight metabolites that influence the specific disease groups. Non-polar metabolites such as fatty acids (FA) and membrane lipids were well resolved and a total of 4,805 features were identified. The most prominent metabolite composition differences in lipid mediators identified at ~2-3 fold higher in both diseases compared to HC were palmitoleic acid, oleic acid and linoleic acid; and dihydrotestosterone was lower in both diseases. We demonstrated that COPD and IPF were characterised by systemic changes in lipid constituents such as essential FA sampled from circulating plasma.

[76] *Seaman KL, Bulsara MK, Sanfilippo FM et al.* **Exploring the association between stroke and acute myocardial infarction and statins adherence following a medicines co-payment increase**. Res Social Adm Pharm 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33558155
ABSTRACT
OBJECTIVES: Patient contributions (co-payments) for one months' supply of a publicly-subsidised medicine in Australia were increased by 21% in January 2005 (US$2.73-$3.31 for social security recipients and $17.05-$20.58 for others). This study investigates the relationship between patients' use of statin medication and hospitalisation for acute coronary syndrome and stroke, following this large increase in co-payments. METHODS: We designed a retrospective cohort study of all patients in Western Australia who were dispensed statin medication between 2004 and 05. Data for the cohort was obtained from State and Federal linked databases. We divided the cohort into those who discontinued, reduced or continued statin therapy in the first six months after the co-payment increase. The primary outcome was two-year hospitalisation for acute coronary syndrome or stroke-related event. Analysis was conducted using Fine and Gray competing risk methods, with death as the competing risk. RESULTS: There were 207,066 patients using statins prior to the co-payment increase. Following the increase, 12.5% of patients reduced their use of statin medication, 3.3% of

patients discontinued therapy, and 84.2% continued therapy. There were 4343 acute coronary syndrome and stroke-related hospitalisations in the two-year follow-up period. Multivariate analysis demonstrated that discontinuing statins increased the risk of hospitalisation for acute coronary syndrome or stroke-related events by 18% (95%CI = 0.1%-40%) compared to continuing therapy. Subgroup analysis showed that men aged <70 years were at increased risk of 54-63% after discontinuing statins compared to those continuing, but that women and older men were not. CONCLUSION: Discontinuing statin medication after a large increase patient cost contribution was associated with higher rates of acute coronary syndrome and stroke-related hospitalisation in men under 70 years. The findings highlight the importance of continued adherence to prescribed statin medication, and that discontinuing therapy for non-clinical reasons (such as cost) can possibly have negative consequences particularly for younger men.

[77] *Shokr H, Gherghel D*. **European Society of Cardiology/European Society of Hypertension versus the American College of Cardiology/American Heart Association guidelines on the cut-off values for early hypertension: a microvascular perspective**. Scientific reports 2021; 11:3473.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33568754
ABSTRACT
The aim of this study was to investigate retinal and peripheral microvascular function in asymptomatic individuals that fall into different BP groups when using either the ESC/ESH or the ACC/AHA guidelines. Retinal and peripheral microvascular function was assessed in 358 participants by means of dynamic retinal vessel analysis and digital thermal monitoring, respectively. Blood pressure and lipid panel were also evaluated. Retinal vascular function measured in all groups belonging to the ACC/ASH classifications were within the normal values for age-matched normal population. Individuals classed as grade 1 hypertension according to the ESC/ESH guidelines, however, exhibited a significantly decreased artery baseline ($p = 0.0004$) and MC ($p = 0.040$), higher slope(AD) ($p = 0.0018$) and decreased vein MC ($p = 0.0446$) compared to age matched normal individuals. In addition, they also had significant lower artery baseline, artery BDF, MD and MC than individuals classed as stage 1 hypertension based on the ACC/ASH guidelines ($p = 0.00022$, $p = 0.0179$, $p = 0.0409$ and $p = 0.0329$ respectively). Peripheral vascular reactivity (aTR) was lower in ESC /ESH grade I compared to those graded ACC/ASH stage I hypertension ($p = 0.0122$). The conclusion of this study is that microvascular dysfunctions is present at multiple levels only in individuals with ESC/ESH grade 1 hypertension. This observation could be important when deciding personalised care in individuals with early hypertensive changes.

[78] Pokhrel B, Yuet WC, Levine SN. PCSK9 Inhibitors. In: StatPearls. Treasure Island (FL): StatPearls Publishing

[79] *Luo Y, Yang Y, Peng P et al.* **Cholesterol synthesis disruption combined with a molecule-targeted drug is a promising metabolic therapy for EGFR mutant non-small cell lung cancer**. Transl Lung Cancer Res 2021; 10:128-142.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33569299
ABSTRACT
BACKGROUND: Acquired resistance is a challenge for epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer. Here, we propose a novel treatment strategy based on recent lipid

metabolism work. METHODS: We applied a variety of experimental methods such as immunoblotting, MTT, si-RNA, and animal models, to demonstrate the relationship between EGFR and low-density lipoprotein receptor (LDLR) and the effects of statin monotherapy, and TKI monotherapy, and their combination on cell proliferation at the cell level and animal level. RESULTS: LDLR has a positive correlation with EGFR, EGFR signaling upregulates LDLR expression through the SREBP-1 dependent pathway, EGFR mutation cells count on lipids to survive and grow. Combined with a molecule-targeted drug, atorvastatin not only enhances the treatment effect in vitro, but also mitigates the growth of NSCLC in vivo. In this animal experiment, the combination medicine (atorvastatin with TKI) has a better tumor suppression effect on NSCLC. In HCC827 cell line, the average tumor shrinkage is about 68% in Gefitinib group, and about 49% in atorvastatin group, but about 89% in combination group. In H1975 cell line, the average tumor shrinkage is about 18% in Osimertinib group, and about 8% in atorvastatin group, but about 44% in combination group. CONCLUSIONS: the combination of an EGFR-TKI and a statin for EGFR mutant NSCLC may be a novel tumor inhibiting treatment.