[1] *Tintut Y, Demer LL.* **Potential Impact of the Steroid Hormone, Vitamin D, on the Vasculature Vitamin D-hormones and cardiovascular disease**. American heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34051171

ABSTRACT

The role of vitamin D in the cardiovascular system is complex because it regulates expression of genes involved in diverse metabolic processes. Although referred to as a vitamin, it is more accurately considered a steroid hormone, because it is produced endogenously in the presence of ultraviolet light. It occurs as a series of sequentially activated forms, here referred to as vitamin D-hormones. A little-known phenomenon, based on pre-clinical data, is that its biodistribution and potential effects on vascular disease likely depend on whether it is derived from diet or sunlight. Diet-derived vitamin D-hormones are carried in the blood, at least in part, in chylomicrons and lipoprotein particles, including LDL. Since LDL is known to accumulate in the artery wall and atherosclerotic plaque, diet-derived vitamin D-hormones may also collect there, and possibly promote the osteochondrogenic mineralization associated with plaque. Also, little known is the fact that the body stores vitamin D-hormones in adipose tissue with a half-life on the order of months, raising doubts about whether the use of the term "daily requirement" is appropriate. Cardiovascular effects of vitamin D-hormones are controversial, and risk appears to increase with both low and high blood levels. Since low serum vitamin D-hormone concentration is reportedly associated with increased cardiovascular and orthopedic risk, oral supplementation is widely used, often together with calcium supplements. However, meta-analyses show that oral vitamin D-hormone supplementation does not protect against cardiovascular events, findings that are also supported by a randomized controlled trial. These considerations suggest that prevalent recommendations for vitamin D-hormone supplementation for the purpose of cardiovascular protection should be carefully reconsidered.

[2] *Fan H, Zhou J, Yuan Z.* **Meta-Analysis Comparing the Effect of Combined Omega-3+Statin Therapy Versus Statin Therapy Alone on Coronary Artery Plaques**. The American journal of cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34049675

ABSTRACT

Statin therapy plays an important role in stabilizing and regressing coronary artery plaques. Omega-3 supplements also have anti-inflammatory and antioxidant effects on coronary plaques. However, the effect of omega-3 supplementation on the basis of statin therapy on the stability and composition of plaques, is still unclear. We searched for randomized controlled trials published prior to November 2020 in the PubMed, Embase and Cochrane databases. Finally, eight studies using different imaging techniques to evaluate coronary atherosclerotic plaque, including optical coherence tomography (OCT), coronary CT angiography (cCTA) and intravascular ultrasound (IB-IVUS), met our inclusion criteria. We pooled data extracted from the included studies using the standardized mean difference (SMD) or mean difference (MD) of the random effects model. Compared with statin treatment alone, the combined treatment further delayed the progression of total plaque volume [SMD -0.36, 95% confidence interval (CI) -0.64 to -0.08, p = 0.01] and fiber content (SMD -0.40, 95% CI -0.68 to -0.13, p = 0.004). The plasma high-sensitivity C-reactive protein (hs-CRP) level of patients in the combination treatment group was significantly lower than that of the patients in the statin treatment group alone (SMD -0.30, 95% CI -0.59 to -0.01, p = 0.04). In addition, the combined use of omega-3 further increases the fibrous cap thickness (FCT) of the plaque with an MD of 29.45 μm. There were

no significant differences in plasma high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or lipid content in plaques between the two groups. Omega-3 combined with statins is superior to the statin treatment group in stabilizing and promoting coronary plaque regression and may help to further reduce the occurrence of cardiovascular events.

[3] *Costantine MM, West H, Wisner KL et al.* **A randomized pilot clinical trial of pravastatin versus placebo in pregnant patients at high risk of preeclampsia**. American journal of obstetrics and gynecology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34033812
ABSTRACT
BACKGROUND: Preeclampsia remains a major cause of maternal and neonatal morbidity and mortality. Biologic plausibility, compelling preliminary data, and a pilot clinical trial support the safety and utility of pravastatin for the prevention of preeclampsia. OBJECTIVE: We previously reported the results of a phase I clinical trial using a low dose (10 mg) of pravastatin in high-risk pregnant women. Here, we report a follow-up, randomized trial of 20 mg pravastatin versus placebo among pregnant women with previous preeclampsia who required delivery before 34+6 weeks' gestation with the objective of evaluating the safety and pharmacokinetic parameters of pravastatin. STUDY DESIGN: This was a pilot, multicenter, blinded, placebo-controlled, randomized trial of women with singleton, nonanomalous pregnancies at high risk for preeclampsia. Women between 12+0 and 16+6 weeks of gestation were assigned to receive a daily pravastatin dose of 20 mg or placebo orally until delivery. In addition, steady-state pravastatin pharmacokinetic studies were conducted in the second and third trimesters of pregnancy and at 4 to 6 months postpartum. Primary outcomes included maternal-fetal safety and pharmacokinetic parameters of pravastatin during pregnancy. Secondary outcomes included maternal and umbilical cord blood chemistries and maternal and neonatal outcomes, including rates of preeclampsia and preterm delivery, gestational age at delivery, and birthweight. RESULTS: Of note, 10 women assigned to receive pravastatin and 10 assigned to receive the placebo completed the trial. No significant differences were observed between the 2 groups in the rates of adverse or serious adverse events, congenital anomalies, or maternal and umbilical cord blood chemistries. Headache followed by heartburn and musculoskeletal pain were the most common side effects. We report the pravastatin pharmacokinetic parameters including pravastatin area under the curve (total drug exposure over a dosing interval), apparent oral clearance, half-life, and others during pregnancy and compare it with those values measured during the postpartum period. In the majority of the umbilical cord and maternal samples at the time of delivery, pravastatin concentrations were below the limit of quantification of the assay. The pregnancy and neonatal outcomes were more favorable in the pravastatin group. All newborns passed their brainstem auditory evoked response potential or similar hearing screening tests. The average maximum concentration and area under the curve values were more than 2-fold higher following a daily 20 mg dose compared with a 10 mg daily pravastatin dose, but the apparent oral clearance, half-life, and time to reach maximum concentration were similar, which is consistent with the previously reported linear, dose-independent pharmacokinetics of pravastatin in nonpregnant subjects. CONCLUSION: This study confirmed the overall safety and favorable pregnancy outcomes for pravastatin in women at high risk for preeclampsia. This favorable risk-benefit analysis justifies a larger clinical trial to evaluate the efficacy of pravastatin for the prevention of preeclampsia. Until then, pravastatin use during pregnancy remains investigational.

[4] *Gu L, Duan L, Xie P et al.* **The effect of sedentary time on the results of exercise therapy in patients with peripheral arterial disease complicated with type 2 diabetes**. Ann Palliat Med 2021; 10:5366-5372.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34044553

ABSTRACT

BACKGROUND: Peripheral artery disease (PAD) is a common chronic complication of type 2 diabetes (T2DM). This study sought to evaluate the effect of supervised exercise therapy (SET) on patients with PAD complicated with T2DM, and to assess the effect of changes in sedentary time on the results of SET treatment. METHODS: A total of 100 PAD patients who were treated in our hospital from January 2019 to October 2020 were included, and the age, gender, body mass index (BMI), hypertension, smoking, and ankle brachial index (ABI) were collected. The patients were required to complete SET treatment 2-3 times a week for 12 weeks. Subsequently, the objective 6-minute walk test (6MWT) and Short Physical Performance Battery (SPPB) were used to assess body function. After adjusting for other key confounding variables such as age, gender, and smoking status, linear regression analysis was used to evaluate the effects of changes in sedentary time on the total distance of the 6MWT. RESULTS: After 12 weeks of treatment, the total SPPB score of the patients increased from a baseline of 9.3±2.7 to 10.1±2.3 (P=0.025), the normal walking distance in the 6MWT increased from 108.9±26.8 to 148.9±29.5 m (P<0.001), the total walking distance increased from 322.5±93.4 to 348.5±86.1 m (P=0.042), and at the same time, the metabolic equivalent on the treadmill increased from 2.6±0.7 to 3.9±1.4 (P<0.001). Compared with the baseline data, the proportion of time that patients spent engaged in mild physical activity at 6 weeks increased by 20%±10% (P=0.003), and the average daily sedentary time decreased by 6.5±2.8 minutes (P=0.008), or by 3.1%±2.1% (P=0.04). Furthermore, compared with the baseline, the proportion of time that patients spent engaged in light and moderate physical activity at 12 weeks increased by 10%±3% (P=0.007) and 20%±10% (P=0.006), respectively, while the average sedentary time per day reduced by 6.8±3.1 minutes (P=0.03), or by 3.6%±1.8% (P=0.005). CONCLUSIONS: The reduction of sedentary time can significantly improve the effectiveness of exercise therapy in patients with PAD complicated by T2DM, and compared with patients with PAD alone, the improvement in patients complicated with T2DM is more significant.

[5] *Zetu C, Popa S, Golli AL et al.* **Long-term improvement of dyslipidaemia, hyperuricemia and metabolic syndrome in patients undergoing laparoscopic sleeve gastrectomy**. Archives of endocrinology and metabolism 2021; 64:704-709.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34033279

ABSTRACT

OBJECTIVE: The aim of the study was to assess the long-term impact of laparoscopic sleeve gastrectomy (LSG) on lipid profile, uric acid level and metabolic syndrome. METHODS: A prospective study was performed between 2009-2014, evaluating long-term percentage of excesso body mass index loss (%EBMIL), lipid profile, uric acid level and metabolic syndrome. RESULTS: Overall sixty subjects were followed-up. %EBMIL increased significantly, reaching a maximum (86,9 ± 6,3%) at 5 years post-LSG. Therapeutic success rate (%EBMIL ≥ 60%) was 80% at 5 years. The triglyceride level decreased significantly (148 ± 72.1 mg/dL baseline vs 130.7 ± 57.5 mg/dL at 1 month vs 110.7 ± 42.6 mg/dL at 3 months vs 92.5 ± 35.2 mg/dL at 1 year vs 84.2 ± 32.3 mg/dL at 5 years; $p < 0.05$ for

all). HDL-cholesterol increased and uric acid decreased significantly in the first year postoperatively, remaining stable afterwards (46.9 ± 12.3 mg/dL baseline vs 47.4 ± 10 mg/dL at 1 month vs 49.8 ± 9.3 mg/dL at 3 months vs 55.4 ± 10.2 mg/dL at 1 year; $p < 0.05$ for all for HDL-cholesterol and 6.4 ± 2 mg/dL baseline vs 6 ± 1.7 mg/dL at 1 month vs 5.2 ± 1.3 mg/dL at 3 months vs 4.8 ± 1 mg/dL at 1 year; $p < 0.05$ for all for uric acid). The prevalence of metabolic syndrome decreased from 66.7% baseline to 8.3% at 5 years postoperatively ($p < 0.01$). CONCLUSION: LSG was effective in terms of %EBMIL and metabolic traits improvement for Romanian patients.

[6] *Cornelissen A, Fuller DT, Fernandez R et al.* **APOL1 Genetic Variants Are Associated With Increased Risk of Coronary Atherosclerotic Plaque Rupture in the Black Population**. Arteriosclerosis, thrombosis, and vascular biology 2021:Atvbaha120315788.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34039022

ABSTRACT

OBJECTIVE: Reported associations between kidney risk variants (G1 and G2) in APOL1, encoding APOL1, and cardiovascular disease have been conflicting. We sought to explore associations of APOL1 risk variants with cause of sudden death using the CVPath Sudden Death Autopsy Registry. Approach and Results: APOL1 haplotypes and causes of sudden death, as determined through autopsy and histopathology, were obtained for 764 Black subjects. Genotyping revealed APOL1 risk alleles in 452 of 764 (59%) subjects with 347 (77%) subjects carrying one risk allele and 105 (23%) subjects harboring 2 risk alleles. APOL1 risk allele carrier status was associated with a significantly increased risk of coronary thrombosis due to plaque rupture, versus noncarriers (odds ratio for rupture, 1.655 [95% CI, 1.079-2.539]; P=0.021). Histological examinations showed coronary plaques in carriers of 2 APOL1 risk alleles had larger necrotic cores compared with noncarriers (necrotic core area/total plaque area: 46.79%±6.47% versus 20.57%±5.11%; P=0.0343 in ruptured plaques, and 41.48%±7.49% versus 18.93%±3.97%; P=0.0342 in nonruptured plaques), and immunohistochemical and immunofluorescent staining revealed APOL1-positive areas localized primarily to the necrotic core. CONCLUSIONS: APOL1 risk alleles were independently associated with an increased risk of thrombotic coronary death due to plaque rupture. Our results suggest that carriers of both 1 and 2 APOL1 risk alleles have greater accumulation of APOL1 protein within culprit plaques and greater necrotic core sizes than noncarriers. These findings suggest that APOL1 plays a role in determining plaque stability.

[7] *Lepor NE, Sun J, Canton G et al.* **Regression in carotid plaque lipid content and neovasculature with PCSK9 inhibition: A time course study**. Atherosclerosis 2021; 327:31-38.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34038761

ABSTRACT

BACKGROUND AND AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce cardiovascular events, but their effects on atherosclerotic plaque remain elusive. Using serial magnetic resonance imaging (MRI), we studied changes in carotid plaque lipid content and neovasculature under PCSK9 inhibition with alirocumab. METHODS: Among patients with low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dl but ineligible for high-dose statin therapy, those with lipid core on carotid MRI were identified to receive alirocumab 150 mg every 2 weeks. Follow-up MRI was performed at 3, 6, and 12 months after treatment. Pre- and post-contrast MRI were acquired to measure percent lipid core volume (% lipid core). Dynamic contrast-enhanced MRI was acquired to

measure the extravasation rate of gadolinium contrast (K(trans)), a marker of plaque neovasculature. RESULTS: Of 31 patients enrolled, 27 completed the study (mean age: 69 ± 9; male: 67%). From 9.8% at baseline, % lipid core was progressively reduced to 8.4% at 3 months, 7.5% at 6 months, and 7.2% at 12 months (p = 0.014 for trend), which was accompanied by a progressive increase in % fibrous tissue (p = 0.009) but not % calcification (p = 0.35). K(trans) was not reduced until 12 months (from 0.069 ± 0.019 min(-1) to 0.058 ± 0.020 min(-1); p = 0.029). Lumen and wall areas did not change significantly during the study period. CONCLUSIONS: Regression in plaque composition and neovasculature were observed under PCSK9 inhibition on carotid MRI, which provides unique insight into the biological process of plaque stabilization with disease-modifying therapies.

[8] *Peng J, Zhao F, Yang X et al.* **Association between dyslipidemia and risk of type 2 diabetes mellitus in middle-aged and older Chinese adults: a secondary analysis of a nationwide cohort**. BMJ open 2021; 11:e042821.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34035089
ABSTRACT
AIMS: To evaluate the type 2 diabetes mellitus (T2DM) risk of individuals with different types of dyslipidaemia and compare the predictive value of distinct lipid parameters in predicting T2DM. METHODS: We conducted a secondary analysis of data from the China Health and Retirement Longitudinal Study (CHARLS). 17 708 individuals over 45 years old were interviewed, and 11 847 blood samples were collected at the baseline survey (2011-2012). Outcome of T2DM was confirmed during two follow-up surveys (2013-2014 and 2015-2016). The HRs and 95% CI of T2DM associated with dyslipidaemia were estimated by Cox proportional hazards regressions model. The discriminatory value of eight lipid parameters were compared by the area under the receiver operating characteristic (ROC) curve (AUC). RESULTS: A total of 7329 participants were enrolled in our analysis; during the mean follow-up time of 3.4 years, 387 (5.28%) participants developed new-onset diabetes. Compared with participants in normal lipid levels, the T2DM risk of those with hypercholesterolaemia, hypertriglyceridaemia and low high-density lipoprotein cholesterol (HDL-C) were significantly increased (HRs (95% CI) were 1.48 (1.11 to 1.96), 1.92 (1.49 to 2.46) and 1.67 (1.35 to 2.07), respectively). The AUCs of non-HDL-C (0.685, 95% CI 0.659 to 0.711), triglyceride (TG) (0.684, 95% CI 0.658 to 0.710), total cholesterol (TC)/HDL-C (0.685, 95% CI 0.659 to 0.712) and TG/HDL-C (0.680, 95% CI 0.654 to 0.706) were significantly ($p<0.005$) larger than that of other lipid parameters. CONCLUSION: Middle-aged and elderly adults with hypertriglyceridaemia, hypercholesterolaemia and low HDL-C were at higher risk for developing diabetes. Non-HDL-C, TG, TC/HDL and TG/HDL have greater performance than other lipid parameters in predicting T2DM incidence.

[9] *Sabanis N, Paschou E, Drylli A et al.* **Rosuvastatin and Colchicine combined myotoxicity: lessons to be learnt**. CEN case reports 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34028728
ABSTRACT
Statins and colchicine co-administration consists of a potentially catastrophic drug-drug interaction since it provokes myotoxicity, myopathy and various degrees of rhabdomyolysis. Lipophilic statins and colchicine are biotransformed in the liver, primarily via CYP3A4 enzyme system leading to elevated blood levels of both agents and resulting in increased potential for combined myotoxicity.

Hence, it would be of great clinical importance not only the awareness of this devastating complication but also the more advantageous type of statin that we should choose to achieve the recommended therapeutic goals regarding LDL levels with minimal myopathy risk. Therefore, once colchicine's use is commenced, a hydrophilic statin selection, such as rosuvastatin, seems favorable regarding the risk of myotoxicity. Herein, we aim to describe a patient with chronic kidney disease stage III and nephrotic syndrome that developed acute rhabdomyolysis soon after the administration of rosuvastatin while receiving colchicine. To the best of our knowledge, this is the first report of the combined effect of rosuvastatin and colchicine in the setting of chronic kidney disease leading to myotoxicity.

[10] *Azarpazhooh MR, Bogiatzi C, Spence JD*. **Stroke Prevention: Little-Known and Neglected Aspects**. Cerebrovasc Dis 2021:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34044404
ABSTRACT
Combining available therapies has the potential to reduce the risk of stroke by 80% or more. A comprehensive review of all aspects of stroke prevention would be very lengthy; in this narrative review, we focus on some aspects of stroke prevention that are little-known and/or neglected. These include the following: (1) implementation of a Mediterranean diet; (2) B vitamins to lower homocysteine; (3) coordinated approaches to smoking cessation; (4) intensive lipid-lowering therapy; (5) lipid lowering in the elderly; (6) physiologically individualized therapy for hypertension based on renin/aldosterone phenotyping; (7) avoiding excessive blood pressure reduction in patients with stiff arteries; (8) treatment of insulin resistance with pioglitazone in stroke patients with prediabetes and diabetes; (9) impaired activation of clopidogrel in patients with variants of CYP2C19; (10) aspirin pseudoresistance due to enteric coating; (11) rationale for anticoagulation in patients with embolic stroke of unknown source; (12) pharmacologic properties of direct-acting oral anticoagulants that should be considered when choosing among them; (13) the identification of which patients with asymptomatic carotid stenosis are at a high enough risk to benefit from carotid endarterectomy or stenting; and (14) the importance of age in choosing between endarterectomy and stenting. Stroke prevention could be improved by better recognition of these issues and by implementation of the principles derived from them.

[11] *Christiansen MK, Winther S, Nissen L et al.* **Polygenic Risk Score-Enhanced Risk Stratification of Coronary Artery Disease in Patients With Stable Chest Pain**. Circulation. Genomic and precision medicine 2021; 14:e003298.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34032468
ABSTRACT
BACKGROUND: Polygenic risk scores (PRSs) are associated with coronary artery disease (CAD), but the clinical potential of using PRSs at the single-patient level for risk stratification has yet to be established. We investigated whether adding a PRS to clinical risk factors (CRFs) improves risk stratification in patients referred to coronary computed tomography angiography on a suspicion of obstructive CAD. METHODS: In this prespecified diagnostic substudy of the Dan-NICAD trial (Danish study of Non-Invasive testing in Coronary Artery Disease), we included 1617 consecutive patients with stable chest symptoms and no history of CAD referred for coronary computed tomography angiography. CRFs used for risk stratification were age, sex, symptoms, prior or active smoking,

antihypertensive treatment, lipid-lowering treatment, and diabetes. In addition, patients were genotyped, and their PRSs were calculated. All patients underwent coronary computed tomography angiography. Patients with a suspected ≥50% stenosis also underwent invasive coronary angiography with fractional flow reserve. A combined end point of obstructive CAD was defined as a visual invasive coronary angiography stenosis >90%, fractional flow reserve <0.80, or a quantitative coronary analysis stenosis >50% if fractional flow reserve measurements were not feasible. RESULTS: The PRS was associated with obstructive CAD independent of CRFs (adjusted odds ratio, 1.8 [95% CI, 1.5-2.2] per SD). The PRS had an area under the curve of 0.63 (0.59-0.68), which was similar to that for age and sex. Combining the PRS with CRFs led to a CRF+PRS model with area under the curve of 0.75 (0.71-0.79), which was 0.04 more than the CRF model (P=0.0029). By using pretest probability (pretest probability) cutoffs at 5% and 15%, a net reclassification improvement of 15.8% (P=3.1×10(-4)) was obtained, with a down-classification of risk in 24% of patients (211 of 862) in whom the pretest probability was 5% to 15% based on CRFs alone. CONCLUSIONS: Adding a PRS improved risk stratification of obstructive CAD beyond CRFs, suggesting a modest clinical potential of using PRSs to guide diagnostic testing in the contemporary clinical setting. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02264717.

[12] *Bourgeois R, Girard A, Perrot N et al.* **A Comparative Analysis of the Lipoprotein(a) and Low-Density Lipoprotein Proteomic Profiles Combining Mass Spectrometry and Mendelian Randomization**. CJC Open 2021; 3:450-459.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34027348
ABSTRACT
BACKGROUND: Lipoprotein(a) (Lp[a]), which consists of a low-density lipoprotein (LDL) bound to apolipoprotein(a), is one of the strongest genetic risk factors for atherosclerotic cardiovascular diseases. Few studies have performed hypothesis-free direct comparisons of the Lp(a) and the LDL proteomes. Our objectives were to compare the Lp(a) and the LDL proteomic profiles and to evaluate the effect of lifelong exposure to elevated Lp(a) or LDL cholesterol levels on the plasma proteomic profile. METHODS: We performed a label-free analysis of the Lp(a) and LDL proteomic profiles of healthy volunteers in a discovery (n = 6) and a replication (n = 9) phase. We performed inverse variance weighted Mendelian randomization to document the effect of lifelong exposure to elevated Lp(a) or LDL cholesterol levels on the plasma proteomic profile of participants of the INTERVAL study. RESULTS: We identified 15 proteins that were more abundant on Lp(a) compared with LDL (serping1, pi16, itih1, itih2, itih3, pon1, podxl, cd44, cp, ptprg, vtn, pcsk9, igfals, vcam1, and ttr). We found no proteins that were more abundant on LDL compared with Lp(a). After correction for multiple testing, lifelong exposure to elevated LDL cholesterol levels was associated with the variation of 18 plasma proteins whereas Lp(a) did not appear to influence the plasma proteome. CONCLUSIONS: Results of this study highlight marked differences in the proteome of Lp(a) and LDL as well as in the effect of lifelong exposure to elevated LDL cholesterol or Lp(a) on the plasma proteomic profile.

[13] *Marchand M, Chen V, Trinder M et al.* **Patient Perspectives Regarding Genetic Testing for Familial Hypercholesterolemia**. CJC Open 2021; 3:557-564.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34027362
ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH) is a common genetic disorder resulting in high levels of low-density lipoprotein cholesterol and increased risk of atherosclerotic cardiovascular disease. Genetic testing for FH is recommended but is not available in most of Canada. Consequently, there is a paucity of data regarding patient experiences with genetic testing. The objectives of this study were to investigate the attitudes and perspectives of patients with FH who underwent genetic testing. METHODS: We administered an anonymous online survey to participants in the British Columbia Familial Hypercholesterolemia Registry who had undergone research-based genetic testing for FH. The survey included 25 questions and explored patients' experiences with the genetic testing process, willingness to recommend genetic screening, and motivation to lower cholesterol levels. RESULTS: Among 183 respondents, 38 (20.7%) had a positive genetic test result, 27 (14.8%) had a negative result, and 118 (64.4%) were awaiting their results. Compared with individuals awaiting their test results, participants with a positive genetic test were more likely to believe lipid-lowering therapy was highly important (74.3% vs 55.4%; P = 0.05). They were also more likely to strongly agree that a diagnosis of FH was important to them (71.1% vs 46.2%; P = 0.008), and were more likely to recommend genetic screening to their family members (85.9% vs 72.9%; P = 0.04). CONCLUSIONS: To our knowledge, this is the first study in Canada to explore the perspectives of patients with FH who underwent genetic testing. These results suggest that genetic testing for FH might offer benefits in important patient-centred outcomes.

[14] *Seedat F, Patel M, Phillip V et al.* **Hyperlipidemic myeloma, a rare form of acquired dysbetalipoproteinemia, in an HIV seropositive African female**. Clinica chimica acta; international journal of clinical chemistry 2021; 520:71-75.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34052205
ABSTRACT
Dysbetalipoproteinemia (DBL) is an uncommon condition characterized by a mixed hyperlipidemia due to accumulation of remnant lipoproteins and is highly atherogenic. Typically, DBL is an autosomal recessive condition requiring an additional metabolic stress with reduced apolipoprotein E (apoE) function. However, DBL is also described in patients with multiple myeloma without the characteristic apoE2/E2 mutation seen in familial DBL. Although the underlying pathogenesis in these cases is not fully characterized, it is thought to occur due to interference with apoE function by antibodies produced from clonal plasma cells. Such cases are referred to as hyperlipidemic myeloma (HLM) and have rarely been described in the literature. To our knowledge there is no prior description of HLM in HIV positive patients in Africa. We describe a case of HLM in an African woman with underlying HIV infection who presented with phenotypic and biochemical features of DBL that responded poorly to lipid lowering therapy.

[15] *Domech CR, Travieso JCF, Guridi ZD et al.* **Comparative study of the effects of Abexol and atorvastatin in patients with non-alcoholic fatty liver disease**. Clin Exp Hepatol 2021; 7:55-65.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34027116
ABSTRACT
AIM OF THE STUDY: To investigate the efficacy and safety of Abexol and atorvastatin in patients with non-alcoholic fatty liver disease (NAFLD).Material and methods: The present study had a monocentric, randomized, double-blinded, comparative design with 4 parallel groups - group 1 (Abexol), group 2 (atorvastatin), group 3 (combined therapy) and group 4 (placebo) - to which dietary

recommendations and physical activity practice were provided twice a day, for 24 weeks. Significant changes in the ultrasound analysis of the liver were considered a primary efficacy variable. Insulin resistance improvement (HOMA2-IR) was considered as a co-primary efficacy criterion. Significant changes in the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), lipid profile variables and the anthropometric variables were evaluated as secondary variables of effectiveness. Statistical analysis of all data was according to the intention to treat method. RESULTS: The groups were statistically homogeneous at baseline conditions. At the end of the 6 months of treatment about 50% of the patients in all groups showed a decrease of at least one degree in echogenicity, while the rest remained the same. There were no significant changes in the values of liver enzymes or anthropometric variables evaluated. Treatment with atorvastatin and combined therapy significantly reduced levels of low-density lipoprotein-cholesterol (LDL-C) and total cholesterol. The treatments were safe and well tolerated, although in the atorvastatin group the number of adverse events reported was greater than in the rest of the groups. CONCLUSIONS: Abexol and atorvastatin showed comparable efficacy and safety in patients with NAFLD, with advantages for treatment with atorvastatin with respect to its effects on the lipid profile of these patients.

[16] *Ali MM, Gul S, Naqvi M et al.* **Utility of Coronary Artery Calcium Scores in Predicting Risk of Subclinical Cardiovascular Atherosclerotic Disease: An Analysis of Limitations to its Adoption With Policy Recommendations**. Cureus 2021; 13:e14647.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34046279
ABSTRACT
This survey-based analysis aims to highlight key limitations to a wider adoption of coronary artery calcium (CAC) scoring as a means of screening asymptomatic individuals for atherosclerotic cardiovascular disease. The need for a screening tool that adds objective anatomical information to historically established risk scores in the aforementioned population has been met by this imaging modality. Despite that, there has been a hesitance towards frequent usage of these scans. Within the pre-set sampling frame of the University of Toledo, a convenience sampling technique was used to reach out to 60 health care providers. The resultant responses were analyzed and discussed. In addition to identifying patients who need to be worked up further, CAC scans can also help re-stratify patients within-risk groups and inform decision-making regarding the use of lipid-lowering therapies. The public health impact of a greater but appropriate utilization of this diagnostic tool will be impactful. This analysis seeks to better understand real-life obstacles to a wider adoption of these scans and attempts to lay out policy recommendations to address these issues.

[17] *Ling P, Zheng X, Luo S et al.* **Targeting angiopoietin-like 3 in atherosclerosis: From bench to bedside**. Diabetes Obes Metab 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34047441
ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is the largest cause of morbidity and mortality worldwide. Lipid-lowering therapies are the current major cornerstone of ASCVD management. Statins, ezetimibe, fibrates and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors effectively reduce the plasma low-density lipoprotein cholesterol (LDL-C) level in most individuals at risk of atherosclerosis. Still, some patients (such as those with homozygous familial

hypercholesterolaemia), who do not respond to standard therapies, and other patients who cannot take these agents, remain at a high risk of ASCVD. In recent years there has been tremendous progress in understanding the mechanism and efficacy of lipid-lowering strategies. Apart from the recently approved PCSK9 and ATP citrate lyase inhibitors, angiopoietin-like 3 (ANGPTL3) is another potential target for the treatment of dyslipidaemia and its clinical sequalae of atherosclerosis. ANGPTL3 is a pivotal modulator of plasma triglycerides (TG), LDL-C and high-density lipoprotein cholesterol (HDL-C) levels, achieved by inhibiting the activities of lipoprotein lipase and endothelial lipase. Familial combined hypolipidaemia is derived from the Angptl3 loss-of-function mutations, which leads to low levels of LDL-C, HDL-C and TG, and has a 34% decreased risk of ASCVD compared with non-carriers. To date, monoclonal antibodies (evinacumab) and antisense oligonucleotides against ANGPTL3 have been investigated in clinical trials for dyslipidaemia therapy. Herein, we review the biology and function of ANGPTL3, as well as the latest developments of ANGPTL3-targeted therapies. We also summarize evidence from basic research to clinical trials, with the aim of providing novel insights into the biological functions of ANGPTL3 and related targeted therapies.

[18] *Alam U, Al-Bazz DY, Soran H*. **Bempedoic Acid: The New Kid on the Block for the Treatment of Dyslipidemia and LDL Cholesterol: A Narrative Review**. Diabetes Ther 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34037950

ABSTRACT

Diabetes is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) in which dyslipidaemia plays a crucial role. Statins are first line therapy for primary and secondary prevention of ASCVD; however, adverse events include reversible musculoskeletal and liver side effects in addition to a diabetogenic association. In this short review, we provide a succinct narrative of the future role and current trial data of a novel first-in-class molecule, bempedoic acid. The authors provide their expert insight with a focus on Phase III randomised controlled trials (RCT) of bempedoic acid. Bempedoic acid was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in February and March 2020, respectively, and is a novel molecule which inhibits cholesterol biosynthesis in the same mechanistic pathway as statins. It is a first-in-class small molecule, delivered as a prodrug and administered as an oral, once-daily dose that decreases low-density lipoprotein cholesterol (LDL-C) levels. Phase II and III RCTs have demonstrated efficacy with adequate safety data as mono- or combination therapy with statins and ezetimibe. Bempedoic acid is hepatically converted to the active drug with a lack of activation in skeletal muscle. Due to this novel mechanism, musculoskeletal-related adverse events exhibit a lower prevalence providing an alternative pharmacotherapy in statin-intolerant patients. Bempedoic acid may be used as an adjunct to diet and maximally tolerated statin therapy or in statin-intolerant patients for the treatment of dyslipidaemia. The recent National Institute of Health and Care Excellence (NICE) (UK) technology appraisal guidance [TA694] published in April 2021 recommended bempedoic acid with ezetimibe as a treatment option for primary hypercholesterolaemia or mixed dyslipidaemia if statins are not tolerated or contraindicated and if there is inadequate control of LDL-C with ezetimibe alone. Additionally, outcomes trials evaluating 'hard' endpoints in statin-intolerant patients or those with ASCVD are currently underway.

[19] *Filppula AM, Hirvensalo P, Parviainen H et al.* **Comparative hepatic and intestinal metabolism and pharmacodynamics of statins**. Drug metabolism and disposition: the biological fate of chemicals 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34045219
ABSTRACT
This study aimed to comprehensively investigate the in vitro metabolism of statins. The metabolism of clinically relevant concentrations of atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin and their metabolites were investigated using human liver microsomes (HLMs), intestine microsomes (HIMs), liver cytosol, and recombinant cytochrome P450 (CYP) enzymes. We also determined the inhibitory effects of statin acids on their pharmacological target, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. In HLMs, statin lactones were metabolized to a much higher extent than their acid forms. Atorvastatin lactone and simvastatin (lactone) showed extensive metabolism (intrinsic clearance (CL(int)) values of 3,700 and 7,400 μl/min/mg), while the metabolism of the lactones of 2-hydroxyatorvastatin, 4-hydroxyatorvastatin, and pitavastatin was slower (CL(int) 20-840 μl/min/mg). The acids had CL(int) values in the range <0.1-80 μl/min/mg. In HIMs, only atorvastatin lactone and simvastatin (lactone) exhibited notable metabolism, with CL(int) values corresponding to 20% of those observed in HLMs. CYP3A4/5 and CYP2C9 were the main statin-metabolizing enzymes. The majority of the acids inhibited HMG-CoA reductase with 50% inhibitory concentrations of 4-20 nM. The present comparison of the metabolism and pharmacodynamics of the various statins using identical methods provides a strong basis for further application, e.g., comparative systems pharmacology modelling. Significance Statement The present comparison of the in vitro metabolic and pharmacodynamic properties of atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin and their metabolites using unified methodology provides a strong basis for further application. Together with in vitro drug transporter and clinical data, our findings are applicable for use in comparative systems pharmacology modelling to predict the pharmacokinetics and pharmacological effects of statins at different dosages.

[20] *Zhang L, Liu Z, Liao S et al.* **Cardiovascular safety of long-term anti-obesity drugs in subjects with overweight or obesity: a systematic review and meta-analysis**. Eur J Clin Pharmacol 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34043049
ABSTRACT
PURPOSE: Anti-obesity therapy can reduce body weight; however, it is not clear whether it can reduce major adverse cardiovascular events (MACEs). We conducted a systematic review and meta-analysis to assess the effect of long-term anti-obesity drugs on MACEs in individuals with overweight or obesity. METHODS: The MEDLINE, Embase, and Cochrane Library databases and clinical trial registries (https://clinicaltrials.gov) were searched up to 3 May 2021 for randomized controlled trials (RCT) that compared anti-obesity drugs with controls and reported cardiovascular events in subjects with overweight or obesity. Heterogeneity was described by the I(2) value. The Mantel-Haenszel randomized effects model was adopted to calculate risk ratios (RR) and weighted mean differences (WMD). Sensitivity analysis was used to assess the stability of the effects. Publication bias was assessed by Begg's funnel plot and Egger's test. The Cochrane Collaboration risk-of-bias tool was used to evaluate the bias of each included RCT. RESULTS: Twelve articles were included; 21,391 and 17,618 subjects were in the anti-obesity drug and placebo groups, respectively. There was no

difference in MACEs between the anti-obesity drug and placebo groups (RR 0.99; 95% CI: 0.88-1.12). Compared with placebo, anti-obesity interventions reduced body weight (WMD: -3.96 kg; 95% CI: -4.89, -3.03) and improved lipid and blood glucose profiles. The intervention also did not increase the incidence of depression or anxiety or the risk of suicidal ideation. CONCLUSION: Long-term anti-obesity drugs did not show a benefit in lowering MACEs in overweight or obese subjects, although the drugs resulted in a decrease in body weight and improved cardiometabolic parameters.

[21] *Wang M, Li Y, Cong L et al.* **High-density lipoprotein cholesterol and brain aging among rural-dwelling older adults: a population-based MRI study**. European journal of neurology : the official journal of the European Federation of Neurological Societies 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34031948

ABSTRACT

BACKGROUND: Current evidence supports the involvement of lipids in brain aging. We explore a range of serum lipids in association with brain structure and cognitive function among rural-dwelling older adults. METHODS: This population-based cross-sectional study included 184 rural-dwelling adults (age ≥65 years, 39.1% women) in Shandong, China. In 2014-2016, we collected data on demographics, lifestyles, health conditions, and serum lipids. Volumes of gray matter, white matter, ventricle, hippocampus, and white matter hyperintensity were automatically estimated on brain MRI. Global cognitive function was assessed with the Mini-Mental State Examination (MMSE), and mild cognitive impairment (MCI) was defined according to the Petersen's criteria. Data were analyzed using the general linear regression, logistic regression, and mediation models. RESULTS: Of the 184 participants, 47 were defined with MCI. Low HDL-C (<1.55 vs. ≥1.55 mmol/L) was significantly associated with reduced volumes of total white matter (multi-adjusted β=-9.77, 95% CI: -19.48--0.06) and hippocampus (-0.23, -0.46--0.01), a lower MMSE score (-1.49, -2.67--0.31), and a higher likelihood of MCI (multi-adjusted odds ratio=3.21, 95% CI: 1.42-7.29). The mediation effects of structural brain measures on the associations between a low level of HDL-C and MMSE score or MCI were not statistically significant (P>0.05). CONCLUSIONS: This study suggests that low HDL-C may be involved in structural brain aging and cognitive dysfunction among rural-dwelling older adults in China, but the association of low HDL-C with cognitive aging phenotypes appears not to be mediated by brain structure.

[22] *Shi J, Li X, Zhang W et al.* **Circulating Proprotein Convertase Subtilisin/Kexin Type 9 Levels and Cardiometabolic Risk Factors: A Population-Based Cohort Study**. Frontiers in cardiovascular medicine 2021; 8:664583.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34041285

ABSTRACT

Aims: To evaluate the prospective association of circulating PCSK9 levels with the cardiometabolic risk profiles (high LDL-cholesterol, high triglycerides, low HDL-cholesterol, hypertension, type 2 diabetes, and metabolic syndrome). Methods: A population-based prospective study was conducted among 7,104 Chinese individuals (age 56.2 ± 7.5 years; 32.0% men). Circulating PCSK9 levels were measured using ELISA. Results: Circulating PCSK9 levels were higher in women than men (286.7 ± 90.1 vs. 276.1 ± 86.4 ng/ml, $p < 0.001$). And circulating PCSK9 was positively correlated with LDL-cholesterol, total cholesterol, and triglycerides both in men and women (all $p < 0.001$). The positive correlation between PCSK9 and waist circumference, fasting glucose, insulin resistance, systolic

blood pressure, diastolic blood pressure and C-reactive protein (all $p < 0.01$) was observed in women only. According to Cox regression analysis, circulating PCSK9 was positively associated with incidence of high LDL-cholesterol both in men (HR 1.33, 95% CI 1.09-1.65, $p < 0.001$) and women (HR 1.36, 95% CI 1.12-1.69, $p < 0.001$). Moreover, PCSK9 was significantly associated with incident high triglycerides (HR 1.31, 95% CI 1.13-1.72, $p < 0.001$), hypertension (HR 1.28, 95% CI 1.08-1.53, $p = 0.011$), type 2 diabetes (HR 1.34, 95% CI 1.09-1.76, $p = 0.005$), and metabolic syndrome (HR 1.30, 95% CI 1.11-1.65, $p = 0.009$) per SD change in women only. No statistically significant association was observed between circulating PCSK9 and incidence of low HDL-cholesterol ($p > 0.1$). Conclusions: Elevated circulating PCSK9 was significantly associated with cardiometabolic risk factors and independently contributed to the prediction of cardiometabolic risks in women.

[23] *Vuorio A, Ramaswami U, Holven KB*. **Editorial: Genetics of Familial Hypercholesterolemia: New Insight**. Frontiers in genetics 2021; 12:669373.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34025723
ABSTRACT

[24] *Lin P, Ji HH, Li YJ, Guo SD*. **Macrophage Plasticity and Atherosclerosis Therapy**. Front Mol Biosci 2021; 8:679797.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34026849
ABSTRACT
Atherosclerosis is a chronic disease starting with the entry of monocytes into the subendothelium and the subsequent differentiation into macrophages. Macrophages are the major immune cells in atherosclerotic plaques and are involved in the dynamic progression of atherosclerotic plaques. The biological properties of atherosclerotic plaque macrophages determine lesion size, composition, and stability. The heterogenicity and plasticity of atherosclerotic macrophages have been a hotspot in recent years. Studies demonstrated that lipids, cytokines, chemokines, and other molecules in the atherosclerotic plaque microenvironment regulate macrophage phenotype, contributing to the switch of macrophages toward a pro- or anti-atherosclerosis state. Of note, M1/M2 classification is oversimplified and only represent two extreme states of macrophages. Moreover, M2 macrophages in atherosclerosis are not always protective. Understanding the phenotypic diversity and functions of macrophages can disclose their roles in atherosclerotic plaques. Given that lipid-lowering therapy cannot completely retard the progression of atherosclerosis, macrophages with high heterogeneity and plasticity raise the hope for atherosclerosis regression. This review will focus on the macrophage phenotypic diversity, its role in the progression of the dynamic atherosclerotic plaque, and finally discuss the possibility of treating atherosclerosis by targeting macrophage microenvironment.

[25] *Ray CY, Wu VC, Wang CL et al.* **Hypoglycemia Associated With Drug-Drug Interactions in Patients With Type 2 Diabetes Mellitus Using Dipeptidylpeptidase-4 Inhibitors**. Frontiers in pharmacology 2021; 12:570835.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34040513
ABSTRACT
Background: Dipeptidylpeptidase-4 inhibitors (DPP-4i's) are considered to be safe for patients with type 2 diabetes mellitus (T2DM). However, little is known about drug-drug interactions between DPP-4i's and concurrent medications. Methods: Data on patients using DPP-4i's for T2DM during 2011-

2017 were retrieved from Chang Gung Research database provided by Chang Gung Memorial Hospital. Patients were excluded if they were aged <30 years or >90 years; had incomplete demographic data; had insulinoma; or had records of concomitant insulin use. A generalized estimating equation-based Poisson model was employed for statistical analysis. The primary outcome was hypoglycemia events. Results: We retrieved data on a total of 97,227 patients using DPP-4i's. After patients were excluded according to the mentioned criteria, the remaining 77,047 DPP-4i users were studied (mean age 64 ± 12 years, men 54.4%). The most common medications coprescribed with DPP4is over all person-quarters were acetaminophen, simvastatin, fluvastatin, and colchicine (all >20,000 person-quarters). The combinations of a DPP-4i with bumetanide, captopril, colchicine, acetaminophen, cotrimoxazole, and pantoprazole were associated with an increased risk of hypoglycemia. Compared with the ratios observed for person-quarters of DPP-4i use alone (reference category), the adjusted prevalence ratios per 100 person-years of hypoglycemia for person-quarters of DPP-4i use in combination with bumetanide, captopril, colchicine, acetaminophen, cotrimoxazole, and pantoprazole were 2.44 (95% confidence interval [CI], 1.78-3.36), 2.97 (95% CI, 2.26-3.90), 1.87 (95% CI, 1.44-2.42), 2.83 (95% CI, 2.44-3.29), 2.27 (95% CI, 1.27-4.04), and 3.03 (95% CI, 1.96-4.68), respectively. Conclusion: Among patients taking DPP-4i's for T2DM, concurrent use of such inhibitors with bumetanide, captopril, acetaminophen, and pantoprazole was associated with an increased risk of hypoglycemia compared with the use of DPP-4i's alone. Physicians prescribing DPP-4i's should consider the potential risks associated with their concomitant use with other drugs.

[26] *Sobrin L, Yu Y, Han S et al.* **Decreased risk of non-infectious anterior uveitis with statin therapy in a large healthcare claims database**. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34050812

ABSTRACT

PURPOSE: The purpose of this study is to determine if statin therapy decreases the incidence of non-infectious uveitis (NIU) using a retrospective cohort study. METHODS: Patients enrolled in a national insurance plan who initiated statin (n = 711,734, statin cohort) or other lipid-lowering therapy (n = 148,044, non-statin cohort) were observed for NIU development. Incident NIU in the primary analysis was defined as a new diagnosis code for NIU followed by a second instance of a NIU code within 120 days. For the secondary outcome definition, a corticosteroid prescription or code for an ocular corticosteroid injection within 120 days of the NIU diagnosis code was used instead of the second NIU diagnosis code. Estimation of NIU incidence used multivariable Cox proportional hazards regression. The proportional hazards assumption was satisfied by creating two time periods of analysis, ≤150 and >150 days. Subanalyses were performed by anatomic subtype. RESULTS: Overall, the primary outcome occurred 541 times over 690,465 person-years in the statin cohort and 103 times over 104,301 person-years in the non-statin cohort. No associations were seen in the ≤150-day analyses ($p > 0.20$ for all comparisons). However, after 150 days, the statin cohort was less likely to develop any uveitis [hazard ratio (HR) = 0.70, 95% confidence interval (CI): 0.51-0.97, P = 0.03] in the primary outcome analysis, but did not meet significance for the secondary outcome (HR = 0.85, 95% CI: 0.63-1.15, P = 0.30). Similarly, in the anatomic subtype analysis, after 150 days, the statin cohort was less likely to develop anterior uveitis (HR = 0.67, 95% CI: 0.47-0.97, P = 0.03) in the primary analysis, but the association did not reach significance for the secondary outcome

(HR = 0.82, 95% CI: 0.56-1.20, P = 0.31). CONCLUSION: Our results suggest that statin therapy for > 150 days decreases the incidence of NIU.

[27] *Nakayama A, Morita H, Kawahara T et al.* **Association between testosterone and lipid profiles under statin therapy and its clinical impact on the cardiovascular event risk**. Heart Vessels 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34036416
ABSTRACT
Statin therapy may decrease the levels of serum steroid hormones, including testosterone and cortisol, accompanied by lowering low-density lipoprotein cholesterol (LDL-C) levels, which remains to be investigated. The aim of this study is to examine the association between steroid hormones and lipids under statin therapy and its clinical impact on the cardiovascular event risk from a viewpoint of steroid hormone metabolism. Using a population dataset extracted from the standard versus intEnsive statin therapy for hyper-cholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) study, we analyzed the correlation between steroid hormones and lipid profiles at registration and 1 year after registration, comparing between male patients with or without cardiovascular events (CV events) within 4 years (CV events + ; n = 100, and CV events - ; n = 100, respectively) after prognostic score matching. The risk for CV events was evaluated using conditional logistic regression analysis. Testosterone levels were lower in the CV events + group than in the CV events - group at registration (5.2 ± 2.2 vs. 7.6 ± 4.1 ng/mL, p < 0.001). Testosterone levels were lowered to 5.1 ng/mL on average in proportion with LDL-C lowering, and Δtestosterone was correlated with ΔLDL-C during 1 year after registration. Cortisol levels were not correlated with LDL-C levels. In addition, testosterone levels at 1 year after registration were not associated with cardiovascular event risk. In male hypercholesterolemic patients with diabetic retinopathy, testosterone levels were positively correlated with LDL-C levels, which were mildly lowered in proportion with LDL-C lowering under mild statin therapy. This decrease in testosterone levels under statin therapy was not related to the increase in cardiovascular event risk.Clinical trial registration: UMIN 000003486. https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000004199.

[28] *Prasad K*. **AGE-RAGE Stress and Coronary Artery Disease**. Int J Angiol 2021; 30:4-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34025091
ABSTRACT
Coronary artery atherosclerosis and atherosclerotic plaque rupture cause coronary artery disease (CAD). Advanced glycation end products (AGE) and its cell receptor RAGE, and soluble receptor (sRAGE) and endogenous secretory RAGE (esRAGE) may be involved in the development of atherosclerosis. AGE and its interaction with RAGE are atherogenic, while sRAGE and esRAGE have antiatherogenic effects. AGE-RAGE stress is a ratio of AGE/sRAGE. A high AGE-RAGE stress results in development and progression of CAD and vice-versa. AGE levels in serum and skin, AGE/sRAGE in patients with CAD, and expression of RAGE in animal model of atherosclerosis were higher, while serum levels of esRAGE were lower in patients with CAD compared with controls. Serum levels of sRAGE in CAD patients were contradictory, increased or decreased. This contradictory data may be due to type of patients used, because the sRAGE levels are elevated in diabetics and end-stage renal disease. AGE/sRAGE ratio is elevated in patients with reduced or elevated levels of serum sRAGE. It is to stress that AGE, RAGE, sRAGE, or esRAGE individually

cannot serve as universal biomarker. AGE and sRAGE should be measured simultaneously to assess the AGE-RAGE stress. The treatment of CAD should be targeted at reduction in AGE levels, prevention of AGE formation, degradation of AGE in vivo, suppression of RAGE expression, blockade of RAGE, elevation of sRAGE, and use of antioxidants. In conclusion, AGE-RAGE stress would initiate the development and progression of atherosclerosis. Treatment modalities would prevent, regress, and slow the progression of CAD.

[29] *Santoso A, Yulianto Y, Simarmata H et al.* **Effect of PCSK9 E670G and R46L Polymorphisms on Major Adverse Cardio-Cerebrovascular Events in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention**. Int J Angiol 2021; 30:22-28.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34025093
ABSTRACT
Major adverse cardio-cerebrovascular events (MACCE) in ST-segment elevation myocardial infarction (STEMI) are still high, although there have been advances in pharmacology and interventional procedures. Proprotein convertase subtilisin/Kexin type 9 (PCSK9) is a serine protease regulating lipid metabolism associated with inflammation in acute coronary syndrome. The MACCE is possibly related to polymorphisms in PCSK9 . A prospective cohort observational study was designed to confirm the association between polymorphism of E670G and R46L in the PCSK9 gene with MACCE in STEMI. The Cox proportional hazards model and Spearman correlation were utilized in the study. The Genotyping of PCSK9 and ELISA was assayed. Sixty-five of 423 STEMI patients experienced MACCE in 6 months. The E670G polymorphism in PCSK9 was associated with MACCE (hazard ratio = 45.40; 95% confidence interval: 5.30-390.30; p = 0.00). There was a significant difference of PCSK9 plasma levels in patients with previous statin consumption (310 [220-1,220] pg/mL) versus those free of any statins (280 [190-1,520] pg/mL) (p = 0.001). E670G polymorphism of PCSK9 was associated with MACCE in STEMI within a 6-month follow-up. The plasma PCSK9 level was higher in statin users.

[30] *Hitchen SA, Lan NSR, Ali US et al.* **Investigating the effect of an education program on diabetes and lipid lowering medication usage following coronary artery bypass graft surgery**. Internal medicine journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34033208
ABSTRACT
BACKGROUND: Guidelines advocate multifactorial cardiovascular risk management in patients with diabetes and atherosclerotic cardiovascular disease. In hospitalised patients with diabetes following coronary artery bypass graft (CABG) we evaluated the impacts of decision-support algorithms for optimising glycaemia and lipid-lowering. We also assessed the safety of initiating sodium-glucose cotransporter 2 (SGLT2) inhibitors near time of hospital discharge. METHODS: This was a single-site, pre- and post-intervention analysis of glucose and lipid management in consecutive hospitalised patients with diabetes undergoing CABG surgery. The intervention involved education and decision-support algorithms designed by a multidisciplinary committee to guide cardiac surgery unit clinicians. RESULTS: A total of 200 patients were included in the study. The pre- and post-intervention groups had similar baseline characteristics (HbA1c 7.9 ±1.9% versus 8.1 ±1.8%). Of 4092 blood glucose measurements the incidence of levels between 5 to 10 mmol/L was not different post-intervention

(55.5% versus 57.0%, p = 0.441). Fewer endocrinology consultations occurred (59.0% versus 45.0%, p = 0.048) and rates of hypoglycaemia remained low. High-intensity statin was prescribed in >90% pre- and post-intervention although non-statin lipid-lowering agents remained <10% despite patients not achieving LDL-C targets. No 30-day readmissions for diabetic ketoacidosis occurred in patients prescribed SGLT2 inhibitors. CONCLUSION: The intervention did not improve inpatient glycaemia or increase non-statin lipid-lowering prescriptions in patients with diabetes following CABG surgery but did reduce reliance on specialty input. Initiation of SGLT2 inhibitor therapy near time of hospital discharge was not associated with safety concerns. Alternative interventions or strategies are required to optimise glycaemia and non-statin lipid-lowering therapy prescribing in this setting.

[31] *Watts GF, Sullivan DR, Hare DL et al.* **Essentials of a new clinical practice guidance on familial hypercholesterolaemia for physicians**. Internal medicine journal 2021; 51:769-779.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34047032
ABSTRACT
Familial hypercholesterolaemia (FH) is a common, heritable and preventable cause of premature coronary artery disease. New clinical practice recommendations are presented to assist practitioners in enhancing the care of all patients with FH. Core recommendations are made on the detection, diagnosis, assessment and management of adults, children and adolescents with FH. Management is under-pinned by the precepts of risk stratification, adherence to healthy lifestyles, treatment of non-cholesterol risk factors and appropriate use of low-density lipoprotein (LDL)-cholesterol-lowering therapies including statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The recommendations need to be utilised using judicious clinical judgement and shared decision-making with patients and families. New government-funded schemes for genetic testing and use of PCSK9 inhibitors, as well as the National Health Genomics Policy Framework, will enable adoption of the recommendations. However, a comprehensive implementation science and practice strategy is required to ensure that the guidance translates into benefit for all families with FH.

[32] *Saadatagah S, Pasha AK, Alhalabi L et al.* **Coronary Heart Disease Risk Associated with Primary Isolated Hypertriglyceridemia; a Population-Based Study**. Journal of the American Heart Association 2021; 10:e019343.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34032140
ABSTRACT
Background Hypertriglyceridemia is associated with increased risk of coronary heart disease but the association is often attributed to concomitant metabolic abnormalities. We investigated the epidemiology of primary isolated hypertriglyceridemia (PIH) and associated cardiovascular risk in a population-based setting. Methods and Results We identified adults with at least one triglyceride level ≥500 mg/dL between 1998 and 2015 in Olmsted County, Minnesota. We also identified age- and sex-matched controls with triglyceride levels <150 mg/dL. There were 3329 individuals with elevated triglyceride levels; after excluding those with concomitant hypercholesterolemia, a secondary cause of high triglycerides, age <18 years or an incomplete record, 517 patients (49.4±14.0 years, 72.0% men) had PIH (triglyceride 627.6±183.6 mg/dL). The age- and sex-adjusted prevalence of PIH in adults was 0.80% (0.72-0.87); the diagnosis was recorded in 60%, 46% were on a lipid-lowering medication for primary prevention and a triglyceride level <150 mg/dL was achieved in 24.1%. The

association of PIH with coronary heart disease was attenuated but remained significant after adjustment for demographic, socioeconomic, and conventional cardiovascular risk factors (hazard ratio [HR], 1.53; 95% CI, 1.06-2.20; P= 0.022). There was no statistically significant association between PIH and cerebrovascular disease (HR, 1.06; 95% CI, 0.65-1.73, P= 0.813), peripheral artery disease (HR, 1.27; 95% CI, 0.43-3.75; P= 0.668), or the composite end point of all 3 (HR, 1.28; 95% CI, 0.92-1.80; P=0.148) in adjusted models. Conclusions PIH was associated with incident coronary heart disease events (although there was attenuation after adjustment for conventional risk factors), supporting a causal role for triglycerides in coronary heart disease. The condition is relatively prevalent but awareness and control are low.

[33] *Amor F, Vu Hong A, Corre G et al.* **Cholesterol metabolism is a potential therapeutic target in Duchenne muscular dystrophy**. Journal of cachexia, sarcopenia and muscle 2021; 12:677-693.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34037326

ABSTRACT

BACKGROUND: Duchenne muscular dystrophy (DMD) is a lethal muscle disease detected in approximately 1:5000 male births. DMD is caused by mutations in the DMD gene, encoding a critical protein that links the cytoskeleton and the extracellular matrix in skeletal and cardiac muscles. The primary consequence of the disrupted link between the extracellular matrix and the myofibre actin cytoskeleton is thought to involve sarcolemma destabilization, perturbation of Ca(2+) homeostasis, activation of proteases, mitochondrial damage, and tissue degeneration. A recently emphasized secondary aspect of the dystrophic process is a progressive metabolic change of the dystrophic tissue; however, the mechanism and nature of the metabolic dysregulation are yet poorly understood. In this study, we characterized a molecular mechanism of metabolic perturbation in DMD. METHODS: We sequenced plasma miRNA in a DMD cohort, comprising 54 DMD patients treated or not by glucocorticoid, compared with 27 healthy controls, in three groups of the ages of 4-8, 8-12, and 12-20 years. We developed an original approach for the biological interpretation of miRNA dysregulation and produced a novel hypothesis concerning metabolic perturbation in DMD. We used the mdx mouse model for DMD for the investigation of this hypothesis. RESULTS: We identified 96 dysregulated miRNAs (adjusted P-value <0.1), of which 74 were up-regulated and 22 were down-regulated in DMD. We confirmed the dysregulation in DMD of Dystro-miRs, Cardio-miRs, and a large number of the DLK1-DIO3 miRNAs. We also identified numerous dysregulated miRNAs yet unreported in DMD. Bioinformatics analysis of both target and host genes for dysregulated miRNAs predicted that lipid metabolism might be a critical metabolic perturbation in DMD. Investigation of skeletal muscles of the mdx mouse uncovered dysregulation of transcription factors of cholesterol and fatty acid metabolism (SREBP-1 and SREBP-2), perturbation of the mevalonate pathway, and the accumulation of cholesterol in the dystrophic muscles. Elevated cholesterol level was also found in muscle biopsies of DMD patients. Treatment of mdx mice with Simvastatin, a cholesterol-reducing agent, normalized these perturbations and partially restored the dystrophic parameters. CONCLUSIONS: This investigation supports that cholesterol metabolism and the mevalonate pathway are potential therapeutic targets in DMD.

[34] *Zhang DM, Chen SL*. **Potential mechanisms of in-stent neointimal atherosclerotic plaque formation**. Journal of cardiovascular pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34029271

ABSTRACT
Percutaneous coronary intervention has become the main revascularization strategy for coronary artery disease. Compared with early percutaneous coronary angioplasty and the extensive clinical application of bare metal stents, drug-eluting stents can significantly reduce the stenosis caused by the elastic retraction of plaque and neoatherosclerosis (NA), but there is still a high incidence of in-stent restenosis (ISR), which restricts the clinical efficacy of stent implantation. In-stent neoatherosclerosis (ISNA), defined as atherosclerotic lesions in the neointima, is one of the main causes of late stent failure. ISNA plays an important role in stent thrombosis and ISR. The rate of target lesion revascularization and in-stent thrombosis is high when NA arises. Therefore, it is of great clinical significance to explore the occurrence of NA and its development mechanism after stent implantation to prevent ISR and improve stent implantation efficacy and associated clinical prognosis. In this paper, we systematically reviewed the existing clinical research on ISNA and the role of optical coherence tomography in its evaluation.

[35] *Alonso R, Muñiz-Grijalvo O, Díaz-Díaz JL et al.* **Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34052174

ABSTRACT
BACKGROUND: PCSK9 inhibitors are a treatment option for patients with familial hypercholesterolemia not on low-density lipoprotein cholesterol goals despite the use of maximally tolerated high intensity-statins dose. OBJECTIVE: To evaluate the efficacy of alirocumab and evolocumab in LDL-C reduction and targets attainment in patients with heterozygous familial hypercholesterolemia in clinical practice setting. METHODS: SAFEHEART is an open, long-term prospective study of a cohort of subjects with molecular diagnosis of familial hypercholesterolemia. This study analyze subjects ≥ 20 years of age on stable lipid-lowering therapy, who received PCSK9 inhibitors during the period 2016 to January 2020. RESULTS: 433 patients (mean age 55 years, 53% male, 39% with cardiovascular disease) were included and followed-up for a median of 2.5 years (IQR 1.6-3.0). Median LDL-C level prior to PCSK9 inhibitors was 145 mg/dL (IQR 125-173). The addition of PCSK9 inhibitors (211 alirocumab, 222 evolocumab) reduced LDL-C by 58% (IQR 41-70) $p<0.001$, in men and women, achieving a median LDL-C level of 62 mg/dL (IQR 44-87) without differences between both PCSK9 inhibitors. Out of them 67% with and 80% without cardiovascular disease reached 2016 ESC/EAS LDL-C targets, and 46% very high risk and 50% high risk patients achieved 2019 ESC/EAS LDL-C goals. Independent predictor factors for attainment of 2019 ESC/EAS LDL-C goals were to be male, smoking and the use of statins with ezetimibe. Both inhibitors were well tolerated. CONCLUSIONS: PCSK9 inhibitors on top of maximum lipid-lowering treatment significantly reduced LDL-C levels in patients with familial hypercholesterolemia and improved the achievement of LDL-C targets.

[36] *Huang L, Wu H, Wu Y et al.* **Pcsk9 Knockout Aggravated Experimental Apical Periodontitis via LDLR**. Journal of dental research 2021:220345211015128.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34036816

ABSTRACT

Apical periodontitis (AP), an inflammatory lesion around the apex of tooth roots, is mostly caused by dental pulp infection. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a vital role in regulating cholesterol homeostasis by targeting low-density lipoprotein receptor (LDLR) and participates in bacterium-induced chronic periodontitis. However, the roles of PCSK9 in AP are unknown. Here, we investigated its role in AP by using Pcsk9(-/-) mice. Micro-computed tomography scanning and histological staining revealed that the periapical bone loss of Pcsk9(-/-) mice was greater than that of wild-type (WT) mice, and increased expression of inflammation-related factors tumor necrosis factor α (TNF-α) and interleukin (IL)-6 was also observed. Immunofluorescence staining and quantitative real-time polymerase chain reaction showed PCSK9 expression in bone marrow macrophages (BMMs) was increased after treatment with lipopolysaccharide (LPS). This finding was consistent with the in vivo results that the expression level of PCSK9 in exposed WT mice increased compared with that in unexposed WT mice. After LPS challenge, the expression levels of TNF-α, IL-1β, and IL-6 in BMMs were increased, and Pcsk9 knockout aggravated the expression of these inflammatory factors. The number of osteoclasts positive for tartrate-resistant acid phosphatase staining around the apical lesion in Pcsk9(-/-) mice was higher than that in WT mice. Then BMMs underwent the osteoclast differentiation. Pcsk9 knockout BMMs induced increased and larger osteoclasts. While this effect of Pcsk9 knockout was abolished by the addition of Ldlr small interfering RNA, revealing that Pcsk9 knockout increased osteoclastogenesis was dependent on the LDLR. Immunohistochemistry staining showed increased expression level of LDLR in exposed Pcsk9(-/-) periapical areas. In vitro experiments showed that LPS promoted the expression level of LDLR in Pcsk9(-/-) BMMs and increased osteoclast formation ability, indicating that LPS promoted the elevation of osteoclasteogenesis caused by the Pcsk9 knockout. In conclusion, Pcsk9 deficiency aggravated the inflammatory response and promoted the osteoclastogenesis in an LDLR-dependent manner in AP experimental mice.

[37] *Chahal J, Gupta S, Chawla SPS, Grewal H*. **Comparative study on fasting and postprandial lipid profile in type 2 diabetes mellitus**. Journal of family medicine and primary care 2021; 10:1288-1293.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34041167

ABSTRACT

CONTEXT: Postprandial dyslipidemia plays a vital role in the pathogenesis of atherosclerosis and possible macrovascular complications in type 2 diabetes mellitus (DM). AIMS: To assess and compare the fasting and postprandial lipid profiles in type 2 DM patients. SETTINGS AND DESIGN: This case-control study was conducted in the Medicine department of a tertiary care teaching hospital. METHODS AND MATERIALS: The study included 100 subjects; 50 type 2 diabetic patients and 50 healthy age- and gender-matched controls. Fasting and postprandial lipid levels were estimated in all the subjects and compared. STATISTICAL ANALYSIS USED: The Student's t-test and the analysis of variance (ANOVA) test were used for comparison between two and more than two groups, respectively, for normally distributed data. RESULTS: Mean total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) levels were significantly higher and high density lipoprotein (HDL) level was significantly lower in the diabetics in comparison to the controls in both fasting (200.82, 172.59, 126.20, 37.63, and 40.74 mg/dL in diabetics versus 179.90, 98.03, 109.54, 19.60, and 50.46 mg/dL in controls) and postprandial states (223.75, 232.99, 139.19, 46.52, and 40.54 mg/dL in diabetics versus 185.36, 102.20, 110.36, 20.24, and 48.96 mg/dL

in controls). The mean postprandial TC and TG levels (223.75, 232.99 mg/dL) in diabetics were significantly higher when compared to their fasting values (200.82, 172.59 mg/dL) in these patients. CONCLUSIONS: Type 2 DM patients show significant postprandial lipid abnormalities particularly postprandial hypertriglyceridemia. Raised postprandial lipid parameters highlight that estimating lipids in the postprandial state is equally important as is estimation of lipids in the fasting state in type 2 DM.

[38] *Landzberg D, Nogueira RG, Al-Bayati AR et al.* **Baseline Characteristics of Patients with Symptomatic Carotid Webs: A Matched Case Control Study**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2021; 30:105823.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34034127

ABSTRACT

BACKGROUND AND PURPOSE: The baseline characteristics of patients with symptomatic carotid web (CaW) are unclear. We investigate demographic and cerebrovascular risk factors in patients with this overlooked stroke etiology. METHODS: We identified consecutive patients diagnosed with symptomatic CaW at a comprehensive stroke center from July 2014-December 2018. These patients were matched at a 1:4 ratio (based on age and NIHSS scores) to create a control group of acute ischemic stroke (AIS) patients with non-CaW etiologies from the local GetWithTheGuidelines stroke database. RESULTS: Thirty patients with symptomatic CaW were compared to 120 AIS patients with non-CaW etiologies. Symptomatic CaW patients were more likely to be female (73.3 vs. 44.2%; p = 0.004) and black (86.7 vs. 64.2%; p = 0.02). Symptomatic CaWs patients had a fewer absolute number of modifiable cerebrovascular risk factors (1.7±1.1 vs. 2.5±1.2; p = 0.002), lower rates of hypertension (43.4 vs. 63.3%; p = 0.04), and a more favorable lipid profile with lower average LDL (89.5±30.3 vs. 111.2±43.7 mg/dL; p = 0.01) and higher average HDL (47.9±11.3 vs. 42.2±13.8 mg/dL; p = 0.01) as compared to strokes with non-CaW etiology. Symptomatic CaW patients were more likely to have a large vessel occlusion (80.0 vs. 51.7%; p = 0.005), despite similar e-ASPECTS between the groups (8.1±2.1 vs. 8.3±2.2; p = 0.30). On multivariable analysis, symptomatic CaW was an independent predictor of independence at discharge (OR 3.72; 95%CI 1.27-10.94). CONCLUSION: A gender and racial predilection of symptomatic CaWs may exist as females and blacks were were found to be more likely affected. Symptomatic CaW patients have a more benign cerebrovascular risk factor profile corroborating the proposed mechanism of local stasis and thromboembolism. Despite presenting more commonly with LVO, symptomatic CaW was associated with good functional outcome, warranting further studies.

[39] *Gao J, Yang YN, Cui Z et al.* **Pcsk9 is associated with severity of coronary artery lesions in male patients with premature myocardial infarction**. Lipids in health and disease 2021; 20:56.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34044829

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (Pcsk9) correlated with incidence and prognosis of coronary heart disease. However, it is unclear whether Pcsk9 contributed to coronary artery lesion severity in patients with premature myocardial infarction (PMI). The present study investigated associations between Pcsk9 and coronary artery lesion severity in PMI patients who underwent coronary angiography (CAG). METHODS: This prospective cohort study included young men (age ≤ 45 years, n = 332) with acute MI who underwent CAG between January 2017 and July 2019. Serum Pcsk9 levels and clinical characteristics were evaluated. SYNTAX scores (SYNergy

between percutaneous coronary intervention with [paclitaxel-eluting] TAXUS stent and cardiac surgery) were calculated to quantify coronary artery lesions. RESULTS: Serum Pcsk9 levels were positively associated with SYNTAX scores (r = 0.173, P < 0.05). The diagnostic cutoff value of PSCK9 level was 122.9 ng/mL, yielding an area under the curve (AUC) of 0.63, sensitivity 81%, and specificity 40%. Serum Pcsk9, LDL-C, Apob, NT-proBnp, CK level, and diabetes history were independent predictors of high SYNTAX scores (P < 0.05). After stratifying by serum LDL-C level (cutoff = 2.6 mmol/L), medium-high Pcsk9 levels had increased risk of high SYNTAX scores in patients with high LDL-C (P < 0.05), and higher serum Pcsk9 levels had increased risk of major adverse cardiac events (MACE) after adjusting for confounding factors (P < 0.05). CONCLUSION: Serum Pcsk9 levels correlates with severity of coronary artery lesion in PMI patients and may serve as a biomarker for severity of coronary artery stenosis in this patient population, which may contribute to risk stratification.

[40] *Huang Q, Wang WT, Wang SS et al.* **Cardiovascular magnetic resonance image analysis and mechanism study for the changes after treatments for primary microvascular angina pectoris**. Medicine (Baltimore) 2021; 100:e26038.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34032727

ABSTRACT

ABSTRACT: Most cases of primary microvascular angina pectoris (PMVA) are diagnosed clinically, but the etiology and pathological mechanisms are unknown. The effect of routine clinical medications is minimal, and PMVA can progress to serious cardiovascular events. To improve the diagnosis and effective treatment of this disease, this study was designed to diagnose PMVA via cardiovascular magnetic resonance (CMR) and the coronary angiography thrombolysis in myocardial infarction (TIMI) blood flow grade, as well as to analyze vascular endothelial function to elucidate the pathogenesis of PMVA and compare the effects of routine clinical medications.The present randomized controlled trial including a parallel control group will be conducted on 63 PMVA patients in our cardiovascular department. The patients will be selected and randomly divided into the control, diltiazem, and nicorandil groups. The control group will be administered routine drug treatments (aspirin, atorvastatin, betaloc ZOK, perindopril, and isosorbidemononitrate sustained-release tablets). The diltiazem group will be additionally treated with 90 mg qd diltiazem sustained-release capsules. The nicorandil group was additionally given 5 mg tid nicorandil tablets. Coronary angiography will be performed before treatment, the severity and frequency of chest pain will be evaluated before and after 9 months of treatment, and homocysteine and von Willebrand factor levels will be measured. Electrocardiography, echocardiography, dynamic electrocardiography, a treadmill exercise test, and CMR will be performed. Sex, age, body mass index, complications, smoking, and family history will also be recorded. The SPSS19.0 statistical software package will be used to analyze the data. The measurements will be expressed as the mean±standard deviation. Measurement data will be compared between the groups using Student's t-test. A relative number description will be used for the counting data, and the chi-squaretest will be used to compare the groups. A multivariate logistic regression analysis will be performed A P-value<.05 will be considered significant.The direct indices (CMR and coronary angiographic TIMI blood flow grade) may improve after adding diltiazem or nicorandil during routine drug treatments (such as aspirin, statins, and nitrates) in PMVA patients, and indirect indices (homocysteine and von Willebrand factor levels) may be reduced. TRIAL REGISTRATION: Chinese Clinical Trial Registry

(http://www.chictr.org.cn/showprojen.aspx?proj=41894), No. CHiCTR1900025319, Registered on August 23, 2019; pre initiation.

[41] *Thong VD, Mong Trinh NT, Phat HT*. **Factors associated with the severity of hypertriglyceridemia induced acute pancreatitis**. Medicine (Baltimore) 2021; 100:e25983.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34032712

ABSTRACT

Hypertriglyceridemia induced acute pancreatitis (HTGP) was associated with increased risk of local complications, recurrent acute pancreatitis (AP), the frequency of other complications, and its high mortality as compared to other causes. Determining the factors associated with the severity of HTGP was necessary and important in the management of patients with AP.This study aims to examine the clinical and biochemical characteristics of HTGP patients, and to determine the factors associated with the severity of HTGP according to the revised Atlanta classification.This retrospective and prospective study enrolled 157 HTGP patients from January 2016 to May 2019 at Cho Ray Hospital who had serum TG levels measured within the first 48 hours of admittance with a TG concentration ≥1000 mg/dL and excluded other causes. The clinical features and outcomes of patients with HTGP were determined in terms of demographics, clinical symptoms, laboratory data, system complications, local complications, disease severity, and length of hospital stay. The primary outcome was the severity of HTGP as based according to the revised Atlanta classification. We evaluated the relationship between general information, clinical factors and laboratory data in the study population.There were 157 HTGP patients participated in this study. Patients with HTGP had evidence of obese or overweight range (61.2%), history of diabetes mellitus (32.5%) or undiagnosed diabetes (28.0%), history of AP (35.7%), alcohol use (23.6%), hypertension (15.9%), dyslipidemia (13.4%). The patients had typical symptoms of AP, including pancreatic abdominal pain (upper abdominal pain) (93%), nausea/vomiting (80.9%), fever (59.2%), distension abdomen (84.7%), and resistance of abdominal wall (24.8%). The severity of HTGP was significantly associated with fever, altered mental status, rapid pulse, and hypotension ($P<.05$). Patients with severe HTGP had significantly more pancreatic necrosis, higher values of Blood urea nitrogen and creatinine, longer prothrombin time and activated partial thromboplastin time on admission and higher CRP48 than not severe HTGP ($P<.05$).The severity of HTGP was significantly related to clinical factors including fever, altered mental status, rapid pulse, hypotension, and pancreatic necrosis. The value of Blood urea nitrogen, creatinine, prothrombin time, and activated partial thromboplastin time at admission is higher and longer in the severe AP group with $P<.05$.

[42] *Ding HS, Yang J, Yang J et al.* **Fluvastatin attenuated ischemia/reperfusion-induced autophagy and apoptosis in cardiomyocytes through down-regulation HMGB1/TLR4 signaling pathway**. Molecular biology reports 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34032975

ABSTRACT

Fluvastatin, a traditional fat-decreasing drug, is widely used for curing cardiovascular disease. Previous reports demonstrated that fluvastatin pretreatment protected against myocardial ischemia/reperfusion (I/R) by inhibiting TLR4 signaling pathway and/or reducing proinflammatory cytokines. However, whether fluvastatin has a cardioprotective effect against apoptosis and autophagy remains unknown. This study aims to evaluate whether the cardioprotective role of

fluvastatin in I/R is mediated by high-mobility group box 1 (HMGB1)/toll-like receptor 4 (TLR4) pathway via anti-apoptotic and anti-autophagic functions. Sprague-Dawley rats were anesthetized, artificially ventilated and subjected to 30 min of coronary occlusion, followed by 4 h of reperfusion. The animals were randomized into four groups: (i) Sham operation; (ii) I/R; (iii) I/R + low-dosage fluvastatin (10 mg/kg); and (iv) I/R + high-dosage fluvastatin (20 mg/kg). After reperfusion, the hemodynamic parameters, myocardial infarct size, structural alteration of myocardium, apoptosis index, pro-inflammatory cytokine production, Beclin-1, Light chain 3 (LC3), HMGB1, TLR4 and Nuclear factor kappa B (NF-κB) protein levels were measured and recorded. It was found that fluvastatin preconditioning improved left ventricular dysfunction, reduced HMGB1/TLR4/NF-κB expressions, and inhibited cardiomyocyte apoptosis, autophagy, and inflammation reaction. Moreover, treatment with fluvastatin ameliorated myocardial injury by reducing infarct size, causing less damage to cardiac structure, downregulating autophagy-related protein expression and releasing pro-inflammation mediators. Our findings indicate that fluvastatin exerts beneficial effects on cardiac ischemic damage, which may be associated with its anti-autophagic and anti-apoptotic functions via inhibition of HMGB1/TLR4-related pathway during I/R injury.

[43] *Kingwell K*. **Pushing the envelope with PCSK9**. Nature reviews. Drug discovery 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34035481
ABSTRACT

[44] *Yoshida K, Uwano I, Sasaki M et al.* **Small Unruptured Aneurysm Verification-prevention Effect against Growth of Cerebral Aneurysm Study Using Statin**. Neurologia medico-chirurgica 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34024878
ABSTRACT
Several basic experimental studies have demonstrated that statins have beneficial effects for intracranial aneurysm (IA). Clinical studies on unruptured IAs, however, remain limited to four retrospective studies that have reached different conclusions. This study was the first open-label, multicenter, randomized controlled trial to assess the preventive effects of atorvastatin. Patients with unruptured small saccular IAs were randomly assigned to statin and control groups. The primary endpoint was a composite of aneurysm growth of ≥0.5 mm, new bleb formation confirmed from magnetic resonance (MR) angiography, and rupture. Enrollment was prematurely terminated due to unexpectedly slow enrollment. Of 231 patients (275 target IAs), 110 patients (128 IAs) were randomly assigned to the statin group and 121 patients (147 IAs) to the control group. After excluding 22 dropout patients, 107 IAs in the 93 statin group patients and 140 IAs in the 116 control group patients were finally analyzed. No significant differences of basic characteristics were evident between groups, except for significantly higher systolic pressure in the statin group (P = 0.03). The primary endpoint occurred in 28 IAs (20.0%) in the control group and in 17 IAs (15.9%) in the statin group. No aneurysm rupture was confirmed in either group. Significant beneficial effects of statin for IAs were not demonstrated for the primary endpoint (log-rank P = 0.359). This randomized trial did not establish any preventive effects of atorvastatin for unruptured small IAs. Further studies of larger cohorts are required to clarify the efficacy of statins for patients with unruptured IAs. Clinical trial registration: UMIN000005135.

[45] *Ortega-Ramírez AD, Cabrera-Macedo A, Del Toro-Equihua M, Sánchez-Ramírez CA*. **Vitamin D and its correlation with blood lipids and intima-media thickness in term infants**. Nutricion hospitalaria 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34024110

ABSTRACT
BACKGROUND: an association between low 25(OH)D levels and blood lipids has been identified in children, adolescents, and adults but not in the early stages of life, and a relation to carotid and aortic intima-media thickness has not been well studied and is controversial. OBJECTIVE: to identify whether 25(OH)D levels are correlated with blood lipids and aortic and carotid intima-media thickness in infants aged 3 to 9 months. METHODS: a cross-sectional study was conducted in 109 healthy term infants between the ages of 3 and 9 months. Serum vitamin D [25(OH)D], total cholesterol, HDL-cholesterol, non-HDL-cholesterol, and aortic and carotid intima media thickness were measured. Feeding method, vitamin D supplementation, and sun exposure habits were recorded. RESULTS: only 2.8 % (n = 3) and 10.1 % (n = 14) had vitamin D deficiency and insufficiency, respectively. Infants with inadequate levels of vitamin D were younger (< 6 months) (p = 0.004), and a lower percentage of their body surface areas was exposed to the sun (p = 0.006). A significant positive correlation was found between 25(OH)D levels and non-HDL-cholesterol in the infants that consumed breastmilk substitutes (rho = 0.600, p ≤ 0.001) or were partially breastfed (rho = 0.371, p = 0.026), whereas a positive correlation was found with total cholesterol in the infants receiving breastmilk substitutes (rho = 0.618, p ≤ 0.001). No significant correlation was found between vitamin D and aortic or carotid intima-media thickness. CONCLUSIONS: there was a positive correlation between 25(OH)D levels and both total and non-HDL-cholesterol only in infants receiving breastmilk substitutes. The frequency of vitamin D deficiency and insufficiency was low.

[46] *Antoniazzi L, Arroyo-Olivares R, Bittencourt MS et al.* **Adherence to a Mediterranean diet, dyslipidemia and inflammation in familial hypercholesterolemia**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34039501

ABSTRACT
BACKGROUND AND AIMS: Familial Hypercholesterolemia (FH) is characterized by elevated LDL-cholesterol (LDL-C) and high atherosclerosis risk. The impact of different dietary patterns on atherosclerosis biomarkers has been poorly studied in FH. This study verified the association of adherence to a Mediterranean diet with biomarkers of dyslipidemia and low-grade inflammation in molecularly proven FH adults from Brazil (BR) and Spain (SP). METHODS AND RESULTS: In this cross-sectional study adherence to the Mediterranean diet was assessed by a validated score and generalized estimating equations were used to evaluate its association with plasma LDL-C, apolipoprotein-B (ApoB) and high sensitivity C-reactive protein (hs-CRP) concentrations. We included 92 (mean age 45 years, 58.7% females) and 98 FH individuals (mean age 46.8 years, 60.2% females) respectively from BR and SP. FH causing variants did not differ between countries. LDL-C, ApoB and hs-CRP concentrations were higher in BR than in SP: 179 (135-250) and 161 (133-193) mg/dL; 141 (109-181) and 103 (88-134) mg/dL; and 1.6 (0.8-4.0) and 0.8 (0.4-1.5) mg/L respectively (all p < 0.001). Most of BR had low adherence (n = 77, 83.7%), while the majority of SP were divided into moderate (n = 35, 35.7%) and strong adherence to the Mediterranean diet (n = 37, 37.8%), p < 0.001. There was a significant inverse association of adherence to the Mediterranean diet score

with higher LDL-C, ApoB, and hs-CRP after adjusting for socio economic parameters, caloric and fatty acid intakes as well as pharmacological lipid lowering therapies. CONCLUSIONS: Higher adherence to a Mediterranean diet was associated with better dyslipidemia and low-grade inflammation profiles in FH.

[47] *Qin J, Liu L, Su XD et al.* **The effect of PCSK9 inhibitors on brain stroke prevention: A systematic review and meta-analysis**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34052073
ABSTRACT
BACKGROUND AND AIMS: Although proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to improve cardiovascular outcomes, their effects on brain stroke risk are unclear. The present meta-analysis aimed to evaluate the effects of PCSK9 inhibitors on brain stroke prevention. METHODS AND RESULTS: We searched PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov for research published until December 30, 2020, to find randomized controlled trials (RCTs) of PCSK9 inhibitors for brain stroke prevention. Relative risk (RR) and 95% confidence intervals (CIs) were used to represent the outcomes. Seven RCTs with 57,440 participants, including 29,850 patients treated with PCSK9 inhibitors and 27,590 control participants, were included. PCSK9 inhibitors were associated with significant reductions in total brain stroke risk (RR, 0.77; 95% CI, 0.67-0.88; $P < 0.001$) and ischemic brain stroke risk (RR, 0.76; 95% CI, 0.66, 0.89; $P < 0.001$) in comparison with the control group. There was no significant difference in cardiovascular mortality (RR, 0.95; 95% CI, 0.84-1.07; $P = 0.382$) and the risk of hemorrhagic brain stroke (RR, 1.00; 95% CI, 0.66-1.51; $P = 0.999$) between patients treated with PCSK9 inhibitors and controls. PCSK9 inhibitors did not significantly increase the incidence of neurocognitive adverse events (RR, 1.02; 95% CI, 0.81-1.29; $P = 0.85$). Moreover, subgroup analysis showed no difference in cognitive function disorder risks among different PCSK9 inhibitors and treatment times. CONCLUSIONS: PCSK9 inhibitors significantly reduced the risk of total brain stroke and ischemic brain stroke without increasing the risk of brain hemorrhage and neurocognitive impairment.

[48] *Krysiak R, Szkróbka W, Okopień B*. **Correction to: The impact of atorvastatin on cardiometabolic risk factors in brothers of women with polycystic ovary syndrome**. Pharmacological reports : PR 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34036550
ABSTRACT

[49] *Achard M, Buhayer A, Dobretz K et al.* **[Long-lasting LDL-C lowering: silence at last]**. Revue medicale suisse 2021; 17:1039-1046.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34042340
ABSTRACT
Proprotein convertase subtilisin/kexin type 9 (PCSK9) is responsible for the degradation of the LDL-receptor. Inclisiran is a new synthetic interfering ribonucleic acid (siRNA) lowers LDL-cholesterol (LDL-C) levels in the blood by using RNA silencing technology to reduce the production of PCSK9. Inclisiran administered subcutaneously at 0 and 3 months, and then every 6 months has been shown to reduce LDL-C by approximately 50 % in patients at high and very-high cardiovascular risk, or with

a diagnosis of familial hypercholesterolemia, but also in patients intolerant to statins. New data are expected, in particular with cardiovascular clinical endpoints, as well as safety for use in adolescents.

[50] *Aghasizadeh M, Bizhaem SK, Baniasadi M et al.* **Evaluation of LDL goal achievement in statin consumption, south east of Iran**. Scientific reports 2021; 11:10786.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34031484

ABSTRACT

Lipid goal achievement and statin consumption were estimated at extreme/very-high/high/moderate and low cardiovascular risk categories. In the cross-sectional study, 585 patients treated with statin therapy referring to the heart clinic of Birjand were recruited. Patients were classified and examined LDL-C values and the proportion reaching targets according to the American Association of Clinical Endocrinologists guideline. Three patterns of statin use (high/moderate/low-intensity statin therapy) in all patients were examined and attainments of LDL-C goal in cardiovascular risk groups have been demonstrated. Over half the populations (57.6%) were in the very-high CVD risk group. The results showed that the proportion of patients meeting total LDL-C goal values according to the guidelines was 43.4%. The frequency of patient had achievement LDL goal lower in high-intensity pattern (N = 13, 2.3%), compared with moderate (N = 496, 86.1%) and low-intensity patterns (N = 67, 11.6%). In general, LDL-C goal achievement was greatest with moderate-intensity statin use. LDL-C reduction after statin consumption was estimated about one-third of the studied population. It seems likely that the achievement of a therapeutic target for serum lipids such as LDL-C improved is far more cost-effective and would be able to reach the target LDL as well changing the type and intensity of statins.

[51] *Omer L, Hudson EA, Hudgins LC, Boyd NL*. **Cohort Generation and Characterization of Patient-Specific Familial Hypercholesterolemia Induced Pluripotent Stem Cells**. Stem Cells Dev 2021; 30:632-640.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34029164

ABSTRACT

Homozygous familial hypercholesterolemia (hoFH) is a rare disorder caused primarily by pathological mutations in the low-density lipoprotein receptor (LDLR), which disrupts LDL-cholesterol (LDL-C) metabolism homeostasis. hoFH patients are at extremely high risk for cardiovascular disease and are resistant to standard therapies. LDLR knockout animals and in vitro cell models overexpressing different mutations have proved useful, but may not fully recapitulate human LDLR mutation biology. We and others have generated induced pluripotent stem cells (iPSC) from hoFH patient's fibroblasts and T cells and demonstrated their ability to recapitulate hoFH biology. In this study, we present the generation and characterization of a cohort of seven hoFH-iPSC lines derived from peripheral blood mononuclear cells (PBMC) collected from four homozygous and three compound heterozygous patients. The hoFH-iPSC cohort demonstrated a wide range of LDLR expression and LDL-C internalization in response to rosuvastatin that correlated with the predicted pathogenicity of the mutation. We were able to confirm that hoFH-iPSC cohort were pluripotent by differentiation toward all three germ layers and specifically to hepatocyte-like cells (HLC), the cell with primary LDL-C metabolic regulatory control, by expression of hepatocyte markers. hoFH patient PBMC-derived iPSC recapitulate the LDLR dysfunction of their specific mutation. They were capable of differentiating to HLC and could be useful for early developmental studies, pharmacology/toxicology, and potentially autologous cell therapy.

[52] *Li LY, Wang X, Zhang TC et al.* **Cardioprotective effects of omega 3 fatty acids from fish oil and it enhances autoimmunity in porcine cardiac myosin-induced myocarditis in the rat model**. Z Naturforsch C J Biosci 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=34049426

ABSTRACT

This experiment proposed to investigate the efficiency of omega 3 fatty acids from fish that improves autoimmune against myocarditis in the rat. Fish oil was extracted from fresh Tuna fish and performed FAME analysis and mice bioassay. The autoimmune myocarditis was induced by subcutaneous injection of porcine cardiac myosin (PCM) into the footpads of rats on the first and seventh day. Rats were dissected on the 21st day to analyze the histopathological, hemodynamic, echocardiographic factors, and immunohistochemistry expressions. In the study, 73.90% of total fatty acids were recorded. Histological analysis revealed that omega 3 fatty acids administrated groups showed tremendous development in the multifocal myocardia hyaline degeneration and necrosis with inflammatory changes. Moreover, omega 3 fatty acids inhabited the expressions of inflammatory cells (CD4, CD8 and CD11b) and suppressed the level of NF-κB. The echocardiographic factors such as heartbeat, SBP, DBP, levels of LVDs, LVDd, LVPW percentage of LVFS, EF, expression levels of inflammatory cytokines (TNF, IL-1β, IFN-ɣ, IL-2, and IL-6) also significantly suppressed by omega 3 fatty acids. Hence, the present study proved that consuming fatty acid-enriched fish might be a successful therapy for improving the inflammatory profile, regenerates the heart tissues, and controlled the production of inflammatory cells.