[1] *Yu B, Chen Y, Qin H et al.* **Using multi-disciplinary teams to treat obese patients helps improve clinical efficacy: the general practitioner's perspective**. American journal of translational research 2021; 13:2571-2580.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34017416

ABSTRACT

OBJECTIVE: This paper aims to explore the influences of multi-disciplinary teams (MDT) from the general practitioner's (GP's) perspective on the clinical efficacy of treating obese patients. METHODS: Admitted to our hospital from January 2018 to October 2019, 127 obese patients were divided into two groups based on the different models of diagnosis and treatment each underwent. The routine diagnostic and treatment model was administered to the patients in the control group (60 cases), and the MDT model was administered to the patients in the research group (67 cases). The weight loss success rates in both groups were observed. Before and after the treatment, the blood glucose, blood lipid, tumor necrosis factor-α (TNF-α), adiponectin (APN), leptin (LP), and recombinant human fibroblast growth factor 21 (FGF-21) levels were measured. The SAS and SDS scores were evaluated. RESULTS: After the treatment, the weight loss success rate in the research group was significantly higher than it was in the control group, and the FPG and the 2hPBG levels were significantly lower in the research group. Compared with the control group, the TC, TG, and LDL-C levels were remarkably lower in the study group, and the HDL-C levels were remarkably higher in the research group. The TNF-α, LP, and FGF-21 levels were significantly lower in the research group, and the APN levels were significantly higher. The research group had significantly lower SAS and SDS scores and higher GSES scores. CONCLUSION: MDTs from the GP's perspective are conducive to increasing the weight loss success rate and improving the blood glucose, blood lipid and adipokine levels in obese patients.

[2] *Wu Z, Huang Z, Lichtenstein AH et al.* **Different associations between HDL cholesterol and cardiovascular diseases in people with diabetes mellitus and people without diabetes mellitus: a prospective community-based study**. The American journal of clinical nutrition 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34019626

ABSTRACT

BACKGROUND: Experimental studies have found that the functionality of HDL cholesterol may be lost in the presence of diabetes mellitus (DM). OBJECTIVES: We aimed to elucidate whether DM modified the association between HDL-cholesterol concentrations and cardiovascular disease (CVD) outcomes. METHODS: Included were 91,354 Chinese adults (8244 participants with DM and 83,110 participants without DM) free of CVD or cancer at baseline (2006) and without use of lipid-lowering drugs at baseline and during follow-up. The primary endpoint of interest was a composite of CVDs (myocardial infarction, ischemic stroke, and hemorrhagic stroke). Cumulative average HDL-cholesterol concentrations were calculated from all available HDL-cholesterol measures at baseline (2006) and during the follow-up period (2008, 2010, 2012, and 2014). RESULTS: During a mean of 10.4 y of follow-up, there were 5076 CVD events identified. There was a significant interaction between DM and HDL-cholesterol concentrations on CVD risk (Pinteraction = 0.003). The association between HDL-cholesterol concentrations and CVD followed a U-shaped curve in individuals without DM (Pnonlinearity < 0.001). The adjusted HR of CVD was 1.26 (95% CI: 1.07, 1.48) for HDL-cholesterol concentrations < 1.04 mmol/L and 1.76 (95% CI: 1.53, 2.03) for HDL-cholesterol concentrations > 2.07 mmol/L, relative to the lowest-risk group (HDL-cholesterol concentrations of

1.30-1.42 mmol/L). In participants with DM, higher HDL-cholesterol concentrations were associated with a higher risk of CVD, in a dose-response manner (Pnonlinearity = 0.44; Ptrend < 0.001). The adjusted HR of CVD was 1.62 (95% CI: 1.19, 2.20) for HDL-cholesterol concentrations >2.07 mmol/L, relative to HDL-cholesterol concentrations of 1.30-1.42 mmol/L. CONCLUSIONS: High HDL-cholesterol concentrations were paradoxically associated with high risk of composite CVD outcomes in individuals with or without DM. However, low HDL-cholesterol concentrations failed to predict future CVD risk in individuals with DM.

[3] *van Bruggen FH, Luijendijk HJ*. **Evolocumab's Long-Term Mortality Risk Unclear Due to Shortened Follow-Up of FOURIER**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34008143
ABSTRACT
The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk) trial was conducted to study cardiovascular outcomes of treatment with evolocumab. The trial was terminated after a median follow-up of 2.2 years instead of the planned 3.6 years. We question this decision. According to the investigators, the event rate was 50% higher than expected. However, the accrued number of key secondary events (1829) was only 12% higher than the targeted number (1630). Also, around one-third of the events consisted of non-atherosclerotic myocardial infarctions, hemorrhagic strokes, and cardiovascular deaths unrelated to myocardial infarction or stroke. Moreover, halfway through the trial, the sample size changed from 22,500 to 27,500, even though the accrual of the targeted number of events was on track. Finally, the rate of all-cause mortality had started to diverge in favor of placebo after 2 years of follow-up. It was 4.8% for evolocumab and 4.3% for placebo in participants with > 2.5 years of follow-up. A long-term follow-up would have yielded more events and thus more power to evaluate the effect of evolocumab on all-cause mortality. We conclude that adaptive designs carry a recognized risk of false-positive efficacy results, but the risk of false-negative safety results is underappreciated.

[4] *Tan H, Liu L, Zheng Q et al.* **Effects of Combined Lipid-Lowering Therapy on Low-Density Lipoprotein Cholesterol Variability and Cardiovascular Adverse Events in Patients with Acute Coronary Syndrome**. Adv Ther 2021; 38:3389-3398.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34018147
ABSTRACT
INTRODUCTION: To investigate the effect of combined lipid-lowering therapy on low-density lipoprotein cholesterol (LDL-C) variability and cardiovascular adverse events in patients with acute coronary syndrome (ACS). METHODS: A total of 200 patients with acute coronary syndrome, admitted to the first Hospital of Hebei Medical University from January 2018 to June 2019, were randomly divided into the observation group (100 cases were treated with combined lipid-lowering drugs, including 10 mg/day atorvastatin and 10 mg/day ezetimibe) and the control group (100 cases were given an intensive statin regimen, including 40 mg/day atorvastatin). The levels of blood lipids, creatine kinase (CK), alanine transaminase (ALT), matrix metalloproteinase-9 (MMP-9) and high-sensitivity C-reactive protein (hsCRP) were observed and compared between the two groups. Focus was laid on the concentration of the above-mentioned parameters and follow-up results including the drug safety and incidence of cardiovascular adverse events. RESULTS: Before treatment, there was

no significant difference in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), CK, ALT, MMP-9, hsCRP and LDL-C between the two groups (P>0.05). After 6 months, 12 months and 24 months of treatment, TC, HDL-C, CK, ALT, MMP-9, hsCRP and LDL-C were improved in both groups, and TC, HDL-C, CK, ALT, MMP-9, hsCRP and LDL-C in the observation group elicited greater results than those in the control group with significant difference (P<0.05). In the course of treatment, the drug safety of the two groups was compared (P>0.05), and the incidence of cardiovascular adverse events in the observation group was significantly lower than that in the control group (6.59% vs. 11.96%) (P<0.05). CONCLUSION: Combination therapy with atorvastatin and ezetimibe potentially provides remarkable effects in terms of treating acute coronary syndrome, controlling the variation of LDL-C, alleviating the inflammatory state and reducing the incidence of cardiovascular adverse events with a safe profile. Combined lipid-lowering drugs are considered valid and alternative approaches for wide clinical practice.

[5] *Macchi C, Ferri N, Sirtori CR et al.* **PCSK9: a view beyond the canonical cholesterol lowering impact**. The American journal of pathology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34019847
ABSTRACT
Proprotein convertase subtilisin kexin/type 9 (PCSK9), mainly synthetized and released by the liver, represents one of the key-regulators of low-density lipoprotein cholesterol (LDL-C). Although genetic and pharmacological studies have undoubtedly demonstrated that lowering PCSK9 levels corresponds to a cardiovascular (CV) benefit, identification of non-cholesterol-related processes have clearly emerged since its discovery. Besides liver, PCSK9 is also expressed in many tissues, e.g., intestine, endocrine pancreas and brain. Thus, aim of the present review is to describe and discuss PCSK9 pathophysiology and possible non-lipid lowering effects whether already extensively characterized (e.g., inflammatory burden of atherosclerosis, triglyceride-rich lipoprotein metabolism, platelet activation), or to be unraveled (e.g., in adipose tissue). The identification of novel transcriptional factors in the promoter region of human PCSK9 (e.g., ChREBP) characterizes new mechanisms explaining how controlling intrahepatic glucose may be a therapeutic strategy to reduce CV risk in type 2 diabetes. Finally, the evidence describing PCSK9 as involved in cell proliferation and apoptosis raises the question of whether or not this protein is involved in cancer risk.

[6] *Guirgis FW, Leeuwenburgh C, Moldawer L et al.* **Lipid and lipoprotein predictors of functional outcomes and long-term mortality after surgical sepsis**. Ann Intensive Care 2021; 11:82.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34018068
ABSTRACT
RATIONALE: Sepsis is a life-threatening, dysregulated response to infection. Lipid biomarkers including cholesterol are dynamically regulated during sepsis and predict short-term outcomes. In this study, we investigated the predictive ability of lipid biomarkers for physical function and long-term mortality after sepsis. METHODS: Prospective cohort study of sepsis patients admitted to a surgical intensive-care unit (ICU) within 24 h of sepsis bundle initiation. Samples were obtained at enrollment for lipid biomarkers. Multivariate regression models determined independent risk factors predictive of poor performance status (Zubrod score of 3/4/5) or survival at 1-year follow-up. MEASUREMENTS AND MAIN RESULTS: The study included 104 patients with surgical sepsis. Enrollment total cholesterol and high-density lipoprotein (HDL-C) levels were lower, and myeloperoxidase (MPO)

levels were higher for patients with poor performance status at 1 year. A similar trend was seen in comparisons based on 1-year mortality, with HDL-C and ApoA-I levels being lower and MPO levels being higher in non-survivors. However, multivariable logistic regression only identified baseline Zubrod and initial SOFA score as significant independent predictors of poor performance status at 1 year. Multivariable Cox regression modeling for 1-year survival identified high Charlson comorbidity score, low ApoA-I levels, and longer vasopressor duration as predictors of mortality over 1-year post-sepsis. CONCLUSIONS: In this surgical sepsis study, lipoproteins were not found to predict poor performance status at 1 year. ApoA-I levels, Charlson comorbidity scores, and duration of vasopressor use predicted 1 year survival. These data implicate cholesterol and lipoproteins as contributors to the underlying pathobiology of sepsis.

[7] *Anagnostis P, Papanikolaou D, Ioannidou PG et al.* **The effect of statins on semen parameters in patients with hypercholesterolemia: A systematic review**. Andrology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33998174
ABSTRACT
BACKGROUND: Statins constitute the mainstay of treatment in patients with hypercholesterolemia. However, their effect on semen parameters is unknown. OBJECTIVE: This study aimed to systematically review the best available evidence regarding the effect of statins on ejaculate volume and sperm concentration, motility, morphology, or vitality. MATERIALS/METHODS: A comprehensive search was conducted in PubMed, CENTRAL and Scopus databases up to January 10, 2021. Either randomized-controlled trials or prospective cohorts, conducted in males with hypercholesterolemia, were included. RESULTS: Four studies, published between 1992 and 2014, were eligible. The number of participants ranged from 8 to 120 (n = 161). Study duration ranged from 14 to 48 weeks. The type and dose of statin used were pravastatin 20-80 mg/day and simvastatin 20-40 mg/day. With regard to ejaculate volume (n = 3) and sperm concentration (n = 4), no effect was shown with either pravastatin or simvastatin. Regarding sperm motility, either an increase (n = 2; pravastatin, simvastatin), decrease (n = 1; pravastatin), or no effect (n = 1; pravastatin, simvastatin) was found. With respect to sperm morphology, either a decrease (n = 2; pravastatin, simvastatin) or no effect (n = 2; pravastatin, simvastatin) was shown. Concerning sperm vitality, a single study showed a decrease with simvastatin. Because of the high heterogeneity of the populations studied and the limited number of studies, a meta-analysis was not performed. CONCLUSION: This is the first systematic review on the effect of statins on semen parameters. As there is no evidence for such a detrimental effect, no specific approach has to be suggested regarding the preservation of reproductive function in men with hypercholesterolemia.

[8] *Szejko N, Kirsch E, Falcone GJ.* **Genetic determinants of LDL cholesterol and risk of intracerebral haemorrhage**. Current opinion in lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34010223
ABSTRACT
PURPOSE OF REVIEW: The role of lipids in spontaneous, nontraumatic intracerebral haemorrhage (ICH) remains controversial, as some studies suggest that lower levels of total and LDL cholesterol could increase the risk of this disease. Because of their random assortment during meiosis, genetic variants known to associate with lipid levels can be used as instruments to evaluate this relationship from a causal perspective. The purpose of this review is to summarize the existing literature related to

genetically determined LDL cholesterol levels and risk of ICH. RECENT FINDINGS: A number of studies have demonstrated that lower LDL levels are associated with a higher risk of ICH and a higher burden of neuroimaging markers of cerebral small vessel disease, such as microbleeds and white matter hyperintensity volume. As for genetically elevated lipid levels, several studies confirmed an inverse association between LDL levels and ICH. However, a number of observational studies and large meta-analyses of clinical trials of statins have failed to show such association. SUMMARY: Observational studies and clinical trials of statins have yielded inconsistent results regarding a possible link between LDL levels and the risk of ICH. Genetic studies focused on genetically elevated LDL levels and risk of ICH have, for the most, found an inverse association.

[9] *Suresh Kumar G, Mathbout MF, Fahsah I, Ghafghazi S*. **Case of homozygous familial hypercholesterolaemia with premature coronary artery disease**. BMJ case reports 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34011640

ABSTRACT

Familial hypercholesterolaemia is a genetic disorder secondary to mutation of one or more of the genes critical for low-density lipoprotein cholesterol (LDL-C) metabolism; these mutation(s) cause highly elevated serum LDL-C, significantly increasing the risk of early cardiovascular events and mortality. Homozygous familial hypercholesterolaemia (HoFH) is rare and often leads to accelerated coronary atherosclerosis presenting within the first two decades of life. We report a case of a 14-year-old boy who presented after surviving a ventricular fibrillation cardiac arrest. His highly elevated LDL-C level prompted further workup and led to a diagnosis of HoFH. The treatment included medical therapy and coronary artery bypass grafting. The patient also required referral for lipid apheresis to meet goal LDL-C level, and an automated implantable cardioverter defibrillator for secondary prevention of sudden cardiac death. HoFH, if left untreated, can have devastating consequences Therefore, timely diagnosis initiating appropriate therapy is important.

[10] *Reeskamp LF, Nurmohamed NS, Bom MJ et al.* **Marked plaque regression in homozygous familial hypercholesterolemia**. Atherosclerosis 2021; 327:13-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34004483

ABSTRACT

BACKGROUND AND AIMS: Both plasma low-density lipoprotein (LDL) cholesterol levels and risk for premature cardiovascular disease are extremely elevated in patients with homozygous familial hypercholesterolemia (HoFH), despite the use of multiple cholesterol lowering treatments. Given its inborn nature, atherosclerotic plaques are commonly observed in young HoFH patients. Whether intensive lipid lowering strategies result in plaque regression in adolescent patients is unknown. METHODS: Two HoFH patients with null/null LDLR variants, who participated in the R1500-CL-1629 randomized clinical trial (NCT03399786) evaluating the LDL cholesterol lowering effect of evinacumab (a human antibody directed against ANGPTL3; 15 mg/kg intravenously once monthly), were included in this study. Patients underwent coronary computed tomography angiography (CCTA) before randomization and after 6 months of treatment. RESULTS: Both patient A (aged 12) and B (aged 16) were treated with a statin, ezetimibe and weekly apheresis. Evinacumab decreased mean pre-apheresis LDL cholesterol levels from 5.51 ± 0.75 and 5.07 ± 1.45 mmol/l to 2.48 ± 0.31 and 2.20 ± 0.13 mmol/l and post-apheresis LDL levels from 1.45 ± 0.26 and 1.37 ± 39 mmol/l to 0.80 ± 0.16 and 0.78 ± 0.13 mmol/l in patient A and B, respectively. Total plaque volumes were

reduced by 76% and 85% after 6 months of evinacumab treatment in patient A and B, respectively. CONCLUSIONS: We describe two severely affected young HoFH patients in whom profound plaque reduction was observed with CCTA after intensive lipid lowering therapy with statins, ezetimibe, LDL apheresis, and evinacumab. This shows that atherosclerotic plaques possess the ability to regress at young age, even in HoFH patients.

[11] *Pérez-Martínez P, Pérez-Jiménez F*. **Treatment of mild-to-moderate hypertriglyceridemia**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 2:69-74.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34006357
ABSTRACT
The atherogenic role of triglycerides (TG) as an independent cardiovascular risk factor has been discussed for many years, largely because hypertriglyceridaemia (HTG) is a complex metabolic entity of multiple aetiology involving processes of diverse nature. In this chapter, a discussion will be presented on the current recommendations for the management of mild-moderate hypertriglyceridaemia (150-880mg/dL). The aim of the interventions used is to decrease the LDL-cholesterol (c-LDL) and control the HTG. This entails reducing apoprotein B (ApoB) levels, the number of remaining TG-rich lipoproteins (LRP), non-HDL-cholesterol (c-non-HDL), and increasing HDL-cholesterol (c-HDL). The management strategy includes healthy lifestyle recommendations, and subsequent use of lipid-lowering drugs, including statins, fibrates, n-3 fatty acids and PCSK9 inhibitors.

[12] *Navarro Hermoso A, Valdivielso P*. **Treatment of chylomicronemia**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 2:75-79.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34006359
ABSTRACT
Fasting chylomicronaemia appears in type V (multifactorial chylomicronaemia syndrome, MCS), and in type I (familial chylomicronaemia syndrome, FCS). MCS needs to be treated as in any general hypertriglyceridaemia: low-calorie diet, avoid sugar and alcohol, reduce body weight, control of diabetes and, in some cases, common lipid lowering-drugs, such as fibrates or omega-3 fatty acids. For type I HLP, FCS, patients should adhere to a strict very low fat diet, usually less than 15-20 g per day. In spite of this, many patients with FCS suffer from recurrent abdominal pain and/or acute pancreatitis. Volanesorsen, an antisense oligonucleotide against apolipoprotein C-III, is the only drug approved to control the disease. As shown in the APPROACH study, the administration of volanesorsen at a weekly dose of 285 mg induced at three month a reduction of triglycerides of 77% (primary end-point) and a reduction of 1712 mg/dL from the baseline. Among patient receiving volanesorsen, 77% reached a fasting triglyceride value below 750 mg/dL. The most frequent side effects were a skin reaction at injection site and low platelet levels, which should be monitored.

[13] *Martínez-Hervás S, Real-Collado JT, Ascaso-Gimilio JF*.
Hypotriglyceridemias/hypolipidemias. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2021; 33 Suppl 2:63-68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34006356

ABSTRACT
Hypolipoproteinemias are characterized by a decrease in the plasma concentration of lipoproteins. Within them, we find two groups: hypobetalipoproteinemias (HBL), due to a decrease in the plasma concentration of lipoproteins containing apolipoprotein B, and hypoalphalipoproteinemias. Hypolipoproteinemias can be classified according to their origin, into primary and secondary. Primary HBLs are rare entities produced by mutations in different genes. So far, more than 140 mutations have been identified in the APOB, PCSK9, ANGPTL3, MTTP, and SAR1 genes. Early diagnosis and treatment are essential to avoid the development of serious complications. In this review we address the diagnosis and treatment of HBL, especially those in which there is hypotriglyceridemia.

[14] *Ma W, Guo X, Ma Y, Hu Z*. **Meta-analysis of randomized clinical trials comparing PCSK9 monoclonal antibody versus ezetimibe/placebo in patients at high cardiovascular risk**. Atherosclerosis 2021; 326:25-34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34004550

ABSTRACT
BACKGROUND AND AIMS: Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9 mAbs) reduce circulating low-density lipoprotein cholesterol (LDL-C) by controlling the expression of LDL-receptor on the surface of hepatocytes. This meta-analysis aimed at evaluating the efficacy of PCSK9 mAbs on clinical and lipid-lowering outcomes. METHODS: PubMed, Embase, and ClinicalTrials.gov were searched from inception until November 2020 for randomized controlled trials (RCTs) that compared PCSK9 mAbs with ezetimibe or placebo in patients at high cardiovascular risk. RESULTS: Twenty eight RCTs with a total of 89,115 participants were included. Compared with placebo, PCSK9 mAbs significantly reduced the risk of major adverse cardiac events (MACEs) (RR 0.83, 95% CI 0.79 to 0.88, $p < 0.00001$). However, no difference was observed in occurring MACEs between PCSK9 mAbs and ezetimibe (RR 0.70, 95% CI 0.40 to 1.20, $p = 0.20$). Secondary analyses show that PCSK9 mAbs were not superior to ezetimibe in preventing stroke (RR 0.38, 95% CI 0.09 to 1.69, $p = 0.20$), myocardial infarction (RR 0.95, 95% CI 0.47 to 1.90, $p = 0.88$), and cardiovascular death (RR 0.44, 95% CI 0.14 to 1.43, $p = 0.17$). Compared with placebo, PCSK9 mAbs significantly reduced the incidence of stroke (RR 0.75, 95% CI 0.66 to 0.86, $p < 0.0001$) and myocardial infarction (RR 0.81, 95% CI 0.76 to 0.87, $p < 0.00001$), but not the risk of cardiovascular death (RR 0.96, 95% CI 0.86 to 1.07, $p = 0.45$). As for lipid-lowering efficacy, PCSK9 mAbs markedly reduced percent change of LDL-C from baseline to week 12 and 24 compared to ezetimibe or placebo. CONCLUSIONS: In patients at high cardiovascular risk, PCSK9 mAbs could effectively reduce MACEs, stroke, and myocardial infarction compared with placebo. However, PCSK9 mAbs were not superior to ezetimibe in preventing adverse cardiovascular events in our study; RCTs with long-term follow-up and cardiovascular events as the research endpoint are still needed.

[15] *Lowenstern A, Li S, Navar AM et al.* **Patient perceptions and use of non-statin lipid lowering therapy among patients with or at risk for atherosclerotic cardiovascular disease: Insights from the PALM registry**. Clinical cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34008247

ABSTRACT
BACKGROUND: Non-statin lipid lowering therapies (LLTs) provide additional treatment options for patients. Use patterns and patient perceptions of non-statin LLT remain incompletely described.

HYPOTHESIS: The guideline-recommended statin intensity remains underutilized in patients treated with and without non-statin LLT. METHODS: The PALM Registry collected LLT information on patients with or at risk of ASCVD treated at 125 US clinics in 2015. We compared patient perceptions, lipid levels and statin use among patients treated with and without non-statin LLT. RESULTS: Among 7720 patients, 1930 (25.0%) were treated with a non-statin LLT (1249 fish oil, 417 fibrates, 329 ezetimibe, 196 niacin). Concurrent statin treatment occurred in 73.7%, of which 45.4% were dosed under the guideline-recommended intensity. Compared with patients on statin alone, patients receiving both a statin and non-statin LLT (n = 1423) were more likely to be male, white race and to perceive themselves as higher risk of ASCVD compared with their peers (38.5% vs. 34.9%, p = .047). Only 27.4% of patients treated with non-statin LLT alone perceived themselves at higher risk. Most (75.7%) patients treated with a non-statin LLT alone reported never being treated with a statin, despite ASCVD in 30.8% of these patients. Among those previously treated with a statin, 59.3% reported being willing to try a statin again. CONCLUSIONS: Non-statin LLT is used in one in four patients with or at risk for ASCVD; its use is frequently in place of statin therapy or in the absence of guideline-recommended statin intensity. More work is needed to establish statins as first line therapy.

[16] *Hashmi A, Smith EI, Ciutac A, Smith JC*. **Lesson of the month: Acute pancreatitis due to hypertriglyceridaemia in a transgender woman: a complication of high-dose oral oestrogen therapy?** Clinical medicine (London, England) 2021; 21:228-230.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34001575
ABSTRACT
Acute pancreatitis (AP) is a medical emergency associated with significant morbidity and mortality. Hypertriglyceridaemia is a well-established but often neglected cause of AP, associated with delayed diagnosis and worse outcome than other more common causes of AP. Although oestrogen-induced hypertriglyceridaemia is known to be a rare cause of AP in females, it is much less well-recognised in biological males. We report the case of a 52-year-old transgender woman receiving high-dose oral oestrogen therapy who was admitted with abdominal pain and found to have AP caused by severe hypertriglyceridaemia. We describe the features underlying the management of AP caused by hypertriglyceridaemia and review the link between oral oestrogen, hypertriglyceridaemia and AP.Given the growth in transgender medicine leading to increasing use of therapeutic high-dose oestrogens in biological males for gender reassignment, it is important that clinicians are alert to the phenomenon of oestrogen-induced-hypertriglyceridaemia and its associated risk of AP.

[17] *Gong J, Harris K, Peters SAE, Woodward M*. **Sex differences in the association between major cardiovascular risk factors in midlife and dementia: a cohort study using data from the UK Biobank**. BMC medicine 2021; 19:110.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34006267
ABSTRACT
BACKGROUND: Sex differences in major cardiovascular risk factors for incident (fatal or non-fatal) all-cause dementia were assessed in the UK Biobank. The effects of these risk factors on all-cause dementia were explored by age and socioeconomic status (SES). METHODS: Cox proportional hazards models were used to estimate hazard ratios (HRs) and women-to-men ratio of HRs (RHR) with 95% confidence intervals (CIs) for systolic blood pressure (SBP) and diastolic blood pressure (DBP), smoking, diabetes, adiposity, stroke, SES and lipids with dementia. Poisson regression was

used to estimate the sex-specific incidence rate of dementia for these risk factors. RESULTS: 502,226 individuals in midlife (54.4% women, mean age 56.5 years) with no prevalent dementia were included in the analyses. Over 11.8 years (median), 4068 participants (45.9% women) developed dementia. The crude incidence rates were 5.88 [95% CI 5.62-6.16] for women and 8.42 [8.07-8.78] for men, per 10,000 person-years. Sex was associated with the risk of dementia, where the risk was lower in women than men (HR = 0.83 [0.77-0.89]). Current smoking, diabetes, high adiposity, prior stroke and low SES were associated with a greater risk of dementia, similarly in women and men. The relationship between blood pressure (BP) and dementia was U-shaped in men but had a dose-response relationship in women: the HR for SBP per 20 mmHg was 1.08 [1.02-1.13] in women and 0.98 [0.93-1.03] in men. This sex difference was not affected by the use of antihypertensive medication at baseline. The sex difference in the effect of raised BP was consistent for dementia subtypes (vascular dementia and Alzheimer's disease). CONCLUSIONS: Several mid-life cardiovascular risk factors were associated with dementia similarly in women and men, but not raised BP. Future bespoke BP-lowering trials are necessary to understand its role in restricting cognitive decline and to clarify any sex difference.

[18] *Zhao Y, Liu L, Yang S et al.* **Mechanisms of Atherosclerosis Induced by Postprandial Lipemia**. Frontiers in cardiovascular medicine 2021; 8:636947.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33996937

ABSTRACT

Postprandial lipemia plays an important role in the formation, occurrence, and development of atherosclerosis, and it is closely related to coronary heart disease and other diseases involving endothelial dysfunction, oxidative stress, inflammation, and other mechanisms. Therefore, it has become a focus area for further research. The studies on postprandial lipemia mainly include TG, TRL, VLDL, CM, and remnant cholesterol. Diurnal triglyceride patterns and postprandial hyperlipidemia are very relevant and are now insufficiently covered. The possible mechanisms between postprandial lipemia and cardiovascular disease have been reviewed in this article by referring to relevant literature in recent years. The research progress on the effects of postprandial lipemia on endothelial function, oxidative stress, and inflammation is highlighted. The intervention of postprandial lipemia is discussed. Non-medicinal intervention such as diet and exercise improves postprandial lipemia. As medicinal intervention, statin, fibrate, ezetimibe, omega-3 fatty acids, and niacin have been found to improve postprandial lipid levels. Novel medications such as pemafibrate, PCSK9, and apoCIII inhibitors have been the focus of research in recent years. Gut microbiota is closely related to lipid metabolism, and some studies have indicated that intestinal microorganisms may affect lipid metabolism as environmental factors. Whether intervention of gut microbiota can reduce postprandial lipemia, and therefore against AS, may be worthy of further study.

[19] *Yang X, Leng J, Liu H et al.* **Maternal gestational diabetes and childhood hyperlipidemia**. Diabetic medicine : a journal of the British Diabetic Association 2021:e14606.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34021927

ABSTRACT

AIMS: Aim of this study is to assess dyslipidemia risk between children exposed to maternal gestational diabetes mellitus (GDM) and those not exposed. METHODS: We recruited 1144 mother-child pairs (572 GDM and 572 non-GDM women matched by their offspring's age and sex). The age

of offspring ranged from 3 to 9 years old. We used general linear models to compare mean values of different lipid profiles among children born to mothers with and without GDM. Logistic regression models were used to assess associations of maternal GDM with abnormal lipid profiles in offspring. RESULTS: After adjustment for maternal and children's characteristics, children born to mothers with GDM had lower mean values of high-density-lipoprotein (HDL) cholesterol (1.40 ± 0.01 vs. 1.50 ± 0.01; p < 0.001) and higher mean levels of triglycerides/HDL cholesterol ratio (0.37 ± 0.01 vs. 0.35 ± 0.01; p < 0.05) in comparison with their counterparts born to mothers without GDM. Multivariate-adjusted odds ratios among children exposed to mothers with GDM compared with the counterparts were 2.11 (95% confidence interval [CI 1.15-3.88]) for low HDL cholesterol and 1.35 (95% CI 1.00-1.81) for high triglycerides/HDL cholesterol ratio, respectively. CONCLUSIONS: Maternal GDM was associated with an increased risk of hyperlipidemia in the offspring during early childhood aged from 3 to 9 years old.

[20] *Viktorinova A, Malickova D, Svitekova K et al.* **Low-density lipoprotein cholesterol-to-apolipoprotein B ratio as a potential indicator of LDL particle size and plasma atherogenicity in type 2 diabetes**. Diabetes Res Clin Pract 2021; 176:108858.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34015391
ABSTRACT
AIMS: Atherogenic dyslipidemia, associated with small, dense low-density lipoprotein-cholesterol (S-LDL) particles and impaired metabolism of triglycerides (TGs) and high-density lipoprotein-cholesterol (HDL-c), leads to the development of atherosclerosis-related complications of type 2 diabetes mellitus. Based on the hypothesis that an LDL-c-to-apolipoprotein B ratio (LDL/ApoB) < 1.2 may predict the prevalence of S-LDL, this study aimed to evaluate the LDL/ApoB ratio in patients with type 2 diabetes with moderately elevated TG levels. METHODS: The study population consisted of 121 outpatients with type 2 diabetes (S-LDL group, LDL/ApoB < 1.2, n = 79; L-LDL group, LDL/ApoB > 1.2, n = 42) and 58 healthy subjects. The LDL/ApoB ratio was calculated from the measured LDL-c and ApoB levels in participants with TG levels lower than 4.5 mmol/L. Since TGs and HDL-c are included in the atherogenic index of plasma (AIP), we evaluated the relationship between LDL/ApoB and the AIP. RESULTS: Higher levels of AIP, TG (both P < 0.0001), and lipid hydroperoxides (LOOH) (P < 0.001) and lower levels of HDL-c, total cholesterol, and non-HDL-c (P < 0.001, <0.01, <0.05, respectively) were found in the S-LDL group compared to the L-LDL group. There were significant relationships between the LDL/ApoB ratio and the AIP, TG (both P < 0.0001), LOOH (P < 0.0005), and HDL-c levels (P < 0.05) in the S-LDL group. CONCLUSIONS: The prevalence of S-LDL particles (65%) and the close association of LDL/ApoB with the AIP suggest that this ratio may be a potential indicator of increased cardiovascular risk in patients with type 2 diabetes.

[21] *Santi RL, Martinez F, Baranchuk A et al.* **Management of Dyslipidaemia in Real-world Clinical Practice: Rationale and Design of the VIPFARMA ISCP Project**. European cardiology 2021; 16:e16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33995586
ABSTRACT
Dyslipidaemia plays a major role in the pathogenesis of atherosclerosis. Every year, scientific institutions publish cardiovascular prevention guidelines with updated goals and recommendations based on new evidence. However, medical barriers exist that make achieving these goals difficult and

gaps between guidelines and best daily clinical practice still persist. The International Society of Cardiovascular Pharmacotherapy designed the Surveillance of Prescription Drugs in the Real World Project (VIPFARMA ISCP), a survey for physicians who manage lipid disorders in high-risk patients. Seven clusters of questions will be analysed comprising demographics, institution profile, access to continuing medical education, clinical practice profile, attitude regarding use of statins, knowledge regarding proprotein convertase subtilisin/kexin type 9 inhibitors and attitudes regarding medical decisions about triglycerides. The present study will be the first part of a larger programme and aims to shed light on barriers between lipid-lowering drug therapy recommendations in the 2019 European Society of Cardiology guidelines and clinical practice in different countries.

[22] *Rose M, Duhamel M, Rodet F, Salzet M*. **The Role of Proprotein Convertases in the Regulation of the Function of Immune Cells in the Oncoimmune Response**. Frontiers in immunology 2021; 12:667850.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33995401

ABSTRACT

Proprotein convertases (PC) are a family of 9 serine proteases involved in the processing of cellular pro-proteins. They trigger the activation, inactivation or functional changes of many hormones, neuropeptides, growth factors and receptors. Therefore, these enzymes are essential for cellular homeostasis in health and disease. Nine PC subtilisin/kexin genes (PCSK1 to PCSK9) encoding for PC1/3, PC2, furin, PC4, PC5/6, PACE4, PC7, SKI-1/S1P and PCSK9 are known. The expression of PC1/3, PC2, PC5/6, Furin and PC7 in lymphoid organs such as lymph nodes, thymus and spleen has suggested a role for these enzymes in immunity. In fact, knock-out of Furin in T cells was associated with high secretion of pro-inflammatory cytokines and autoantibody production in mice. This suggested a key role for this enzyme in immune tolerance. Moreover, Furin through its proteolytic activity, regulates the suppressive functions of Treg and thus prevents chronic inflammation and autoimmune diseases. In macrophages, Furin is also involved in the regulation of their inflammatory phenotype. Similarly, PC1/3 inhibition combined with TLR4 stimulation triggers the activation of the NF-κB signaling pathway with an increased secretion of pro-inflammatory cytokines. Factors secreted by PC1/3 KD macrophages stimulated with LPS exert a chemoattractive effect on naive auxiliary T lymphocytes (Th0) and anti-tumoral activities. The link between TLR and PCs is thus very important in inflammatory response regulation. Furin regulates TL7 and TLR8 processing and trafficking whereas PC1/3 controls TLR4 and TLR9 trafficking. Since PC1/3 and Furin are key regulators of both the innate and adaptive immune responses their inhibition may play a major role in oncoimmune therapy. The role of PCs in the oncoimmune response and therapeutic strategies based on PCs inhibition are proposed in the present review.

[23] *Polychronopoulos G, Tzavelas M, Tziomalos K*. **Heterozygous familial hypercholesterolemia: prevalence and control rates**. Expert review of endocrinology & metabolism 2021:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33993819

ABSTRACT

Introduction: Heterozygous familial hypercholesterolemia (heFH) is associated with a very high risk for cardiovascular events. Treatment with potent statins substantially reduces cardiovascular morbidity in these patients. Moreover, combination therapy with statins plus ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors facilitates achievement of low-density

lipoprotein cholesterol (LDL-C) targets in patients with heFH. However, heFH remains underdiagnosed and undertreated worldwide.Areas covered: In this review, we summarize current evidence on the prevalence and control rates of heFH. Accumulating data suggest that heFH is one of the most common hereditary metabolic disorders, affecting approximately 1 in every 300 individuals. However, only a small minority of patients with heFH achieve LDL-C targets, even in high-income countries and in subjects followed-up in specialized lipid clinics.Expert opinion: Given the underdiagnosis of heFH using cascade and opportunistic screening, wider, population-based screening strategies should be evaluated for their feasibility and cost-effectiveness if we aspire to timely diagnosis and therefore prevention of cardiovascular morbidity and mortality in this very high risk population. Overcoming inertia in uptitrating statin dose, adding ezetimibe and/or PCSK9 inhibitors along with more generous reimbursement for lipid-lowering agents in patients with heFH are essential for improving goal attainment rates.

[24] *Hageman SHJ, Dorresteijn JAN, Bots ML et al.* **Residual cardiovascular risk reduction guided by lifetime benefit estimation in patients with symptomatic atherosclerotic disease: effectiveness and cost-effectiveness**. European journal of preventive cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34009323

ABSTRACT

AIMS: To determine the (cost)-effectiveness of blood pressure lowering, lipid-lowering, and antithrombotic therapy guided by predicted lifetime benefit compared to risk factor levels in patients with symptomatic atherosclerotic disease. METHODS AND RESULTS : For all patients with symptomatic atherosclerotic disease in the UCC-SMART cohort (1996-2018; n = 7697) two treatment strategies were compared. The lifetime benefit-guided strategy was based on individual estimation of gain in cardiovascular disease (CVD)-free life with the SMART-REACH model. In the risk factor-based strategy, all patients were treated the following: low-density lipoprotein cholesterol (LDL-c) < 1.8 mmol/L, systolic blood pressure <140 mmHg, and antithrombotic medication. Outcomes were evaluated for the total cohort using a microsimulation model. Effectiveness was evaluated as total gain in CVD-free life and events avoided, cost-effectiveness as incremental cost-effectivity ratio (ICER). In comparison to baseline treatment, treatment according to lifetime benefit would lead to an increase of 24243 CVD-free life years [95% confidence interval (CI) 19980-29909] and would avoid 940 (95% CI 742-1140) events in the next 10 years. For risk-factor based treatment, this would be an increase of 18564 CVD-free life years (95% CI 14225-20456) and decrease of 857 (95% CI 661-1057) events. The ICER of lifetime benefit-based treatment with a treatment threshold of ≥1 year additional CVD-free life per therapy was €15092/QALY gained and of risk factor-based treatment €9933/QALY gained. In a direct comparison, lifetime benefit-based treatment compared to risk factor-based treatment results in 1871 additional QALYs for the price of €36538/QALY gained. CONCLUSION : Residual risk reduction guided by lifetime benefit estimation results in more CVD-free life years and more CVD events avoided compared to the conventional risk factor-based strategy. Lifetime benefit-based treatment is an effective and potentially cost-effective strategy for reducing residual CVD risk in patients with clinical manifest vascular disease.

[25] *Gierach MA, Junik R.* **Insulin resistance in metabolic syndrome depending on the occurrence of its components**. Endokrynol Pol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34010436

ABSTRACT
Metabolic syndrome (MetS) is described as a cluster of several commonly occurring disorders including abdominal obesity, hypertension (HT) (≥130/85 mmHg), carbohydrates disorders: impaired fasting glucose or type 2 diabetes mellitus and lipids disorders such as hypertriglyceridemia (TG) and low level of high-density-lipoprotein cholesterol (HDL-C). Insulin resistance (IR) is defined as a glucose homoeostasis disorder involving a decreased sensitivity of muscles, adipose tissue, liver and other body tissues to insulin, despite its normal or increased concentration in blood. The study group included 424 subjects with MetS (260 females, 164 males). All patients were recruited from the Internal Ward of the District Hospital in Wąbrzeźno, Poland and Department of Endocrinology and Diabetology Collegium Medicum in Bydgoszcz, Poland. The diagnosis of the MetS was made on the basis of the International Diabetes Federation (IDF) criteria. MetS diagnosis was established when three or more criteria were met. The study group was divided into 6 subgroups according to the constellation of 3 particular components of MetS. All patients of the study group were diagnosed with obesity, 73,5% with high pre-meal blood glucose levels, 66.9% with HT, 48.3% with lower level of HDL-C and 38.2% with TG. Insulin resistance of different degree was diagnosed in all patients of the study group. The occurrence of insulin resistance in patients with metabolic syndrome is obvious. However, despite they are high or very high cardiovascular risk patients, they are not a homogeneous group. Such patients differ from each other depending on the presence and constellation of particular disorders that make up the diagnosis of the metabolic syndrome. Patients with MetS are heterogeneous group differing in degree of insulin resistance and the risk of cardiovascular diseases. The results of our study show that the highest insulin resistance is observed in patients with central obesity accompanied by type 2 diabetes and hypertriglyceridemia.

[26] *Bravo M, Raurell I, Barberá A et al.* **Synergic effect of atorvastatin and ambrisentan on sinusoidal and hemodynamic alterations in a rat model of NASH**. Disease models & mechanisms 2021; 14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34014280

ABSTRACT
In non-alcoholic steatohepatitis (NASH), decreased nitric oxide and increased endothelin-1 (ET-1, also known as EDN1) released by sinusoidal endothelial cells (LSEC) induce hepatic stellate cell (HSC) contraction and contribute to portal hypertension (PH). Statins improve LSEC function, and ambrisentan is a selective endothelin-receptor-A antagonist. We aimed to analyse the combined effects of atorvastatin and ambrisentan on liver histopathology and hemodynamics, together with assessing the underlying mechanism in a rat NASH model. Diet-induced NASH rats were treated with atorvastatin (10 mg/kg/day), ambrisentan (30 mg/kg/day or 2 mg/kg/day) or a combination of both for 2 weeks. Hemodynamic parameters were registered and liver histology and serum biochemical determinations analysed. Expression of proteins were studied by immunoblotting. Conditioned media experiments were performed with LSEC. HSCs were characterized by RT-PCR, and a collagen lattice contraction assay was performed. Atorvastatin and ambrisentan act synergistically in combination to completely normalize liver hemodynamics and reverse histological NASH by 75%. Atorvastatin reversed the sinusoidal contractile phenotype, thus improving endothelial function, whereas ambrisentan prevented the contractile response in HSCs by blocking ET-1 response. Additionally, ambrisentan also increased eNOS (also known as Nos3) phosphorylation levels in LSEC, via facilitating the stimulation of endothelin-receptor-B in these cells. Furthermore, the serum alanine

aminotransferase of the combined treatment group decreased to normal levels, and this group exhibited a restoration of the HSC quiescent phenotype. The combination of atorvastatin and ambrisentan remarkably improves liver histology and PH in a diet-induced NASH model. By recovering LSEC function, together with inhibiting the activation and contraction of HSC, this combined treatment may be an effective treatment for NASH patients.

[27] *Agarwala A, Quispe R, Goldberg AC, Michos ED*. **Bempedoic Acid for Heterozygous Familial Hypercholesterolemia: From Bench to Bedside**. Drug design, development and therapy 2021; 15:1955-1963.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34007155

ABSTRACT

Bempedoic acid is a first-in-class, oral, inhibitor of cholesterol biosynthesis that is approved for use in patients with atherosclerotic cardiovascular disease (ASCVD) and for primary prevention in individuals with heterozygous familial hypercholesterolemia (HeFH) by the United States Food and Drug Administration. Pooled data from the phase III clinical trials, CLEAR Harmony and CLEAR Wisdom, have demonstrated the safety and efficacy of bempedoic acid with regard to lowering of low-density lipoprotein cholesterol (LDL-C) in patients with HeFH as an adjunct or alternative to currently existing lipid-lowering therapies. CLEAR Outcomes is a cardiovascular outcomes trial that is currently underway that will provide additional insight as to where bempedoic acid will fit into treatment regimens among the non-statin lipid-lowering therapy options. Patients who might particularly benefit from bempedoic acid are those with HeFH and those unable to take adequate doses of statins or take any statin therapy altogether who need additional LDL-C lowering. In this review, we will discuss the profile of bempedoic acid from its design, development, and its place in therapy for the management of LDL-C for the purposes of ASCVD prevention.

[28] *Zhang Y, Ma L, Lu E, Huang W*. **Atorvastatin Upregulates microRNA-186 and Inhibits the TLR4-Mediated MAPKs/NF-κB Pathway to Relieve Steroid-Induced Avascular Necrosis of the Femoral Head**. Frontiers in pharmacology 2021; 12:583975.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33995003

ABSTRACT

Steroid-induced avascular necrosis of the femoral head (SANFH) is caused by the death of active components of the femoral head owing to hormone overdoses. The use of lipid-lowering drugs to prevent SANFH in animals inspired us to identify the mechanisms involving Atorvastatin (Ato) in SANFH. However, it is still not well understood how and to what extent Ato affects SANFH. This study aimed to figure out the efficacy of Ato in SANFH and the underlying molecular mechanisms. After establishment of the SANFH model, histological evaluation, lipid metabolism, inflammatory cytokines, oxidative stress, apoptosis, and autophagy of the femoral head were evaluated. The differentially expressed microRNAs (miRs) after Ato treatment were screened out using microarray analysis. The downstream gene and pathway of miR-186 were predicted and their involvement in SANFH rats was analyzed. OB-6 cells were selected to simulate SANFH in vitro. Cell viability, cell damage, inflammation responses, apoptosis, and autophagy were assessed. Ato alleviated SANFH, inhibited apoptosis, and promoted autophagy. miR-186 was significantly upregulated after Ato treatment. miR-186 targeted TLR4 and inactivated the MAPKs/NF-κB pathway. Inhibition of miR-186 reversed the protection of Ato on SANFH rats, while inhibition of TLR4 restored the protective effect of Ato. Ato

reduced apoptosis and promoted autophagy of OB-6 cells by upregulating miR-186 and inhibiting the TLR4/MAPKs/NF-κB pathway. In conclusion, Ato reduced apoptosis and promoted autophagy, thus alleviating SANFH via miR-186 and the TLR4-mediated MAPKs/NF-κB pathway.

[29] *Umbarawan Y, Enoura A, Ogura H et al.* **FABP5 Is a Sensitive Marker for Lipid-Rich Macrophages in the Luminal Side of Atherosclerotic Lesions**. Int Heart J 2021; 62:666-676.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33994513

ABSTRACT

Lipid-rich macrophages in atherosclerotic lesions are thought to be derived from myeloid and vascular smooth muscle cells. A series of studies with genetic and pharmacological inhibition of fatty acid binding protein 4 (FABP4) and FABP5 and bone marrow transplant experiments with FABP4/5 deficient cells in mice have demonstrated that these play an important role in the development of atherosclerosis. However, it is still uncertain about the differential cell-type specificity and distribution between FABP4- and FABP5-expressing cells in early- and late-stage atherosclerotic lesions. In this study, we first explored spatial distribution of FABP4/5 in atherosclerotic lesions in apolipoprotein E deficient (ApoE(-/-)) mice. FABP4 was only marginally detected in early and advanced lesions, whereas FABP5 was abundantly expressed in these lesions. In advanced lesions, the FABP5-positive area was mostly restricted to the foam cell layer adjacent to the lumen above collagen and elastic fibers with a high signal/noise ratio. Oil red O (ORO) staining revealed that FABP5-positive cells were lipid-rich in early and advanced lesions. Together, most of lipid-rich FABP5-positive cells reside adjacent to the lumen above collagen and elastic fibers. We next studied involvement of FABP5 in lesion formation of atherosclerosis using ApoE(-/-) FABP5(-/-) mice. However, deletion of FABP5 did not affect the development of atherosclerosis. These findings, along with previous reports, suggest a novel notion that FABP5 is a sensitive marker for bone marrow-derived lipid-rich macrophages in the luminal side of atherosclerotic lesions, although its functional significance remains elusive.

[30] *Raghu Subramanian C, Khan SU, Lone AN et al.* **Representation of Women Authors in Trials of Lipid-Lowering Therapy**. Journal of the American Heart Association 2021; 10:e020663.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34013740

ABSTRACT

[31] *Qureshi N, Patel RS.* **Hiding in plain sight: supporting primary care to find familial hypercholesterolaemia and save lives**. Heart 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34016697

ABSTRACT

[32] *Liu K, Wilkins JT, Colangelo LA, Lloyd-Jones DM.* **Does Lowering Low-Density Lipoprotein Cholesterol With Statin Restore Low Risk in Middle-Aged Adults? Analysis of the Observational MESA Study**. Journal of the American Heart Association 2021; 10:e019695.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33998284

ABSTRACT

Background It is unclear if statin therapy in midlife can restore low cardiovascular risk in hypercholesterolemic individuals. Methods and Results At baseline, we grouped 5687 MESA (Multi-

Ethnic Study of Atherosclerosis) participants aged ≥50 years without clinical cardiovascular disease (CVD) by Adult Treatment Panel III statin treatment recommendation and statin treatment status. We used Cox regression to compare the risks for coronary heart disease and CVD between the untreated group with low-density lipoprotein cholesterol (LDL-C) <100 mg/dL (reference) and other groups, adjusting for CVD risk factors. We also grouped participants by LDL-C level (< or ≥100 mg/dL), coronary artery calcium score (0 or >0 Agatston units), and statin status (untreated or treated) with the untreated LDL-C <100 mg/dL and coronary artery calcium=0 Agatston units as the reference. There were 567 coronary heart disease and 848 CVD events over 15 years of follow-up. The hazard ratios (HRs) for coronary heart disease and CVD in the group with statin-treated LDL-C <100 mg/dL were 1.16 (95% CI, 0.85-1.58) and 1.02 (95% CI, 0.78-1.32), respectively. However, participants with coronary artery calcium >0 Agatston units, treated to LDL-C <100 mg/dL had HRs of 2.6 (95% CI, 1.7-4.2) for coronary heart disease and 1.8 (95% CI, 1.2-2.6) for CVD. Conclusions Individuals treated with statins to LDL-C <100 mg/dL had similar levels of risk for atherosclerotic CVD as individuals with untreated LDL-C <100 mg/dL. However, individuals with coronary artery calcium >0 Agatston units have substantially higher risks despite lipid-lowering therapy, suggesting that statin treatment in midlife may not restore a low-risk state in primary prevention patients with established coronary atherosclerosis.

[33] *Kuyama N, Kataoka Y, Takegami M et al.* **Circulating Mature PCSK9 Level Predicts Diminished Response to Statin Therapy**. Journal of the American Heart Association 2021; 10:e019525.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33998287

ABSTRACT

Background Statin-mediated efficacy of lowering low-density lipoprotein (LDL) cholesterol varies in each individual, and its diminished response is associated with worse outcomes. However, there is no established approach to predict hyporesponse to statins. PCSK9 (proprotein convertase subxilisin/kexin type 9) is a serine-protease associated with LDL metabolism, which circulates as mature and furin-cleaved PCSK9. Since mature PCSK9 more potently degrades the LDL receptor, its evaluation may enable the identification of statin hyporesponders. Methods and Results We analyzed 101 statin-naive patients with coronary artery disease who commenced a statin. PCSK9 subtypes at baseline and 1 month after statin use were measured by ELISA. Hyporesponse to statins was defined as a percent reduction in LDL cholesterol <15%. The relationship between each PCSK9 subtype level and hyporesponse to statins was investigated. Statins significantly lowered LDL cholesterol level (percent reduction, 40%±21%), whereas 11% of study participants exhibited a hyporeseponse to statins. Multivariable logistic regression analysis demonstrated that baseline mature PCSK9 level was an independent predictor for hyporesponse to statins even after adjusting clinical characteristics (mature PCSK9 per 10-ng/mL increase: odds ratio [OR], 1.12; 95% CI, 1.01-1.24 [P=0.03]), whereas furin-cleaved level was not (per 10-ng/mL increase: OR, 1.37; 95% CI, 0.73-2.58 [P=0.33]). Receiver operating characteristic curve analysis identified mature PCSK9 level of 228 ng/mL as an optimal cutoff to predict hyporesponse to statins (area under the curve, 0.73 [sensitivity, 0.91; specificity, 0.56]). Conclusions Baseline mature PCSK9 level >228 ng/mL is associated with hyporesponse to statins. This finding suggests that mature PCSK9 might be a potential determinant of hyporesponse to statins.

[34] *Huang CC, Niu DM, Charng MJ.* **Genetic Analysis in a Taiwanese Cohort of 750 Index Patients with Clinically Diagnosed Familial Hypercholesterolemia**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33994402

ABSTRACT

AIM: Familial hypercholesterolemia (FH) is underdiagnosed in most countries. The genetic heterogeneity of FH requires an algorithm to efficiently integrate genetic testing into clinical practice. We aimed to report the spectrum of genetic mutations from patients with clinically diagnosed FH in Taiwan. METHODS: Patients with LDL-C＞190 mg/dL or those with probable or definite FH according to the Taiwan Lipid Guidelines underwent genetic testing. Samples from 750 index patients from the Taiwan FH registry were screened using custom-made mass spectrometry, followed by targeted next generation sequencing (NGS) and/or multiplex ligation-dependent probe amplification (MLPA) if found negative. RESULTS: The mean age of the patients was 52.4±15.1 years and 40.9% were male. Mutations were detected in 445 patients (59.3%). The distribution of mutations was as follows: LDLR (n=395), APOB (n=58), PCSK9 (n=0), and ABCG5 (n=3). The most common mutations were APOB c.10579 C＞T (p.R3527W) (12.6%), LDLR c.986 G＞A (p.C329Y) (11.5%), and LDLR c.1747 C＞T (p.H583Y) (10.8%). LDLR c.1187-10 G＞A (IVS 8-10) and APOB c.10580 G＞A (p.R3527Q) were detected using targeted NGS in Taiwan for the first time. Four novel mutations were identified, including LDLR c.1060＋2 T＞C (IVS 7＋2), LDLR c.1139 A＞C (p.E380A), LDLR c.1322 T＞C (p.A431T)＋c.1867 A＞G (p.I623V), and ABCG5 c.1337 G＞A (p.R447Q). CONCLUSION: LDLR and APOB, but not PCSK9, mutations were the major genetic causes of FH. Four novel mutations in LDLR or ABCG5 were identified. This genetic screening method using mass spectrometry, targeted NGS, and MLPA analysis provided an efficient algorithm for genetic testing for clinically diagnosed FH in Taiwan.

[35] *Ghanbari M, Momen Maragheh S, Aghazadeh A et al.* **Interleukin-1 in obesity-related low-grade inflammation: From molecular mechanisms to therapeutic strategies**. Int Immunopharmacol 2021; 96:107765.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34015596

ABSTRACT

Since adipose tissue (AT) can upregulate pro-inflammatory interleukins (ILs) via storing extra lipids in obesity, obesity is considered the leading cause of chronic low-grade inflammation. These ILs can pave the way for the infiltration of immune cells into the AT, ultimately resulting in low-grade inflammation and dysregulation of adipocytes. IL-1, which is divided into two subclasses, i.e., IL-1α and IL-1β, is a critical pro-inflammatory factor. In obesity, IL-1α and IL-1β can promote insulin resistance via impairing the function of adipocytes and promoting inflammation. The current study aims to review the detailed molecular mechanisms and the roles of IL-1α and IL-1β and their antagonist, interleukin-1 receptor antagonist(IL-1Ra), in developing obesity-related inflammatory complications, i.e., type II diabetes (T2D), non-alcoholic steatohepatitis (NASH), atherosclerosis, and cognitive disorders. Besides, the current study discusses the recent advances in natural drugs, synthetic agents, and gene therapy approaches to treat obesity-related inflammatory complications via suppressing IL-1.

[36] *Boruzs K, Fekete Z, Dombrádi V et al.* **Differences in Beliefs About Cholesterol-Lowering Medications Among the Visegrad Group Countries: A Cross-Sectional Study**. Frontiers in public health 2021; 9:645043.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33996721

ABSTRACT

Background: New cholesterol guidelines highlight more personalized risk assessments and new cholesterol-lowering drugs for people at the highest risk for cardiovascular disease. Adherence due to fear of and lack of trust in medications prevents treatment to provide better health outcomes. Objectives: The aim of our study was to investigate the possible differences in the beliefs about the necessity and concerns regarding lipid-lowering drugs among the Visegrad Group countries. Methods: The Beliefs About Medicines Questionnaire (BMQ-Specific) was used in our research. The responses of 205 Hungarian, 200 Slovak, 235 Czech, and 200 Polish participants, all taking cholesterol-lowering medications, were compared to each other. Results: Hungarian participants' belief in the necessity of cholesterol-lowering drugs was significantly lower compared to the Slovak ($P = 0.001$), Czech ($P = 0.037$), and Polish ($P < 0.001$) participants. While no difference was observed between the Czech and Slovak responses ($P = 0.154$), both the Czech ($P < 0.001$) and Slovak ($P = 0.006$) respondents' belief regarding necessity was lower than that of the Polish. Regarding concerns, the only significant difference was observed between the Czech and the Polish respondents ($P = 0.011$). Conclusions: While the beliefs about benefits (necessity) are most prominent among the Polish participants, except in comparison to Czech responses, the Visegrad Group countries do not differ considerably regarding their beliefs about the fear (concerns) of the treatment.

[37] *Zhatkina MV, Gavrilova NE, Metelskaya VA et al.* **Visual Scale as a Non-Invasive Method for Evaluation of Risk and Severity of Coronary Atherosclerosis**. Kardiologiia 2021; 61:46-52.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33998408

ABSTRACT

Aim To evaluate quantitative and qualitative characteristics of atherosclerotic plaques (ASP) in carotid arteries (CA) and femoral arteries (FA) and to use these data for developing a visual scale (VS) for noninvasive diagnosis and determination of severity of coronary atherosclerosis.Material and methods This study included 216 patients (115 men and 101 women) aged 24 to 87 years (mean age, 61.5±10.73 years). All patients underwent coronary angiography (CAG) for detecting and determining severity of CA atherosclerosis and duplex scanning (DS) for detecting atherosclerosis of CA and FA.Results Analysis of ultrasound parameters of ASP in CA and FA showed that the maximal ASP height, moderate stenosis and maximal stenosis of the arterial bed had higher predictive values than other ultrasound parameters. These parameters were used for forming diagnostic complexes, on the basis of which two individual VSs for CA and FA were developed. Based on the high prognostic value of both scales, they were combined into one that was named VSCOMB. A ROC analysis determined cut-off points of the VSCOMB for diagnosis of CA atherosclerosis of various severity. VSCOMB scores >4 indicated pronounced CA atherosclerosis with sensitivity of 86.1% and specificity of 87.5% whereas VSCOMB scores ≤4 excluded it. Thus, VSCOMB score 0-1 indicated the absence of CA atherosclerosis; score 2-4 indicated the presence of subclinical CA atherosclerosis; and score >4 indicated severe CA atherosclerosis.Conclusion A VSCOMB was developed that includes a set of ultrasound parameters for CA and FA and is useful for noninvasive

diagnosis of CA atherosclerosis of various severity. Simple and convenient use of VSCOMB allows it to be used at the screening stage to detect subclinical CA atherosclerosis and to prevent its progression.

[38] *Pek SLT, Yap F, Sreedharan AV et al.* **Persistent hypercholesterolemia in child with homozygous autosomal recessive hypercholesterolemia: A decade of lipid management**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33994332

ABSTRACT

Autosomal recessive hypercholesterolemia (ARH) is a rare form of genetic hypercholesterolemia caused by mutations in low density lipoprotein receptor adaptor protein 1 (LDLRAP1). The proband first presented with linear eruptive xanthomas over her ankles, knees and elbows, with low density lipoprotein cholesterol (LDL-C) of 16.0 mmol/L (618.7 mg/dL), at 2.5 years old. Next generation sequencing revealed a novel homozygous mutation in LDLRAP1 exon 5 (c.466delG). In the first year, drug regimens of either cholestyramine or simvastatin, reduced her LDL-C to 10.5 mmol/L (406 mg/dL) and 11.7 mmol/L (452.4 mg/dL), respectively. Combination simvastatin and ezetimibe was the mainstay of therapy from age 5 - 10 years. Her lowest achieved LDL-C was 6.3 mmol/L (243.6 mg/dL). Switching to atorvastatin did not lead to further reduction. Carotid intima-media thickness was 0.47 mm (> 97(th) percentile) and 0.32 mm (75 - 95(th) percentile) at ages 8 years and 11 years, respectively. Addition of monthly injections of evolocumab for 3 months, led to an increase in LDL-C, from 7.0 mmol/L (270.7 mg/dL) to a range of [(8.4 - 9.1) mmol/L or (324.8 - 351.9) mg/dL]. In this report, a decade-long lipid management is described in a patient with ARH. Residual activity of LDLRAP1 is a likely determinant of her response. Clinical management remains sub-optimal and options for the paediatric population are limited. Novel classes of cholesterol-lowering medications are needed for this ultra-rare and severe hypercholesterolemia.

[39] *Nagahara K, Nishibukuro T, Ogiwara Y et al.* **Genetic Analysis of Japanese Children Clinically Diagnosed with Familial Hypercholesterolemia**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34011801

ABSTRACT

AIM: This study aimed to elucidate the gene and lipid profiles of children clinically diagnosed with familial hypercholesterolemia (FH). METHODS: A total of 21 dyslipidemia-related Mendelian genes, including FH causative genes (LDLR, APOB, and PCSK9) and LDL-altering genes (APOE, LDLRAP1, and ABCG5/8), were sequenced in 33 Japanese children (mean age, 9.7±4.2 years) with FH from 29 families. RESULTS: Fifteen children (45.5%) with pathogenic variants in LDLR (eight different heterozygous variants) and one child (3.0%) with the PCSK9 variant were found. Among 17 patients without FH causative gene variants, 3 children had variants in LDL-altering genes, an APOE variant and two ABCG8 variants. The mean serum total cholesterol (280 vs 246 mg/dL), LDL-cholesterol (LDL-C, 217 vs 177 mg/dL), and non-HDL cholesterol (228 vs 188 mg/dL) levels were significantly higher in the pathogenic variant-positive group than in the variant-negative group. In the variant-positive group, 81.3% of patients had LDL-C levels ≥ 180 mg/dL but 35.3% in the variant-negative group. The mean LDL-C level was significantly lower in children with missense variants, especially with the p.Leu568Val variant, than in children with other variants in LDLR, whereas the

LDL-altering variants had similar effects on the increase in serum LDL-C to LDLR p.Leu568Val. CONCLUSION: Approximately half of the children clinically diagnosed with FH had pathogenic variants in FH causative genes. The serum LDL-C levels tend to be high in FH children with pathogenic variations, and the levels are by the types of variants. Genetic analysis is useful; however, further study on FH without any variants is required.

[40] *Liu YQ, Li DD, Chai M et al.* **Real world effectiveness of PCSK-9 inhibitors combined with statins versus statins-based therapy among patients with very high risk of atherosclerotic cardiovascular disease in China (RWE-PCSK study)**. Journal of geriatric cardiology : JGC 2021; 18:261-270.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33995505
ABSTRACT
BACKGROUND: The efficacy and safety of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors were confirmed by several clinical trials, but its effectiveness in routine clinical practice in China has not been evaluated. This study aims to describe the real world effectiveness of PCSK-9 inhibitors combined with statins compared with statins-based therapy among patients with very high risk of atherosclerotic cardiovascular disease (ASCVD). METHODS: This is a multi-center observational study, enrolled patients from 32 hospitals who underwent percutaneous coronary intervention (PCI) from January to June in 2019. There are 453 patients treated with PCSK-9 inhibitors combined with statins in PCSK-9 inhibitor group and 2,610 patients treated with statins-based lipid lowering therapies in statins-based group. The lipid control rate and incidence of major adverse cardiovascular events (MACE) over six months were compared between two groups. A propensity score-matched (PSM) analysis was used to balance two groups on confounding factors. Survival analysis using Kaplan-Meier methods was applied for MACE. RESULTS: In a total of 3,063 patients, 89.91% of patients had received moderate or high-intensity statins-based therapy before PCI, but only 9.47% of patients had low-density lipoprotein cholesterol (LDL-C) levels below 1.4 mmol/L at baseline. In the PSM selected patients, LDL-C level was reduced by 42.57% in PCSK-9 inhibitor group and 30.81% ($P < 0.001$) in statins-based group after six months. The proportion of LDL-C ≤ 1.0 mmol/L increased from 5.29% to 29.26% in PCSK-9 inhibitor group and 0.23% to 6.11% in statins-based group, and the proportion of LDL-C ≤ 1.4 mmol/L increased from 10.36% to 47.69% in PCSK-9 inhibitor group and 2.99% to 18.43% in statins-based group ($P < 0.001$ for both). There was no significant difference between PCSK-9 inhibitor and statins-based treatment in reducing the risk of MACE (hazard ratio = 2.52, 95% CI: 0.49-12.97, P = 0.250). CONCLUSIONS: In the real world, PCSK-9 inhibitors combined with statins could significantly reduce LDL-C levels among patients with very high risk of ASCVD in China. The long-term clinical benefits for patients received PCSK-9 inhibitor to reduce the risk of MACE is still unclear and requires further study.

[41] *Jones WS, Mulder H, Wruck LM et al.* **Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease**. The New England journal of medicine 2021; 384:1981-1990.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33999548
ABSTRACT
BACKGROUND: The appropriate dose of aspirin to lower the risk of death, myocardial infarction, and stroke and to minimize major bleeding in patients with established atherosclerotic cardiovascular disease is a subject of controversy. METHODS: Using an open-label, pragmatic design, we randomly

assigned patients with established atherosclerotic cardiovascular disease to a strategy of 81 mg or 325 mg of aspirin per day. The primary effectiveness outcome was a composite of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke, assessed in a time-to-event analysis. The primary safety outcome was hospitalization for major bleeding, also assessed in a time-to-event analysis. RESULTS: A total of 15,076 patients were followed for a median of 26.2 months (interquartile range [IQR], 19.0 to 34.9). Before randomization, 13,537 (96.0% of those with available information on previous aspirin use) were already taking aspirin, and 85.3% of these patients were previously taking 81 mg of daily aspirin. Death, hospitalization for myocardial infarction, or hospitalization for stroke occurred in 590 patients (estimated percentage, 7.28%) in the 81-mg group and 569 patients (estimated percentage, 7.51%) in the 325-mg group (hazard ratio, 1.02; 95% confidence interval [CI], 0.91 to 1.14). Hospitalization for major bleeding occurred in 53 patients (estimated percentage, 0.63%) in the 81-mg group and 44 patients (estimated percentage, 0.60%) in the 325-mg group (hazard ratio, 1.18; 95% CI, 0.79 to 1.77). Patients assigned to 325 mg had a higher incidence of dose switching than those assigned to 81 mg (41.6% vs. 7.1%) and fewer median days of exposure to the assigned dose (434 days [IQR, 139 to 737] vs. 650 days [IQR, 415 to 922]). CONCLUSIONS: In this pragmatic trial involving patients with established cardiovascular disease, there was substantial dose switching to 81 mg of daily aspirin and no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily. (Funded by the Patient-Centered Outcomes Research Institute; ADAPTABLE ClinicalTrials.gov number, NCT02697916.).

[42] *Ikeda S, Shinohara K, Enzan N et al.* **Effectiveness of statin intensive therapy in type 2 diabetes mellitus with high visit-to-visit blood pressure variability**. Journal of hypertension 2021; 39:1435-1443.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34001809
ABSTRACT
BACKGROUND: Intensive lipid-lowering therapy is recommended in type 2 diabetes mellitus (T2DM) patients with target organ damage. However, the evidence is insufficient to stratify the patients who will benefit from the intensive therapy among them. High visit-to-visit variability in systolic blood pressure (SBP) is associated with increased risk of cardiovascular events. We investigated the effectiveness of intensive versus standard statin therapy in the primary prevention of cardiovascular events among T2DM patients with retinopathy stratified by visit-to-visit SBP variability. METHODS: The standard versus intensive statin therapy for hypercholesterolemic patients with diabetic retinopathy study was the first trial comparing statin intensive therapy targeting low-density lipoprotein cholesterol (LDL-C) <70 mg/dl and standard therapy targeting LDL-C ≥100 to <120 mg/dl in T2DM patients with retinopathy without known cardiovascular disease. Using this dataset, we divided the patients into two subpopulations based on standard deviation (SD) and average real variability (ARV) of clinic SBP within the initial 6 months. RESULTS: In a total of 4899 patients, 240 composite cardiovascular events were observed during a median follow-up of 37.3 months. In multivariable-adjusted model comparing intensive versus standard therapy, the hazard ratios for composite cardiovascular events were 0.64 (95% CI 0.45-0.90) and 1.21 (95% CI 0.82-1.80) in patients with high and low SBP variability as defined by SD, respectively. Interaction between SBP variability and statin therapy was significant (P=0.018). The analysis using ARV of SBP showed similar results. CONCLUSION: Statin intensive therapy targeting LDL-C <70 mg/dl had benefits in primary prevention

of cardiovascular events compared with standard therapy among T2DM patients with retinopathy having high, but not low, visit-to-visit SBP variability.

[43] *Fragoulis GE, Soulaidopoulos S, Sfikakis PP et al.* **Effect of Biologics on Cardiovascular Inflammation: Mechanistic Insights and Risk Reduction**. Journal of inflammation research 2021; 14:1915-1931.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34017189
ABSTRACT
It is increasingly recognized that atherosclerosis and consequently cardiovascular disease (CVD) are closely linked with inflammatory processes. The latter is in the center of the pathogenic mechanism underlying autoimmune rheumatic diseases (ARD). It follows then, that optimal control of inflammation in ARDs may lead to a decrease of the accompanied CVD risk. Major trials (eg, CANTOS, CIRT), aimed at examining the possible benefits of immunomodulatory treatments in CVD, demonstrated conflicting results. On the other hand, substantial evidence is accumulating about the possible beneficial effects of biologic disease modifying antirheumatic drugs (bDMARDs) in patients with ARDs, particularly those with rheumatoid arthritis (RA). It seems that bDMARDs (some more than others) alter the lipid profile in RA patients but do not adversely affect, in most cases, the TC/HDL ratio. Favorable effects are noted for arterial stiffness and endothelial function. This is reflected in the lower risk for CVD events, seen in observational studies of RA patients treated with bDMARDs. It should be stressed that more data exist for the TNF-inhibitors than for other bDMARDs, such as tocilizumab, abatacept and rituximab. As regards the spondyloarthropathies (SpA), data are less robust. For TNF-inhibitors, effects appear to be on par with those seen in RA but no conclusions can be drawn for newer biologic drugs used in SpA (eg, IL-17 blockers). Finally, there is accumulating evidence for a beneficial effect of immunosuppressive treatment in cardiac inflammation and function in several ARDs. Introduction of newer therapeutic options in clinical practice seem to have a positive impact on CVD in the setting of ARD. This is probably due to better control of inflammation, but direct improvement in vascular pathology is also a valid hypothesis. Most data are derived from observational studies and, therefore, randomized controlled trials are needed to assess the possible favorable effect of bDMARDs on CVD outcomes.

[44] *Ebert T, Qureshi AR, Lamina C et al.* **Time-dependent lipid profile inversely associates with mortality in hemodialysis patients - independent of inflammation/malnutrition**. Journal of internal medicine 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33998741
ABSTRACT
BACKGROUND: Patients with end-stage kidney disease have an extremely high cardiovascular mortality rate, but there is a paradoxical relationship between lipid profile and survival in haemodialysis patients. To investigate whether inflammation/malnutrition confounds the associations between lipids and mortality, we studied a full lipid profile comprising of five clinically well-established lipid parameters and its associations with mortality in a large, multinational European cohort with a median follow-up >3 years. METHODS: The association between quartiles of total, high-density lipoprotein (HDL), non-HDL, low-density lipoprotein (LDL) cholesterol, as well as triglyceride, levels and the end-points of all-cause, cardiovascular and non-cardiovascular mortality was assessed in a cohort of 5,382 incident, adult haemodialysis patients from >250 Fresenius Medical Care dialysis

centres out of 14 participating countries using baseline and time-dependent Cox models. Analyses were fully adjusted and stratified for inflammation/malnutrition status and other patient-level variables. RESULTS: Time-dependent quartiles of total, HDL, non-HDL and LDL cholesterol were inversely associated with the hazard for all-cause, cardiovascular and non-cardiovascular mortality. Compared with the lowest quartile of the respective lipid parameter, hazard ratios of other quartiles were <0.86. Similar, albeit weaker, associations were found with baseline lipid profile and mortality. Neither time-dependent nor baseline associations between lipid profile and mortality were affected by inflammation/malnutrition, statin use or geography. CONCLUSIONS: Baseline and time-dependent lipid profile are inversely associated with mortality in a large, multicentre cohort of incident haemodialysis patients. Inflammation/malnutrition is not a confounder nor effect modificator of the associations between lipid profile and mortality in European haemodialysis patients.

[45] *A GO*. **[Are triglyceride rich lipoproteins more dangerous than LDL cholesterol?]**. Lakartidningen 2021; 118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33997946
ABSTRACT
Two prospective epidemiological studies have pointed to the importance of triglyceride rich lipoproteins in causing atherosclerosis. Lipoprotein analyses show that it is the cholesterol content of the lipoproteins that relates to atherosclerotic cardiovascular disease. As high blood levels of these lipoproteins are mostly seen in obese people changes in lifestyle seem to be the most relevant therapeutic measure.

[46] *Wallimann-Annema W*. **[The Current Significance of Measuring HDL-Cholesterol in Cardiovascular Risk Assessment]**. Praxis 2021; 110:383-390.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34019448
ABSTRACT
The Current Significance of Measuring HDL-Cholesterol in Cardiovascular Risk Assessment Abstract. In clinical practice, high-density lipoprotein cholesterol (HDL-C) levels are frequently used for cardiovascular risk prediction. HDL particles perform numerous functions that theoretically protect against atherosclerosis. Accordingly, extensive studies have clearly demonstrated that low HDL-C is an important independent risk factor for cardiovascular diseases. However, it is now considered questionable whether very high HDL-C levels are always cardioprotective. This may be explained by the structural heterogeneity of HDL particles and the loss of HDL protective functions in the context of disease, which cannot be detected by the simple measurement of HDL-C. In the future new markers of the functional capacity of HDL particles may replace HDL-C as a traditional parameter for cardiovascular risk assessment.

[47] *Tsu LV, Carroll K, Kindler K, Early N*. **Pharmacological Management of Hyperlipidemia in Older individuals**. Sr Care Pharm 2021; 36:284-303.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34016226
ABSTRACT
OBJECTIVE: To provide an up-to-date review of current hyperlipidemia guidelines and discuss pharmacotherapeutic management of hyperlipidemia in older individuals. DATA SOURCES: A PubMed search of articles published through October 2020 was performed using a combination of the

following words: older adults, hyperlipidemia, statin, ezetimibe, fibrate, fish oil, niacin, bile acid sequestrant, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor. STUDY SELECTION/DATA EXTRACTION: Relevant original research, review articles, and guidelines were assessed for the management of hyperlipidemia in the older individuals. References from the above literature were also evaluated. Articles were selected for inclusion based on relevance to the topic, detailed methods, and complete results. DATA SYNTHESIS: Hyperlipidemia is a common chronic disease state in the elderly population, though there is limited evidence for clinical outcomes in older people when compared withwith the general adult population. Statins have the most evidence for primary and secondary prevention of cardiovascular disease in older people, though ezetimibe and PCSK9 inhibitors have a role as add-on or monotherapy in patients who do not tolerate statins. CONCLUSION: Optimal management of hyperlipidemia in older people is important in order to avoid further complications and improve outcomes. Pharmacists can help improve management in the elderly by incorporating up-to-date evidence from guidelines and providing medication education specifically for this population.

[48] *Steffens D, Bramlage P, Müller J et al.* **Intensified lipid-lowering treatment with alirocumab in patients with coronary heart disease**. Open heart 2021; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34001653
ABSTRACT
BACKGROUND: Atherosclerotic cardiovascular disease is the leading cause of death and disability in the Western world. OBJECTIVE: To characterise adults with confirmed coronary heart disease (CHD) and primary heterozygous familial or non-familial hypercholesterolaemia or mixed dyslipidaemia who received alirocumab in a real-world setting. METHODS: This open, prospective, multicentre, non-interventional study, conducted in Germany, enroled patients with confirmed CHD who were treated with alirocumab according to its summary of product characteristics. Prescription was at the physician's discretion and independent of study participation. Patients were followed for 12 weeks after alirocumab initiation. RESULTS: In total, 245 patients (mean age 62.2 years; 34.0% female) were documented at 90 sites. Overall, 47.7% had familial hypercholesterolaemia, 48.9% non-familial hypercholesterolaemia and 43.8% mixed dyslipidaemia; 74.6% had hypertension and 29.2% diabetes mellitus. The most common lipid-lowering therapy in the 12 months preceding alirocumab was a statin, often in combination with ezetimibe (73.5%). Statin contraindications were documented for 46.2% patients and statin intolerance for 63.8%. The mean low-density lipoprotein cholesterol (LDL-C)-level prior to alirocumab was 150.5±51.6 mg/dL. Alirocumab prescription was in compliance with German national recommendations and/or European guidelines. The most common starting dose was 75 mg every other week. Overall, 57% patients reached target LDL-C levels (<70 mg/dL) after 12 weeks of treatment. Alirocumab was generally well tolerated. CONCLUSION: In a real-world setting in Germany, alirocumab was prescribed for patients with atherosclerotic cardiovascular disease who had high baseline LDL-C levels with or without statin intolerance. Efficacy and safety were consistent with findings observed in the ODYSSEY Phase III programme.

[49] *Rothgangl T, Dennis MK, Lin PJC et al.* **In vivo adenine base editing of PCSK9 in macaques reduces LDL cholesterol levels**. Nature biotechnology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34012094
ABSTRACT

Most known pathogenic point mutations in humans are C•G to T•A substitutions, which can be directly repaired by adenine base editors (ABEs). In this study, we investigated the efficacy and safety of ABEs in the livers of mice and cynomolgus macaques for the reduction of blood low-density lipoprotein (LDL) levels. Lipid nanoparticle-based delivery of mRNA encoding an ABE and a single-guide RNA targeting PCSK9, a negative regulator of LDL, induced up to 67% editing (on average, 61%) in mice and up to 34% editing (on average, 26%) in macaques. Plasma PCSK9 and LDL levels were stably reduced by 95% and 58% in mice and by 32% and 14% in macaques, respectively. ABE mRNA was cleared rapidly, and no off-target mutations in genomic DNA were found. Re-dosing in macaques did not increase editing, possibly owing to the detected humoral immune response to ABE upon treatment. These findings support further investigation of ABEs to treat patients with monogenic liver diseases.

[50] *Pokhrel S, Giri N, Pokhrel R et al.* **Vitamin D deficiency and cardiovascular risk in type 2 diabetes population**. Open Life Sci 2021; 16:464-474.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34017921

ABSTRACT

This study aims to assess vitamin D deficiency-induced dyslipidemia and cardiovascular disease (CVD) risk in poor glycemic control among type 2 diabetes mellitus (T2DM) patients. This study was carried out among 455 T2DM patients involving poor glycemic control (n = 247) and good glycemic control (n = 208). Fasting plasma glucose (FPG) and HbA(1)c were measured to assess glycemic control. Cardiac risk ratio, atherogenic index plasma, and atherogenic coefficient were calculated to assess and compare the CVD risk in different groups. Patients with poor control had a significantly higher level of total cholesterol (TC), triglyceride (TG), and non-high-density lipoprotein lipase cholesterol (non-HDL-C), atherogenic variables, and lower level of high-density lipoprotein lipase cholesterol (HDL-C) as compared to patients with good glycemic control. We also observed significant negative correlation of vitamin D with lipid markers and atherogenic variables in poor glycemic control diabetic population. The serum vitamin D levels were inversely associated with HbA(1)c, FPG, TG, TC, and non-HDL-C. Furthermore, hypercholesterolemia, hypertriglyceridemia, and elevated non-HDL-C were the independent risks in hypovitaminosis D population. Vitamin D deficiency in poor glycemic control is likely to develop dyslipidemia as compared to vitamin D insufficient and sufficient groups. Thus, vitamin D supplementation and an increase in exposure to sunlight may reduce the risk of cardiovascular complications in diabetes.

[51] *Ortland I, Mirjalili M, Kullak-Ublick GA, Peymani P*. **Drug-induced liver injury in Switzerland: an analysis of drug-related hepatic disorders in the WHO pharmacovigilance database VigiBase from 2010 to 2020**. Swiss Med Wkly 2021; 151:w20503.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34000058

ABSTRACT

AIMS OF THE STUDY: Our aim was to explore drug-induced liver injury (DILI) in Switzerland using the real-world data of the global pharmacovigilance database VigiBaseÔ, with a special focus on the new drug class of checkpoint inhibitors. This is the first study investigating drug-related hepatic disorders in Switzerland in a global pharmacovigilance database. METHODS: This was a retrospective study analysing the ICSRs (individual case safety reports) of the global pharmacovigilance database VigiBaseÔ. We explored all ICSRs submitted in Switzerland within

the last 10 years (1 July 2010 to 30 June 2020). For data extraction, the standardised MedDRA query (SMQ) “narrow drug-related hepatic disorders – severe events only” was applied. The ICSRs, drug-reaction pairs and adverse drug reactions were analysed descriptively, including a special focus on checkpoint inhibitors. For comparing the hepatic adverse drug reactions of pembrolizumab, nivolumab and ipilimumab, the reporting odds ratios (RORs) were calculated in a disproportionality analysis. RESULTS: In total, 2042 ICSRs could be investigated, comprising 10,646 drugs and 6436 adverse drug reactions. Gender was equally distributed between male and female. Patients were on average 57 years old. The mortality rate was high, with fatal adverse reactions in over 10% of cases. On average, patients used five drugs including two suspected drugs. Paracetamol, amoxicillin/clavulanic acid, esomeprazole and atorvastatin ranked among the most frequently suspected drugs for severe drug-related hepatic disorders. However, VigibaseÔ data are not appropriate for judging causality and these results should be interpreted with caution owing to the possible influences of comedication or comorbidity. An average of three adverse drug reactions per ICSR were reported, most frequently including hepatocellular injury, cholestatic liver injury, and liver injury. For checkpoint inhibitors, hepatitis was the most frequently reported hepatic adverse drug reaction. In comparison with nivolumab and ipilimumab, pembrolizumab had a significantly higher ROR for hepatitis (2.41, p = 0.016), but also a lower ROR for autoimmune hepatitis (0.11, p = 0.009). CONCLUSION: Our findings highlight the importance for healthcare providers in Switzerland to pay special attention to possible drug-induced liver injuries because of their high mortality rate. The analysis of real-world data confirms the previous assumption that hepatitis is the most frequent hepatic adverse event for checkpoint inhibitors. Further clinical studies are warranted to directly compare hepatic adverse drug reactions to different checkpoint inhibitors.

[52] *Musunuru K, Chadwick AC, Mizoguchi T et al.* **In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates**. Nature 2021; 593:429-434.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34012082
ABSTRACT
Gene-editing technologies, which include the CRISPR-Cas nucleases(1-3) and CRISPR base editors(4,5), have the potential to permanently modify disease-causing genes in patients(6). The demonstration of durable editing in target organs of nonhuman primates is a key step before in vivo administration of gene editors to patients in clinical trials. Here we demonstrate that CRISPR base editors that are delivered in vivo using lipid nanoparticles can efficiently and precisely modify disease-related genes in living cynomolgus monkeys (Macaca fascicularis). We observed a near-complete knockdown of PCSK9 in the liver after a single infusion of lipid nanoparticles, with concomitant reductions in blood levels of PCSK9 and low-density lipoprotein cholesterol of approximately 90% and about 60%, respectively; all of these changes remained stable for at least 8 months after a single-dose treatment. In addition to supporting a 'once-and-done' approach to the reduction of low-density lipoprotein cholesterol and the treatment of atherosclerotic cardiovascular disease (the leading cause of death worldwide(7)), our results provide a proof-of-concept for how CRISPR base editors can be productively applied to make precise single-nucleotide changes in therapeutic target genes in the liver, and potentially in other organs.

[53] *Khirfan G, Li M, Wang X et al.* **Abnormal levels of apolipoprotein A-I in chronic thromboembolic pulmonary hypertension**. Pulmonary circulation 2021; 11:20458940211010371.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33996028

ABSTRACT

Recent studies have shown low high-density lipoprotein cholesterol (HDL-C) and dysregulated lipid metabolism in chronic thromboembolic pulmonary hypertension (CTEPH). Apolipoprotein A-I (ApoA-I) is the major protein component of HDL-C and mediates most of its functions. We hypothesize that ApoA-1 and its oxidative state might be more sensitive biomarkers in CTEPH. Plasma levels of HDL-C, ApoA-I, paraoxonase-1 enzyme activity (PON1), and the oxidized dysfunctional ApoA-I (oxTrp72-ApoA-I) were measured in patients with CTEPH and compared to those in healthy controls. Association with markers of disease severity in CTEPH was assessed. We included a total of 61 patients with CTEPH (age: 61.2 ± 15 years; male 52.5%) and 28 control subjects (age: 60.1 ± 8 years; male 59.3%). When adjusting for age, sex, body mass index, and statin use, ApoA-I was lower in CTEPH compared to controls (CTEPH:125.2 ± 27 mg/dl; control:158.3 ± 29.4 mg/dl; $p < 0.001$), but HDL-C levels were not statistically different. There were no significant differences in PON and oxTrp72-ApoA-I/ApoA-I ratio. In exploratory analyses, ApoA-I was associated with mean right atrial pressure ($r(s) = -0.32$, $p = 0.013$) and N-terminal pro B-type natriuretic peptide ($r(s) = -0.31$, $p = 0.038$). There were no significant associations between HDL-C, PON1, or oxTrp72-ApoA-I/ApoA-I ratio and markers of disease severity. We conclude that ApoA-I is a more sensitive biomarker than HDL-C in CTEPH, and may be associated with right heart dysfunction.

[54] *Feng R, Guo X, Kou Y et al.* **Association of lipid profile with decompensation, liver dysfunction, and mortality in patients with liver cirrhosis**. Postgraduate medicine 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33993838

ABSTRACT

BACKGROUND AND AIMS: Lipid metabolism is often disrupted in liver cirrhosis. The present study aimed to evaluate the impact of lipid profile on decompensation events, severity of liver dysfunction, and death in patients with liver cirrhosis. METHODS: In a cross-sectional study, 778 patients with lipid profile data were enrolled, and then were divided into 240 and 538 patients with and without liver cirrhosis, respectively. In a cohort study, 314 cirrhotic patients with lipid profile data, who were prospectively followed, were enrolled. Lipid profile included total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), triglycerides (TG), and lipoprotein(a). RESULTS: In the cross-sectional study, cirrhotic patients with decompensation events had significantly lower levels of TC and lipoprotein(a) than those without; and cirrhotic patients with Child-Pugh class B and C had significantly lower levels of TC, HDL-c, LDL-c, and lipoprotein(a) than those with Child-Pugh class A. In the cohort study, there was an inverse association of survival with TC, HDL-c, and lipoprotein(a) levels; after adjusting for MELD score, TC (Hazard Ratio [HR]=1.703, P=0.034) and HDL-c (HR=2.036, P=0.005), but not lipoprotein(a) (HR=1.377, P=0.191), remained a significant predictor of death; when TC, HDL-c, lipoprotein(a), and MELD score were included in the multivariate Cox regression analysis, HDL-c (HR=1.844, P=0.024) was the only independent predictor of death. CONCLUSIONS: Decreased levels in specific components of lipid profile indicate more decompensation events, worse liver function, and reduced survival in liver cirrhosis. MELD score combined with HDL-c should be promising for the assessment of outcomes of cirrhotic patients.

[55] *Yu Q, Zheng H, Zhang Y*. **Inducible degrader of LDLR: A potential novel therapeutic target and emerging treatment for hyperlipidemia**. Vascular pharmacology 2021:106878.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34015522

ABSTRACT

Statins are the most effective lipid-lowering drugs ever developed, and numerous patients with cardiovascular disease (CVD) have obtained remarkable benefits from statin therapy. However, issues with statin resistance and intolerance cannot be ignored in clinical practice. Additionally, adverse effects, such as an increased risk of new-onset diabetes and muscle symptoms, may limit the utilization of statins. Therefore, the development of new lipid-lowering agents is necessary to reduce CVD risk in patients who are unable to receive statin therapy. Among these new lipid-lowering strategies, inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) is an effective way to enhance clearance of LDL-C from the circulation by impeding the degradation of LDL receptor (LDLR) in hepatocytes. Interestingly, given that upregulation of LDLR is an effective method for lowering lipid levels, the question arises as to whether other LDLR-mediated genes could serve as potential therapeutic targets for CVD. As an E3-ubiquitin ligase, inducible degrader of LDLR (IDOL) can cause ubiquitination and degradation of LDLR in lysosome and is a novel regulator of LDLR expression similar to PCSK9. Although there are no approved drugs for targeting the IDOL-LDLR pathway, recent studies demonstrate that IDOL could serve as a potential therapeutic target for hyperlipidemia. Herein, we have summarized these novel studies to present the pathological role of IDOL in CVD, further assessing its pharmacological effects for lipid-lowering therapy.

[56] *Mitrofanova A, Burke G, Merscher S, Fornoni A*. **New insights into renal lipid dysmetabolism in diabetic kidney disease**. World journal of diabetes 2021; 12:524-540.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33995842

ABSTRACT

Lipid dysmetabolism is one of the main features of diabetes mellitus and manifests by dyslipidemia as well as the ectopic accumulation of lipids in various tissues and organs, including the kidney. Research suggests that impaired cholesterol metabolism, increased lipid uptake or synthesis, increased fatty acid oxidation, lipid droplet accumulation and an imbalance in biologically active sphingolipids (such as ceramide, ceramide-1-phosphate and sphingosine-1-phosphate) contribute to the development of diabetic kidney disease (DKD). Currently, the literature suggests that both quality and quantity of lipids are associated with DKD and contribute to increased reactive oxygen species production, oxidative stress, inflammation, or cell death. Therefore, control of renal lipid dysmetabolism is a very important therapeutic goal, which needs to be archived. This article will review some of the recent advances leading to a better understanding of the mechanisms of dyslipidemia and the role of particular lipids and sphingolipids in DKD.

[57] *Majid S, Keith RJ, Fetterman JL et al.* **Lipid profiles in users of combustible and electronic cigarettes**. Vascular medicine (London, England) 2021:1358863x211009313.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34013801

ABSTRACT

Electronic cigarette use has especially risen among adolescents and young adults. The aim of this study was to investigate fasting blood glucose and lipid profiles in chronic combustible cigarette and electronic cigarette users. We evaluated participants aged 21 to 45 (n = 525, mean age 31 ± 7 years, 45% women) without established cardiovascular disease or risk factors who were combustible cigarette users (n = 290), electronic cigarette users (n = 131; 65 sole users and 66 dual users), or

never users (n = 104). In the first wave of enrollment (2014-2017), electronic cigarette users reported their products as first, second and third generation devices (e-cig users) and were all largely current (i.e. dual) or former (sole) combustible cigarette users, whereas in the second wave of enrollment (2019-2020), electronic cigarette users all reported pod-based device use (pod users) and included more sole users who were never smokers. In multivariable-adjusted analyses comparing to never users, both sole e-cig users and combustible cigarette users had higher glucose and triglycerides and lower high-density lipoprotein (HDL) cholesterol levels. Dual e-cig users showed higher triglycerides and very-low-density lipoprotein cholesterol, and lower HDL cholesterol compared to never users. In contrast, pod users (both sole and dual) had lipid profiles and glucose levels similar to never users. Overall, users of early generation electronic cigarettes display adverse metabolic profiles. In contrast, pod-based electronic cigarette users have similar lipid profiles to never users. Future studies are needed to understand the cumulative effects of electronic cigarette use on cardiometabolic health.