[1] *Peters EB, Kibbe MR*. **Nanomaterials to Resolve Atherosclerosis**. ACS Biomater Sci Eng 2020; 6:3693-3712.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33463318
ABSTRACT
Cardiovascular disease is the leading cause of death and disability in the world. Atherosclerosis, the buildup of fatty deposits in arteries, is a major underlying cause. Nanomedicine is an emerging treatment option to manage atherosclerotic plaque burden. Nanomaterials are critical to the success of nanomedicine therapies through their ability to enable targeted, controlled drug release. However, nanocarriers must be designed to ensure that nanomaterials and therapeutics work in tandem, tailored to respond to the unique physiochemical properties of atherosclerotic lesions, in order to move beyond slowing disease progression toward actively resolving atherosclerosis. This perspective serves to equip biomaterial scientists with the foundational knowledge needed to meet the challenge of designing such nanomaterials by reviewing the pathophysiology of atherosclerosis and highlighting design parameters that have shown success in targeted therapeutic delivery to atheromatous lesions.

[2] *Khazaei M, Khosravi M, Mazaheri S et al.* **The effect of atorvastatin on the common carotid artery intima-media thickness in patients with ischemic stroke**. Acta clinica Croatica 2020; 59:223-226.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33456108
ABSTRACT
Occlusion of the initial segment of internal carotid artery is the most common reason for vascular events in the brain. The purpose of this study was to investigate the effect of one-year treatment with atorvastatin on intima-media thickness (IMT) of carotid arteries as a measure of atherosclerosis in stroke patients. In this prospective interventional study, 44 patients with ischemic stroke were investigated. Patients were treated with atorvastatin 40 mg once a day for one year. IMT of carotid arteries was measured by extracranial Doppler ultrasonography in the distal part of the common carotid artery at the beginning of the study, at 6 months and one year of treatment with atorvastatin. The IMT of both right and left carotid arteries decreased after 6- and 12-month atorvastatin treatment. Based on the results of this study, long-term administration of atorvastatin was associated with reduction in carotid artery IMT in patients with ischemic stroke. Such a decrease in IMT may prevent subsequent stroke or cardiovascular events in these patients.

[3] *Nicholls SJ, Lincoff AM, Bays HE et al.* **Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of Bempedoic acid on cardiovascular events in patients with statin intolerance**. American heart journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33470195
ABSTRACT
BACKGROUND: Although statins play a pivotal role in the prevention of atherosclerotic cardiovascular disease, many patients fail to achieve recommended lipid levels due to statin-associated muscle symptoms. Bempedoic acid is an oral pro-drug that is activated in the liver and inhibits cholesterol synthesis in hepatocytes, but is not activated in skeletal muscle which has the potential to avoid muscle-related adverse events. Accordingly, this agent effectively lowers atherogenic lipoproteins in patients who experience statin-associated muscle symptoms. However, the effects of bempedoic acid on cardiovascular morbidity and mortality have not been studied. STUDY DESIGN: Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes is a randomized, double-blind, placebo-controlled clinical trial. Included patients must have

all of the following: (i) established atherosclerotic cardiovascular disease or have a high risk of developing atherosclerotic cardiovascular disease, (ii) documented statin intolerance, and (iii) an LDL-C≥100mg/dL on maximally-tolerated lipid-lowering therapy. The study randomized 14,014 patients to treatment with bempedoic acid 180mg daily or matching placebo on a background of guideline-directed medical therapy. The primary outcome is a composite of the time to first cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. The trial will continue until 1620 patients experience a primary endpoint, with a minimum of 810 hard ischemic events (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) and minimum treatment duration of 36months and a projected median treatment exposure of 42months. CONCLUSIONS: CLEAR Outcomes will determine whether bempedoic acid 180mg daily reduces the incidence of adverse cardiovascular events in high vascular risk patients with documented statin intolerance and elevated LDL-C levels.

[4] *Venuraju SM, Lahiri A, Jeevarethinam A et al.* **Association of Epicardial Fat Volume With the Extent of Coronary Atherosclerosis and Cardiovascular Adverse Events in Asymptomatic Patients With Diabetes**. Angiology 2021:3319720984607.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33467865
ABSTRACT
Epicardial adipose tissue has a paracrine effect, enhancing coronary artery atherosclerotic plaque development. This study evaluated epicardial fat volume (EFV), adipokines, coronary atherosclerosis, and adverse cardiovascular events in a cohort of asymptomatic patients with type 2 diabetes mellitus (T2DM). Epicardial fat volume was calculated using data from computed tomography coronary angiograms. Adipokines and inflammatory cytokines were also assayed and correlated with EFV. Epicardial fat volume was also assessed as a predictor of coronary artery calcium (CAC) score, number of coronary artery plaques, and significant plaque (>50% luminal stenosis). Data from the EFV analysis were available for 221 (85.7%) participants. Median EFV was 97.4 cm(3), mean body mass index was 28.1 kg/m(2), and mean duration of T2DM was 13 years. Statistically significant, but weak, correlations were observed between several adipokines, inflammatory cytokines, and EFV. Epicardial fat volume was a significant univariate (P = .01), but not multivariate, predictor of the number of coronary plaques, but not of CAC score or significant plaque. After a mean follow-up of 22.8 months, 12 adverse cardiovascular events were reported, exclusively in participants with EFV >97.4 cm(3). Epicardial fat volume has limited utility as a marker of coronary artery plaque in patients with T2DM and is weakly correlated with adipokine expression.

[5] *Famularo G, Sarrecchia C*. **Atorvastatin-Associated Gynecomastia**. The Annals of pharmacotherapy 2021:1060028021988994.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33472378
ABSTRACT

[6] *Çağlar A, Tuğçe Çağlar H*. **Vitamin D intoxication due to misuse: 5-year experience**. Arch Pediatr 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33483193
ABSTRACT
INTRODUCTION: Vitamin D intoxication (VDI) is a well-known cause of hypercalcemia in children and leads to serious kidney, heart, and neurological problems. In the treatment of VDI, the goal is to correct hypercalcemia. Our aim was to evaluate the clinical features of patients with VDI, identify the

causes of VDI in our region, and help guide precautions and treatment of VDI. MATERIALS AND METHODS: The medical records of patients with VDI presenting between January 2015 and December 2019 were retrospectively analyzed. RESULTS: In total, 38 patients aged 0.3-4 years including 20 males (52.6%) were included in the study. Vomiting (65.8%), loss of appetite (47.4%), and constipation (31.6%) were the most common symptoms. The cause of intoxication was prescribed D(3) vials in 23 patients, non-prescribed D(3) vials in nine patients, and incorrectly produced fish oil supplement in six patients. Admission serum calcium and 25 (OH) D levels were 3.75±0.5mmol/L and 396±110ng/mL, respectively. A statistically significant correlation was found between the serum calcium levels at the time of diagnosis and the dose of vitamin D received, serum 25 (OH) D, phosphorus, and parathyroid (PTH) levels. Nephrocalcinosis was present in 15 (39.5%) patients. The mean time to achieve normocalcemia was 6.18±2 days. The mean time to achieve normocalcemia in patients treated with pamidronate was 5.94±0.7 days. CONCLUSION: Stoss therapy should not be administered for children of families with problems of adherence to treatment. It should be noted that VDI may develop as a result of improperly produced nutritional supplements. General practitioners and pediatricians must be aware of VDI risks and explain them to parents. Pamidronate is effective for treating VDI in children.

[7] *Xian JZ, Lu M, Fong F et al.* **Statin Effects on Vascular Calcification: Microarchitectural Changes in Aortic Calcium Deposits in Aged Hyperlipidemic Mice**. Arteriosclerosis, thrombosis, and vascular biology 2021:Atvbaha120315737.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33472400
ABSTRACT
OBJECTIVE: Statins lower cardiovascular event risk, yet, they paradoxically increase coronary artery calcification, a marker consistently associated with increased cardiovascular risks. As calcium deposits influence rupture risk due to stress from compliance mismatch at their surfaces, we hypothesized that statins may lower cardiovascular risk by altering the microarchitecture of calcium deposits. Thus, using mice with preexisting vascular calcification, we tested whether pravastatin reduces the mineral surface area of calcium deposits. Approach and Results: Aged Apoe(-)(/-) mice were treated with pravastatin or vehicle for 20 weeks. Aortic calcification was assessed by in vivo sodium fluoride labeled with fluoride 18 isotope-micro-positron emission tomography/micro-computed tomography imaging at weeks 0, 10, and 20 and by histomorphometry at euthanasia. Micro-computed tomography analysis showed that, in both groups, the amount of vascular calcification increased significantly over the 20-week period, but pravastatin treatment did not augment over the controls. In contrast, the micro-positron emission tomography analysis showed that, at week 10, the pravastatin group had less (18)F uptake, suggesting reduced surface area of actively mineralizing deposits, but this decrease was not sustained at week 20. However, a significant difference in the mineral deposit size was found by histomorphometry. The pravastatin group had significantly more aortic microcalcium deposits (<50 μm in diameter) than the controls. The pravastatin group also had more vascular cells positive for alkaline phosphatase activity than the controls. The amount of collagen and osteopontin, additional osteoblastic markers, were not significantly different between the 2 groups. CONCLUSIONS: These results suggest that pravastatin treatment alters the microarchitecture of aortic calcium deposits with potential effects on plaque stability.

[8] *Frostegård J, Ahmed S, Hafström I et al.* **Low levels of PCSK9 are associated with remission in patients with rheumatoid arthritis treated with anti-TNF-α: potential underlying mechanisms**. Arthritis research & therapy 2021; 23:32.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33461620

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin kexin 9 (PCSK9) targets the LDL-receptor (LDLR) which raises LDL-levels. In addition, PCSK9 has proinflammatory immunological effects. Here, we investigate the role of PCSK9 in relation to the inflammatory activity in patients with rheumatoid arthritis (RA). METHODS: PCSK9-levels were determined at baseline by ELISA in 160 patients with RA not previously treated with biologics. The patients started anti-TNF-α (adalimumab, infliximab, or etanercept) treatment and were followed-up for 1 year. Disease activity was determined by DAS28. Effects of PCSK9 on cytokine production from macrophages of healthy individuals and synoviocytes from RA patients and inhibition by anti-PCSK9 antibodies were studied in supernatants by ELISA. RESULTS: A significantly lower level of PCSK9 at baseline, p = 0.035, was observed in patients who reached remission within 1 year, defined as DAS28 < 2.6, compared to those not in remission. At 12 months of TNF-α antagonist treatment, the mean DAS28 was reduced but was significantly greater in patients with highest quartile PCSK9 (Q4) compared to those at lowest PCSK9 (Q1) in both crude (p = 0.01) and adjusted analysis (p = 0.004). In vitro, PCSK9 induced TNF-alpha and IL-1beta in macrophages and monocyte chemoattractant protein-1 (MCP1) in synoviocytes. These effects were inhibited by anti-PCSK9 antibodies. CONCLUSIONS: Low levels of PCSK9 at baseline are associated with being DAS28-responder to anti-TNF-α treatment in RA. An underlying cause could be that PCSK9 stimulates the production of proinflammatory cytokines from macrophages and synoviocytes, effects inhibited by anti-PCSK9 antibodies. PCSK9 could thus play an immunological role in RA.

[9] *Atar D, Jukema JW, Molemans B et al.* **New cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention?** Atherosclerosis 2021; 319:51-61.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33476944

ABSTRACT

Elevated low-density lipoprotein cholesterol (LDL-C) is a principally modifiable cause of atherosclerotic cardiovascular disease; accordingly, recent European and US multisociety dyslipidaemia guidelines emphasise the importance of lowering LDL-C to reduce cardiovascular risk. This review provides perspectives on established and emerging agents that reduce LDL-C to help providers synthesize the abundance of new evidence related to prevention of cardiovascular disease. We provide hypothetical cases of patients with different cardiovascular risk factors and medical histories to illustrate application of current lipid-lowering guidelines in various clinical settings. As a core focus of preventive therapy, both European and US lipid management guidelines emphasise the importance of identifying patients at very high cardiovascular risk and treating to achieve LDL-C levels as low as possible, with European guidelines setting a goal of <1.4 mmol/L (<55 mg/dL) in patients with very high-risk cardiovascular disease. The proprotein convertase subtilisin/kexin type 9 inhibitors are now included in the guidelines and may fulfil an important unmet need for very high-risk patients who are not able to achieve LDL-C goals with conventional agents. The recently approved bempedoic acid and other promising agents under development will add to the armamentarium of lipid-lowering drugs available for clinicians to help patients meet their treatment goals.

[10] *Banach M, Penson PE*. **Lipid-lowering therapies: Better together**. Atherosclerosis 2021.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33482997

ABSTRACT

[11] *Svendsen K, Krogh HW, Igland J et al.* **2.5-fold increased risk of recurrent acute myocardial infarction with familial hypercholesterolemia**. Atherosclerosis 2020; 319:28-34.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33465659
ABSTRACT
BACKGROUND AND AIMS: A first-time acute myocardial infarction (AMI) is a severe diagnosis that leads to initiation or intensification of lipid-lowering medication to prevent recurrent events. Individuals with familial hypercholesterolemia (FH) already use high-intensity lipid-lowering medication at the time of an incident AMI due to their diagnosis. Hence, we hypothesized that compared with matched non-FH controls, individuals with genetically verified FH have increased mortality and risk of recurrent AMI after their first event. METHODS: The study population comprised 4871 persons with genetically verified FH, and 96,251 age and sex matched controls randomly selected from the Norwegian population. Data were obtained from the Cardiovascular Disease in Norway Project, the Norwegian Patient Registry and the Norwegian Cause of Death Registry. Incidence of AMI, all-cause mortality and recurrent AMI after incident AMI were analyzed for the period 2001-2017. Incidence and mortality were compared using hazard ratios (HR) from Cox regression. Risk of recurrent AMI was compared using sub-hazard ratios (SHR) from competing risk regression with death as a competing event. RESULTS: We identified 232 individuals with FH and 2118 controls with an incident AMI [HR 2.10 (95% CI 1.83-2.41)]. Among survivors ≥29 days after the incident AMI, both mortality [HR = 1.45 (95% CI: 1.07-1.95)] and recurrent AMI [SHR = 2.53 (95% CI: 1.88-3.41)] were significantly increased among individuals with FH compared with non-FH controls. CONCLUSIONS: Individuals with FH have increased mortality and increased risk of recurrent AMI after the first AMI event compared with controls. These findings call for intensive follow-up of individuals with FH following an AMI.

[12] *Varshney AS, Coskun AU, Siasos G et al.* **Spatial relationships among hemodynamic, anatomic, and biochemical plaque characteristics in patients with coronary artery disease**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33468315
ABSTRACT
BACKGROUND AND AIMS: We aimed to characterize the spatial proximity of plaque destabilizing features local endothelial shear stress (ESS), minimal luminal area (MLA), plaque burden (PB), and near-infrared spectroscopy (NIRS) lipid signal in high- vs. low-risk plaques. METHODS: Coronary arteries imaged with angiography and NIRS-intravascular ultrasound (IVUS) underwent 3D reconstruction and computational fluid dynamics calculations of local ESS. ESS, PB, MLA, and lipid core burden index (LCBI), for each 3-mm arterial segment were obtained in arteries with large lipid-rich plaque (LRP) vs. arteries with smaller LRP. The locations of the MLA, minimum ESS (minESS), maximum ESS (maxESS), maximum PB (maxPB), and maximum LCBI in a 4-mm segment (maxLCBI(4mm)) were determined along the length of each plaque. RESULTS: The spatial distributions of minESS, maxESS, maxPB, and maxLCBI(4mm), in reference to the MLA, were significantly heterogeneous within and between each variable. The location of maxLCBI(4mm) was spatially discordant from sites of the MLA ($p<0.0001$), minESS ($p = 0.003$), and maxESS ($p = 0.003$) in arteries with large LRP (maxLCBI(4mm) ≥ 400) and non-large LRP. Large LRP arteries had higher maxESS (9.31 ± 4.78 vs. 6.32 ± 5.54 Pa; $p = 0.023$), lower minESS (0.41 ± 0.16 vs. 0.61 ± 0.26 Pa; $p = 0.007$), smaller MLA (3.54 ± 1.22 vs. 5.14 ± 2.65 mm(2); $p = 0.002$), and larger maxPB (70.64 ± 9.95% vs. 56.70 ± 13.34%, $p<0.001$) compared with non-large LRP arteries. CONCLUSIONS: There is significant spatial heterogeneity of destabilizing plaque features along the

course of both large and non-large LRPs. Large LRPs exhibit significantly more abnormal destabilizing plaque features than non-large LRPs. Prospective, longitudinal studies are required to determine which patterns of heterogeneous destabilizing features act synergistically to cause plaque destabilization.

[13] *Pedersen E, Garcia BH, Halvorsen KH et al.* **Adherence to prescription guidelines and achievement of treatment goals among persons with coronary heart disease in Tromsø 7**. BMC cardiovascular disorders 2021; 21:44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33478404
ABSTRACT
BACKGROUND: Adherence to clinical practice guidelines for coronary heart disease (CHD) reduces morbidity, mortality and treatment costs. We aimed to describe and compare adherence to prescription guidelines for persons with CHD, and explore its association with treatment goal achievement. METHOD: We included all participants reporting myocardial infarction, angina, percutaneous coronary intervention and/or coronary artery bypass surgery in the seventh wave of the Tromsø Study (2015-2016, n = 1483). Medication use and treatment goal measures (blood pressure, low-density lipoprotein (LDL)-cholesterol and HbA1c) were compared to clinical practice guidelines on secondary CHD prevention. Propensity score matched logistic regression was used to assess the association between the use of antihypertensive drugs and achievement of treatment goal for blood pressure, and the use of lipid-lowering drugs (LLDs) and achievement of treatment goal for LDL-cholesterol. RESULTS: The prevalence of pharmacological CHD treatment was 76% for LLDs, 72% for antihypertensive drugs and 66% for acetylsalicylic acid. The blood pressure goal (< 140/90 mmHg, < 140/80 mmHg if diabetic) was achieved by 58% and the LDL-cholesterol goal (< 1.8 mmol/l or < 70 mg/dL) by 9%. There was a strong association between using LLDs and achieving the treatment goal for LDL-cholesterol (OR 14.0, 95% CI 3.6-54.7), but not between using antihypertensive drugs and blood pressure goal achievement (OR 1.4, 95% CI 0.7-2.7). CONCLUSION: Treatment goal achievement of LDL-cholesterol and blood pressure was low, despite the relatively high use of LLDs and antihypertensive drugs. Further research is needed to find the proper actions to increase achievement of the treatment goals.

[14] *Wang X, Wang S, Yu X et al.* **Impact of pharmacist-led medication therapy management in ambulatory elderly patients with chronic diseases**. British journal of clinical pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33474758
ABSTRACT
AIMS: This study aimed to assess the impact of pharmacist-led medication therapy management (MTM) performed on ambulatory elderly patients with chronic diseases. METHODS: Patients who came to a pharmacist-led outpatient clinic between January 2016 and June 2018 were enrolled in this study. Eligible subjects received MTM services from the pharmacists at least twice a year and the clinical data of these patients were complete. Drug-related problems (DRPs) and recommendations were evaluated using The Pharmaceutical Care Network Europe Classification for Drug related problems V8.03. RESULTS: A total of 525 DRPs were identified during the study period. Treatment effectiveness (53.71%) was the most common DRP. The most frequently recommended intervention was changing the drug (48.76%). There were 92.38% patients accepting the interventions and 90.48% patients completely implemented. The number of drugs taken was the significant associated factor for DRPs. Postintervention data collection showed lower levels in systolic blood pressure (BP) and diastolic BP compared to the preintervention data collection. There were statistically significant

changes in total cholesterol, low-density lipoprotein cholesterol and triglycerides between the pre- and postintervention data collections. The average cost of medications per patient for every month decreased from 387.72 to 355.17 renminbi (P = .009). CONCLUSION: We confirmed that pharmacists had a valuable role to perform MTM services for ambulatory elderly patients, not only in identifying and solving the DRPs, but also in improving clinical outcomes (BP and lipid level) and cost-saving effect.

[15] *Ding WY, Protty MB, Davies IG, Lip GYH*. **Relationship between lipoproteins, thrombosis and atrial fibrillation**. Cardiovascular research 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33483737
ABSTRACT
The prothrombotic state in atrial fibrillation (AF) occurs as a result of multifaceted interactions, known as Virchow's triad of hypercoagulability, structural abnormalities and blood stasis. More recently, there is emerging evidence that lipoproteins are implicated in this process, beyond their traditional role in atherosclerosis. In this review, we provide an overview of the various lipoproteins and explore the association between lipoproteins and AF, the effects of lipoproteins on haemostasis, and the potential contribution of lipoproteins to thrombogenesis in AF. There are several types of lipoproteins based on size, lipid composition and apolipoprotein category, namely: chylomicrons, very low density lipoprotein, low density lipoprotein (LDL), intermediate density lipoprotein and high density lipoprotein. Each of these lipoproteins may contain numerous lipid species and proteins with a variety of different functions. Furthermore, the lipoprotein particles may be oxidised causing an alteration in their structure and content. Of note, there is a paradoxical inverse relationship between total cholesterol and LDL-C levels, and incident AF. The mechanism by which this occurs may be related to the stabilising effect of cholesterol on myocardial membranes, along with its role in inflammation. Overall, specific lipoproteins may interact with haemostatic pathways to promote excess platelet activation and thrombin generation, as well as inhibiting fibrinolysis. In this regard, LDL-C has been shown to be an independent risk factor for thromboembolic events in AF. The complex relationship between lipoproteins, thrombosis and AF warrants further research with an aim to improve our knowledge base and contribute to our overall understanding of lipoprotein-mediated thrombosis.

[16] *Shea S, Navas-Acien A, Shimbo D et al.* **Spatially Weighted Coronary Artery Calcium Score and Coronary Heart Disease Events in the Multi-Ethnic Study of Atherosclerosis**. Circulation. Cardiovascular imaging 2021:Circimaging120011981.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33461306
ABSTRACT
BACKGROUND: A limitation of the Agatston coronary artery calcium (CAC) score is that it does not use all of the calcium density information in the computed tomography scan such that many individuals have a score of zero. We examined the predictive validity for incident coronary heart disease (CHD) events of the spatially weighted coronary calcium score (SWCS), an alternative scoring method for CAC that assigns scores to individuals with Agatston CAC=0. METHODS: The MESA (Multi-Ethnic Study of Atherosclerosis) is a longitudinal study that conducted a baseline exam from 2000 to 2002 in 6814 participants including computed tomography scanning for CAC. Subsequent exams and systematic follow-up of the cohort for outcomes were performed. Statistical models were adjusted using the MESA risk score based on age, sex, race/ethnicity, systolic blood pressure, use of hypertension medications, diabetes, total and HDL (high-density lipoprotein) cholesterol, use of lipid-lowering medications, smoking status, and family history of heart attack.

RESULTS: In the 3286 participants with Agatston CAC=0 at baseline and for whom SWCS was computed, 98 incident CHD events defined as definite or probably myocardial infarction or definite CHD death occurred during a median follow-up of 15.1 years. In this group, SWCS predicted incident CHD events after multivariable adjustment (hazard ratio=1.30 per SD of natural logarithm [SWCS] [95% CI, 1.04-1.60]; P=0.005); and progression from Agatston CAC=0 at baseline to CAC>0 at subsequent exams (multivariable-adjusted incidence rate difference per SD of natural logarithm [SWCS] per 100 person-years 1.68 [95% CI, 1.03-2.33]; P<0.0001). CONCLUSIONS: SWCS predicts incident CHD events in individuals with Agatston CAC score=0 as well as conversion to Agatston CAC>0 at repeat computed tomography scanning at later exams. SWCS has predictive validity as a subclinical phenotype and marker of CHD risk in individuals with Agatston CAC=0.

[17] *Drouin-Chartier JP, Tremblay AJ, Godbout D et al.* **Correlates of Coronary Artery Calcification Prevalence and Severity in Patients With Heterozygous Familial Hypercholesterolemia**. CJC Open 2021; 3:62-70.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33458634
ABSTRACT
BACKGROUND: Determinants of coronary artery calcification (CAC) prevalence and severity in heterozygous familial hypercholesterolemia (HeFH) remain understudied. The objective of this cross-sectional study was to investigate correlates of CAC in patients with HeFH. METHODS: A CAC score was calculated by a noncontrast computed tomography scan in women (n = 68) and men (n = 78) with genetically defined HeFH. We classified CAC prevalence and severity using 3 categories: CAC score = 0 Agatston Unit (AU), CAC score = 1-100 AU, and CAC score > 100 AU. Information on potential correlates of CAC including familial and personal health history, cardiovascular risk factors, lipid-lowering medication, and lifestyle habits was collected. RESULTS: A total of 95 patients had prevalent CAC. Independent correlates of CAC prevalence and severity included age (odds ratio [OR] per 10 years: 5.06, 95% confidence interval [CI]: 3.19, 7.93, P < 0.0001), family history of premature cardiovascular disease (OR: 3.88, 95% CI: 1.71, 8.81, P = 0.001), male sex (OR: 3.40, 95% CI: 1.49, 7.78, P = 0.004), statin use (OR: 15.5, 95% CI: 1.89, 126, P = 0.01), diet quality assessed with the Alternative Healthy Eating Index score (OR per 1 standard deviation: 0.59, 95% CI: 0.39, 0.90, P = 0.01), ever smoking (OR: 3.06, 95% CI: 1.20, 7.81, P = 0.02), receptor-negative genotype (OR: 3.17, 95% CI: 1.16, 8.66, P = 0.02), lipoprotein(a) year-score (OR per 1 standard deviation of log-transformed year-score: 1.53, 95% CI: 0.99, 2.36, P = 0.05). CONCLUSIONS: In individuals with HeFH, age, family history of premature cardiovascular disease, sex, statin use, diet quality, smoking status, the LDLR genotype, and lipoprotein(a) concentrations were independently associated with CAC prevalence and severity.

[18] *Shawish MI, Bagheri B, Musini VM et al.* **Effect of atorvastatin on testosterone levels**. The Cochrane database of systematic reviews 2021; 1:Cd013211.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33482034
ABSTRACT
BACKGROUND: Statins are one of the most prescribed classes of drugs worldwide. Atorvastatin, the most prescribed statin, is currently used to treat conditions such as hypercholesterolaemia and dyslipidaemia. By reducing the level of cholesterol, which is the precursor of the steroidogenesis pathway, atorvastatin may cause a reduction in levels of testosterone and other androgens. Testosterone and other androgens play important roles in biological functions. A potential reduction in androgen levels, caused by atorvastatin might cause negative effects in most settings. In contrast, in

the setting of polycystic ovary syndrome (PCOS), reducing excessive levels of androgens with atorvastatin could be beneficial. OBJECTIVES: Primary objective To quantify the magnitude of the effect of atorvastatin on total testosterone in both males and females, compared to placebo or no treatment. Secondary objectives To quantify the magnitude of the effects of atorvastatin on free testosterone, sex hormone binding globin (SHBG), androstenedione, dehydroepiandrosterone sulphate (DHEAS) concentrations, free androgen index (FAI), and withdrawal due to adverse effects (WDAEs) in both males and females, compared to placebo or no treatment. SEARCH METHODS: The Cochrane Hypertension Information Specialist searched the following databases for randomized controlled trials (RCTs) up to 9 November 2020: the Cochrane Hypertension Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; Embase; ;two international trials registries, and the websites of the US Food and Drug Administration, the European Patent Office and the Pfizer pharmaceutical corporation. These searches had no language restrictions. We also contacted authors of relevant articles regarding further published and unpublished work. SELECTION CRITERIA: RCTs of daily atorvastatin for at least three weeks, compared with placebo or no treatment, and assessing change in testosterone levels in males or females. DATA COLLECTION AND ANALYSIS: Two review authors independently screened the citations, extracted the data and assessed the risk of bias of the included studies. We used the mean difference (MD) with associated 95% confidence intervals (CI) to report the effect size of continuous outcomes,and the risk ratio (RR) to report effect sizes of the sole dichotomous outcome (WDAEs). We used a fixed-effect meta-analytic model to combine effect estimates across studies, and risk ratio to report effect size of the dichotomous outcomes. We used GRADE to assess the certainty of the evidence. MAIN RESULTS: We included six RCTs involving 265 participants who completed the study and their data was reported. Participants in two of the studies were male with normal lipid profile or mild dyslipidaemia (N = 140); the mean age of participants was 68 years. Participants in four of the studies were female with PCOS (N = 125); the mean age of participants was 32 years. We found no significant difference in testosterone levels in males between atorvastatin and placebo, MD -0.20 nmol/L (95% CI -0.77 to 0.37). In females, atorvastatin may reduce total testosterone by -0.27 nmol/L (95% CI -0.50 to -0.04), FAI by -2.59 nmol/L (95% CI -3.62 to -1.57), androstenedione by -1.37 nmol/L (95% CI -2.26 to -0.49), and DHEAS by -0.63 µmol/l (95% CI -1.12 to -0.15). Furthermore, compared to placebo, atorvastatin increased SHBG concentrations in females by 3.11 nmol/L (95% CI 0.23 to 5.99). We identified no studies in healthy females (i.e. females with normal testosterone levels) or children (under age 18). Importantly, no study reported on free testosterone levels. AUTHORS' CONCLUSIONS: We found no significant difference between atorvastatin and placebo on the levels of total testosterone in males. In females with PCOS, atorvastatin lowered the total testosterone, FAI, androstenedione, and DHEAS. The certainty of evidence ranged from low to very low for both comparisons. More RCTs studying the effect of atorvastatin on testosterone are needed.

[19] *Škrha J, Jr.* **Diabetes, Lipids, and CV Risk**. Current atherosclerosis reports 2021; 23:8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33464402

ABSTRACT

PURPOSE OF REVIEW: Diabetes is often associated with diabetic dyslipidemia. Both hyperglycemia and disorders of lipid metabolism strongly contribute to development of atherosclerosis, the crucial factor of cardiovascular disease. The aim of the manuscript is to summarize possible treatment to reduce cardiovascular risk. RECENT FINDINGS: Maximal cardiovascular risk reduction is maintained by targeting more pathologic disturbances together. While antihypertensive treatment has not

changed much recently, novel PCSK9 inhibitors have significantly improved management of dyslipidemia. Similarly, modern antihyperglycemic agents (SGLT2 inhibitors and GLP-1 receptor agonists) show both significant metabolic effects and cardiovascular benefits. Diabetes treatment is no longer glucocentric. Apart from glucose management, there are effective pharmacologic tools for significant reduction of cardiovascular risk.

[20] *Rymer JA, Swaminathan RV, Aday AW et al.* **The Current Evidence for Lipid Management in Patients with Lower Extremity Peripheral Artery Disease: What Is the Therapeutic Target?** Current cardiology reports 2021; 23:13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33483872
ABSTRACT
PURPOSE OF REVIEW: There is a lack of consistency among the ACC/AHA and ESC Guidelines on the treatment of patients with lower extremity PAD to a targeted LDL-c level. A review of the current guidelines, as well as the evidence that exists for use of various lipid-lower therapies in patients with PAD, is needed to guide clinical practice and to examine the current gaps in evidence that exist. RECENT FINDINGS: There is evidence that statins and PCSK9 inhibitors reduce the risks of major adverse cardiovascular and limb events in patients with PAD. Most statin and non-statin trials have examined the association of LLT use with clinical outcomes, and not the association between the degree of LDL-c lowering and the reduction in risk of clinical outcomes. As such, there is a lack of agreement between the American and European PAD Guidelines over whether to treat patients with PAD to a targeted LDL-c goal. Both statins and PCSK9 inhibitors have been shown to reduce the risk of major cardiovascular and limb events in patients with PAD. Further research is needed to determine if target driven LDL-c lowering is associated with improved outcomes in patients with PAD.

[21] *Balasubramanian R, Maideen NMP*. **HMG-CoA reductase inhibitors (Statins) and their Drug Interactions involving CYP enzymes, P-glycoprotein and OATP Transporters - An Overview**. Current drug metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33459228
ABSTRACT
BACKGROUND: Hydroxymethyl glutaryl-CoA (HMG-CoA) reductase inhibitors (Statins) are used to treat dyslipidemia. Generally, the statins are the substrates of CYP enzymes, P-glycoprotein (P-gp), and organic anion transporting polypeptides transporters (OATP1B1). OBJECTIVE: This review article focuses on the clinical significance of statins, and their interactions in real practice. METHOD: The databases like Medline/PubMed Central/PubMed, Google Scholar, Science Direct, Cochrane Library, Directory of open access journals (DOAJ), and reference lists were searched to identify relevant articles. RESULTS: Most of the drug interactions of statins result in elevated plasma concentrations and toxicity of statins due to the inhibition of CYP3A4, P-gp and/or OATP1B1 transporters. The toxicity of statins includes myopathy, rhabdomyolysis, elevated liver enzymes, acute kidney injury, and diabetes. The statins like Simvastatin, Lovastatin, and Atorvastatin are substrates of CYP3A4 enzyme and P-glycoprotein and their concomitant use with the drugs inhibiting or inducing them would result in changes in plasma concentrations and toxicity/efficacy. However, the statins like Pravastatin, Rosuvastatin and Pitavastatin are not substrates of CYP enzymes and hence the concomitant use of CYP inhibitors or inducers do not affect them. Almost all the statins are the substrates of OATP1B1 transporter, and the co-prescription of inhibitors of OATP1B1 elevates the plasma concentrations and muscle toxicity of statins. CONCLUSION: Understanding the interacting

potential of each statin will enable the prescribers, pharmacists, and other health care professionals to use statins effectively without compromising patient safety.

[22] *Reyes-Soffer G*. **Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease risk: current status and treatments**. Current opinion in endocrinology, diabetes, and obesity 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33481422
ABSTRACT
PURPOSE OF REVIEW: The role of triglyceride-rich lipoproteins (TRLs) in the development of atherosclerotic cardiovascular disease (ASCVD) is at the forefront of current research and treatment development programs. Despite extreme lowering of LDL-cholesterol there remains a high risk of cardiovascular disease and mortality. Recent large epidemiological, genomic wide association studies and Mendelian randomization studies have identified novel mechanisms and targets regulating TRL. This review will focus on recent and ongoing clinical trials that aim to reduce cardiovascular risk by decreasing plasma levels of TRL. RECENT FINDINGS: Ongoing efforts of basic and clinical scientist have described novel TRL regulating mechanism. The concentration on lifestyle changes is key to prevention and treatment guidelines. There is continue evidence that supports previous guidelines using fibrates alone and in combination with niacin to reduce TRLs, in special cases. The recent results from the REDUCE-IT study support the use of eicosapentaenoic acid (EPA) for risk reduction and ASCVD, but recently presented data from the Long-Term Outcome Study to Assess Statin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia and Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction studies do not support the use of combination EPA/docosahexaenoic acid. The latter highlights the need for further studies into the pathways regulating ASCVD risk reduction after EPA administration. The identification of novel targets, such as apolipoprotein C3 and angiopoietin-like protein-3, are driving the development of novel treatments, and is the focus of this review. SUMMARY: The current management of elevated triglyceride levels and the effect on cardiovascular outcomes is an emerging area of research. New data from fish oil studies suggest differences in EPA vs. EPA/docosahexaenoic acid cardio protection outcomes. The preliminary data from ongoing clinical trials of novel triglyceride-lowering therapeutics are promising. These programs will ultimately provide foundations for future triglyceride-lowering guidelines.

[23] *Hu D, Wang Z, Wang Y, Liang C*. **Targeting Macrophages in Atherosclerosis**. Current pharmaceutical biotechnology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33480337
ABSTRACT
BACKGROUND: Atherosclerosis (AS) is an important pathological basis for the occurrence of coronary atherosclerotic disease (CAD), stroke and other adverse cardiovascular events. AS is an inflammatory disease, and macrophages are the main inflammatory cells in AS lesions, playing a leading role in the formation of atherosclerotic plaques and the development and regression of AS. Various pro-inflammatory and anti-inflammatory factors act on macrophages to regulate AS. Pro-inflammatory factors recruit monocytes to accumulate in the inflammatory site and promote the transformation of monocytes to macrophages. A large number of aggregated macrophages secrete various inflammatory mediators to promote AS. Pro-inflammatory factors can induce the polarization of M1-type macrophages to start and maintain inflammation, promote the accumulation of lipids in macrophages, and accelerate the formation of foam cells; Anti-inflammatory factors can not only induce M2-type macrophages polarization, promote tissue remodeling and repair, and reduce the

occurrence of AS, but also promote the metabolism of fatty acid oxidation and oxidative phosphorylation of macrophages, regulate lipid metabolism, stabilize plaques, and induce the transformation of helper T cells type 1/2 (Th1/Th2) to Th2 cells, thus reducing inflammation. CONCLUSION: This review summarizes the effect and underlying regulatory mechanism of macrophages in the development of AS, which can provide new ideas for the diagnosis and treatment of AS targeting macrophages.

[24] *Larsen JV, Martinsen MH, Mortensen MB et al.* **Contemporary lipid clinic and achievements in low-density lipoprotein-cholesterol reductions in very high-risk patients**. Danish medical journal 2020; 68.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33463509
ABSTRACT
INTRODUCTION: Numerous studies have shown that lowering of low-density lipoprotein-cholesterol (LDL-C) reduces the risk of cardiovascular disease (CVD). To optimise treatment, some patients are referred to a lipid clinic. The reduction in LDL-C achieved in a lipid clinic in contemporary practice is, however, not well described. The aim of the present study was to assess the LDL-C lowering effect among very high-risk patients with or without statin-associated muscle symptoms (SAMS) after treatment at a specialised lipid clinic endorsing European guidelines. METHODS: Medical records from 653 patients referred to our Lipid Clinic from 1 January 2013 to 1 May 2017 were examined retrospectively. Very high-risk patients were defined as either having CVD or diabetes mellitus Type 2 who were active smokers and/or had hypertension. The reduction in LDL-C and the number of patients reaching the LDL-C treatment target were investigated by comparing baseline data with the most recent values recorded. RESULTS: We identified 208 patients at a very high-risk for CVD. They obtained an LDL-C reduction of 23% corresponding to a reduction in LDL-C of 0.7 mmol/l (p less than 0.001). The percentage of patients reaching their LDL-C goal increased from 13% to 32%. In patients who had experienced SAMS, LDL-C was reduced by 26% corresponding to a reduction in LDL-C of 0.9 mmol/l (p less than 0.001), and the percentage of patients reaching their LDL-C goal increased from 8% to 23%. CONCLUSIONS: Very high-risk patients with or without SAMS obtained a clinically meaningful reduction in LDL-C of approximately 25% owing to their Lipid Clinic treatment. FUNDING: none. TRIAL REGISTRATION: not relevant.

[25] *Merkel M*. **[Diabetic Dyslipidemia]**. Deutsche medizinische Wochenschrift (1946) 2021; 146:85-91.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33465804
ABSTRACT
Diabetic dyslipidemia is a major cause of the increased cardiovascular risk in diabetes. This lipid disorder is characterized by increased plasma triglycerides, increased remnant particles of triglyceride-rich lipoproteins, small dense LDL particles and reduced HDL cholesterol. The main pathogenetic triggers are obesity and insulin resistance. In addition to lifestyle measures, statins, ezetimibe and eventually PCSK9 inhibitors are available to treat diabetic dyslipidemia and to reduce the cardiovascular risk. Fibrates and omega-3 fatty acids currently do not play a significant therapeutic role. A consistent and target-oriented therapy of diabetic dyslipidemia is a prerequisite for a cardiovascular risk reduction in patients with diabetes, which has been well proven in clinical studies.

[26] *Sinning D, Landmesser U*. **[New Lipid-lowering Agents]**. Deutsche medizinische Wochenschrift (1946) 2021; 146:92-101.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33465805
ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality. The fact that elevated levels of low-density lipoprotein-cholesterol (LDL-C) play a causal role in the development of ASCVD is now well accepted, given the results of numerous epidemiological and genetic studies, as well as randomized controlled clinical trials. Statins have become a primary therapeutic cornerstone in ASCVD prevention since they have been shown to reduce CV events by reducing levels of LDL-C. But despite the proven efficacy and safety of statin therapy, several aspects indicate a substantial need for additional or alternative LDL-C lowering therapies. These aspects include not only a high variability in individual response to therapy, but also possible side effects, potentially reducing adherence to treatment. Most importantly, an elevated risk for cardiovascular (CV) events remains in a large proportion of high-risk patients, especially in those with persistent elevation of LDL-C levels despite a maximum tolerated dose of statin therapy. Also, large clinical trials currently investigate a potential CV benefit of drug therapies targeting elevated levels of triglycerides and lipoprotein (a), respectively.

[27] *Vogt A, Weingärtner O*. **[Management of dyslipidaemias: The New 2019 ESC/EAS-Guideline]**. Deutsche medizinische Wochenschrift (1946) 2021; 146:75-84.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33465803
ABSTRACT
The updated guidelines for the management of dyslipidaemias 2019 sticks to the concept of individual risk-based intervention strategies, but intensifies LDL-C goals. Next to the established SCORE system non-invasive imaging techniques such as coronary CT or ultrasound of carotid or femoral arteries are now recommended for improved risk stratification. Screening for lipoprotein(a) identifies persons at higher cardiovascular risk. Non-statin trials with ezetimibe and PSCK9-inhibitors demonstrated further relative risk reduction for cardiovascular events. Cardiovascular risk reduction depends on the absolute lowering of LDL-C, duration of therapy and the individual cardiovascular risk. For patients at very high risk the new LDL-C goal is <1.4 mmol/l (55 mg/dl) and reduction of ≥50 % from baseline. The overall aim is to reduce "cholesterol life years".

[28] *Handelsman Y, Jellinger PS, Guerin CK et al.* **Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2020; 26:1196-1224.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471721
ABSTRACT
The treatment of lipid disorders begins with lifestyle therapy to improve nutrition, physical activity, weight, and other factors that affect lipids. Secondary causes of lipid disorders should be addressed, and pharmacologic therapy initiated based on a patient's risk for atherosclerotic cardiovascular disease (ASCVD). Patients at extreme ASCVD risk should be treated with high-intensity statin therapy to achieve a goal low-density lipoprotein cholesterol (LDL-C) of <55 mg/dL, and those at very high ASCVD risk should be treated to achieve LDL-C <70 mg/dL. Treatment for moderate and high ASCVD risk patients may begin with a moderate-intensity statin to achieve an LDL-C <100 mg/dL,

while the LDL-C goal is <130 mg/dL for those at low risk. In all cases, treatment should be intensified, including the addition of other LDL-C-lowering agents (i.e., proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe, colesevelam, or bempedoic acid) as needed to achieve treatment goals. When targeting triglyceride levels, the desirable goal is <150 mg/dL. Statin therapy should be combined with a fibrate, prescription-grade omega-3 fatty acid, and/or niacin to reduce triglycerides in all patients with triglycerides ≥500 mg/dL, and icosapent ethyl should be added to a statin in any patient with established ASCVD or diabetes with ≥2 ASCVD risk factors and triglycerides between 135 and 499 mg/dL to prevent ASCVD events. Management of additional risk factors such as elevated lipoprotein(a) and statin intolerance is also described.

[29] *Schade DS, Burchiel S, Eaton RP*. **A Pathophysiologic Primary Prevention Review of Aspirin Administration to Prevent Cardiovascular Thrombosis**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2020; 26:787-793.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471648
ABSTRACT
OBJECTIVE: Cardiovascular disease is the leading metabolic cause of mortality in the United States. Among current therapies, low-dose aspirin has been shown to reduce cardiovascular thrombosis. However, aspirin also causes major complications (hemorrhagic stroke and gastrointestinal bleeding). The American Heart Association recommends that aspirin only be prescribed for "high-risk" individuals. No guidelines are available as to the duration of aspirin therapy. METHODS: A reasonable approach to aspirin administration is to determine the appropriateness of aspirin therapy based on the pathophysiology of coronary artery thrombosis. It suggests that the coronary artery calcium (CAC) score be used as the basis for determining "high risk." This score was shown to accurately predict future cardiovascular events. The greater the CAC score, the greater the extent of coronary artery atherosclerotic plaque and future cardiovascular risk. RESULTS: A CAC score >400 places an individual at very-high 10-year risk for an atherosclerotic event. Since aggressive medical therapy initiates stabilization of unstable atherosclerotic plaques within 1 month and reversal within 2 years, this treatment significantly reduces the risk of the individual for a cardiovascular event. Thus, most individuals aged <75 years with a CAC score of >400 should receive aspirin therapy for a maximum of 2 years. CONCLUSION: Utilization of a CAC score greatly simplifies the decision of whom to treat with aspirin and for what duration. Importantly, focusing on two factors (hemorrhage and plaque stabilization) is easily understood by both the physician and the patient. ABBREVIATIONS: CAC = coronary artery calcium; CVD = cardiovascular disease; LDL = low-density lipoprotein; OCT = optical coherence tomography.

[30] *Schade DS, Shey L, Eaton RP*. **Cholesterol Review: A Metabolically Important Molecule**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2020; 26:1514-1523.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471744
ABSTRACT
OBJECTIVE: Cholesterol is an important molecule in humans and both its excess and its deficiency cause disease. Most clinicians appreciate its role in stabilizing cellular plasma membranes but are unaware of its myriad other functions. METHODS: This review highlights cholesterol's newly recognized important roles in human physiology and pathophysiology. RESULTS: The basis for cholesterol's ubiquitous presence in eukaryote organisms is its three part structure involving

hydrophilic, hydrophobic, and rigid domains. This structure permits cholesterol to regulate multiple cellular processes ranging from membrane fluidity and permeability to gene transcription. Cholesterol not only serves as a molecule of regulation itself, but also forms the backbone of all steroid hormones and vitamin D analogs. Cholesterol is responsible for growth and development throughout life and may be useful as an anticancer facilitator. Because humans have a limited ability to catabolize cholesterol, it readily accumulates in the body when an excess from the diet or a genetic abnormality occurs. This accumulation results in the foremost cause of death and disease (atherosclerosis) in the Western world. Identification of cholesterol's disease-producing capabilities dates back 5,000 years to the Tyrolean iceman and more recently to ancient mummies from many cultures throughout the world. In contrast, a deficiency of cholesterol in the circulation may result in an inability to distribute vitamins K and E to vital organs with serious consequences. CONCLUSION: Understanding the benefits and hazards of cholesterol in the clinical setting will improve the endocrinologist's ability to control diseases associated with this unique molecule. ABBREVIATIONS: CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NPC1L1 = Niemann-Pick C-1-like-1 protein; U.S. = United States; USDA = U.S. Department of Agriculture.

[31] *Tripathi M, Wong A, Solomon V, Yassine HN*. **THE PREVALENCE OF PROBABLE FAMILIAL CHYLOMICRONEMIA SYNDROME IN A SOUTHERN CALIFORNIA POPULATION**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2021; 27:71-76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33475504
ABSTRACT
OBJECTIVE: To estimate the prevalence of probable familial chylomicronemia syndrome (FCS) in a major Southern California Academic Center as well as to provide a systematic review of past FCS studies and management recommendations. METHODS: Electronic medical records were queried based on single fasting plasma triglyceride (TG) levels of ≥880 mg/dL and at least 1 episode of acute pancreatitis. After the exclusion of secondary causes (diabetes, alcohol misuse, gallbladder disease, chronic kidney disease, uncontrolled hypothyroidism, estrogen, and drug use) and responses to lipid-lowering treatment, probable patients with FCS were identified. A systematic review of all published literature on the prevalence and management guidelines for FCS was then presented and discussed. RESULTS: Out of 7 699 288 charts queried, 138 patients with TG levels of ≥880 mg/dL and documented evidence of at least 1 episode of acute pancreatitis were identified. Nine patients did not have any documented secondary causes of chylomicronemia. Four of the 9 patients had >20% decrease in TG levels after lipid-lowering treatment, 2 patients were not responsive to lipid-lowering medication, and data on lipid-lowering medications were missing in 3 patients. CONCLUSION: Our study estimates the prevalence of probable FCS at a range of 0.26 to 0.66 per million. Using the recommended criteria, probable FCS cases can be identified to allow early diagnosis and management.

[32] *Karagiannis AD, Mehta A, Dhindsa DS et al.* **How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol**. European heart journal 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33463677
ABSTRACT
Low-density lipoprotein cholesterol (LDL-C) is a proven causative factor for developing atherosclerotic cardiovascular disease. Individuals with genetic conditions associated with lifelong very low LDL-C levels can be healthy. We now possess the pharmacological armamentarium (statins, ezetimibe,

PCSK9 inhibitors) to reduce LDL-C to an unprecedented extent. Increasing numbers of patients are expected to achieve very low (<30 mg/dL) LDL-C. Cardiovascular event reduction increases log linearly in association with lowering LDL-C, without reaching any clear plateau even when very low LDL-C levels are achieved. It is still controversial whether lower LDL-C levels are associated with significant clinical adverse effects (e.g. new-onset diabetes mellitus or possibly haemorrhagic stroke) and long-term data are needed to address safety concerns. This review presents the familial conditions characterized by very low LDL-C, analyses trials with lipid-lowering agents where patients attained very low LDL-C, and summarizes the benefits and potential adverse effects associated with achieving very low LDL-C. Given the potential for cardiovascular benefit and short-term safe profile of very low LDL-C, it may be advantageous to attain such low levels in specific high-risk populations. Further studies are needed to compare the net clinical benefit of non-LDL-C-lowering interventions with very low LDL-C approaches, in addition to comparing the efficacy and safety of very low LDL-C levels vs. current recommended targets.

[33] *Pulipati VP, Davidson MH*. **How I treat statin-associated side effects in an outpatient setting**. Future cardiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33464124
ABSTRACT
Dyslipidemia promotes atherosclerosis and causes cardiovascular diseases. Statins are potent lipid-lowering medications with a cardiovascular mortality benefit. They are generally safe and well tolerated but sometimes can be associated with side effects of variable severity. The most common side effect is statin-associated muscle symptoms. Uncommon side effects include new-onset diabetes mellitus and elevation in liver enzymes. These effects can lead to noncompliance and premature discontinuation of the medication. Hence, it is crucial to identify patients with true statin-associated side effects (SASE) to ensure optimal statin use. The appropriate evaluation of the patient before starting statins and proactive utilization of available diagnostic tests to rule out alternate etiologies mimicking adverse effects are essential for accurate diagnosis of SASE. In patients with true SASE, timely intervention with modified statin or non-statins is beneficial. Herein, we discuss key clinical trial data on statins and non-statins, and describe our center's approach toward patients with SASE.

[34] *Zhou J, Bai J, Guo Y et al.* **Higher Levels of Triglyceride, Fatty Acid Translocase, and Toll-Like Receptor 4 and Lower Level of HDL-C in Pregnant Women with GDM and Their Close Correlation with Neonatal Weight**. Gynecol Obstet Invest 2021:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33486480
ABSTRACT
OBJECTIVES: In this study, we aimed to compare the levels of maternal blood lipids, placental and venous blood lipid transporters, and inflammatory factor receptors in pregnant women with and without gestational diabetes mellitus (GDM). We also aimed to figure out the relationship between these values and neonatal weight. METHODS: Fifty pregnant women with GDM under blood glucose control belong to the case group, and 50 pregnant women with normal glucose tolerance in concurrent delivery belong to the control group. Fasting venous blood of these pregnant women was taken 2 weeks before delivery, and umbilical cord blood was collected after delivery. The levels of triglyceride (TG), serum total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (HDL-C) in maternal blood and umbilical cord blood were tested in the laboratory department of our hospital. The level of toll-like receptor 4 (TLR4) in serum of umbilical

veins was detected by the double-antibody sandwich ELISA. Western blot and RT-PCR were used to detect the protein and mRNA expressions of TLR4, LPL, and FAT/CD36 in the placenta. RESULTS: The level of TG in maternal blood in the case group was remarkably higher than that in the control group, which was opposite to the level of HDL-C. In the umbilical cord blood of women with GDM, the expression of TLR4 increased and was closely correlated with neonatal weight. In the placenta of women with GDM, the expressions of FAT/CD36 and TLR4 increased, and both of them were closely correlated with neonatal weight. Besides, TLR4 in umbilical cord blood increased and was closely correlated with neonatal weight. Although the expression of LPL in the placenta decreased, it had no obvious correlation with neonatal weight. CONCLUSIONS: TG in maternal blood, TLR4 in the placenta and umbilical cord blood, and FAT/CD36 in the placenta were positively correlated with neonatal weight. However, HDL-C in maternal blood was negatively correlated with neonatal weight. Although the expression of LPL in the placenta reduced due to GDM, it had no correlation with neonatal weight.

[35] *Costantino S, Paneni F*. **The Epigenome in Atherosclerosis**. Handbook of experimental pharmacology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33474673
ABSTRACT
Emerging evidence suggests the growing importance of "nongenetic factors" in the pathogenesis of atherosclerotic vascular disease. Indeed, the inherited genome determines only part of the risk profile as genomic approaches do not take into account additional layers of biological regulation by "epi"-genetic changes. Epigenetic modifications are defined as plastic chemical changes of DNA/histone complexes which critically affect gene activity without altering the DNA sequence. These modifications include DNA methylation, histone posttranslational modifications, and non-coding RNAs and have the ability to modulate gene expression at both transcriptional and posttranscriptional level. Notably, epigenetic signals are mainly induced by environmental factors (i.e., pollution, smoking, noise) and, once acquired, may be transmitted to the offspring. The inheritance of adverse epigenetic changes may lead to premature deregulation of pathways involved in vascular damage and endothelial dysfunction. Here, we describe the emerging role of epigenetic modifications as fine-tuners of gene transcription in atherosclerosis. Specifically, the following aspects are described in detail: (1) discovery and impact of the epigenome in cardiovascular disease, (2) the epigenetic landscape in atherosclerosis; (3) inheritance of epigenetic signals and premature vascular disease; (4) epigenetic control of lipid metabolism, vascular oxidative stress, inflammation, autophagy, and apoptosis; (5) epigenetic biomarkers in patients with atherosclerosis; (6) novel therapeutic strategies to modulate epigenetic marks. Understanding the individual epigenetic profile may pave the way for new approaches to determine cardiovascular risk and to develop personalized therapies to treat atherosclerosis and its complications.

[36] *Cohen H, Durst R, Avizohar O et al.* **[UPDATED ISRAELI GUIDELINES FOR THE TREATMENT OF DYSLIPIDEMIA 2020]**. Harefuah 2021; 160:38-44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33474877
ABSTRACT
Despite the impressive decline in mortality from atherosclerotic cardiovascular diseases (ASCVD), these diseases still account for a large proportion of the overall morbidity and mortality worldwide. A vast amount of research has demonstrated the key role played by circulating lipoproteins, and especially low-density lipoprotein (LDL), in the etiology of atherosclerosis, and numerous studies

have proven the efficacy of interventions that lower the atherogenic lipoproteins in reducing morbidity and mortality from ASCVD. While previous guidelines placed an emphasis on the use HMG-CoA reductase inhibitors (statins) for the treatment of dyslipidemia, recent studies have shown that other LDL cholesterol lowering drugs, including ezetimibe and the PCSK9 inhibitors, can provide additional benefit when used in combination with (and in certain cases instead of) statins. These studies have also shown that blood LDL cholesterol levels lower than previously recommended targets provide additional benefit, without evidence of a threshold beyond which the benefit ceases and without excess adverse effects. The updated guidelines were formulated by a committee that consisted of representatives from the Israeli Society for the Research, Prevention and Treatment of Atherosclerosis, the Israel Society of Internal Medicine, the Israeli Heart Association, the Israeli Neurology Association and the Israel Association of Family Medicine. They provide recommendations for revised risk stratification of patients, novel target goals, and the use of evidence-based treatment and follow-up strategies with reference to specific patient sub-groups.

[37] *Kuk M, Ward NC, Dwivedi G*. **Extrinsic and Intrinsic Responses in the Development and Progression of Atherosclerosis**. Heart, lung & circulation 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33468387
ABSTRACT
Atherosclerosis is a multifactorial disease that is thought to be primarily inflammatory in origin. Given the contribution of inflammation to the development and progression of atherosclerosis, other conditions that are characterised by a dysregulated inflammatory response have also been proposed to play a role. The purpose of this review is to organise and present the various inflammatory processes that can affect atherosclerosis into two broad categories: extrinsic or host-independent and intrinsic or host-dependent. Within these two categories, we will discuss various processes that may contribute to the development and progression of atherosclerosis and the clinical studies describing these associations. Although the clinical trials investigating anti-inflammatory therapies have to date provided mixed results, further studies, particularly in conjunction with lipid-lowering and blood pressure lowering therapies should be considered.

[38] *Kurup R, Galougahi KK, Figtree G et al.* **The Role of Colchicine in Atherosclerotic Cardiovascular Disease**. Heart, lung & circulation 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33461916
ABSTRACT
Colchicine, an inexpensive immunomodulatory drug used traditionally to treat gout and familial Mediterranean fever, is rapidly accumulating basic and clinical evidence for a therapeutic role in atherosclerotic cardiovascular disease. Its athero-protective properties are thought to be mainly related to its effect on tubulin polymerisation, enabling a broad range of effect on multiple atherosclerotic plaque cell types and cellular processes, including cell division, cell migration as well as pro-inflammatory cytokine and chemokine secretion. These properties indicate the potential to favourably affect all stages of atherosclerotic plaque development including formation, progression, destabilisation, and plaque rupture. This review focusses on the pharmacology of colchicine, the mechanisms by which it modulates atherosclerosis pathobiology, and summarises the current clinical evidence for its use along with the upcoming clinical trial landscape. Given the current lack of primary immunomodulatory drugs in the treatment of atherosclerosis, colchicine is a promising candidate to fill this therapeutic gap.

[39] *Li YC, Shen TY, Chen CC et al.* **Automatic Detection of Atherosclerotic Plaque and Calcification from Intravascular Ultrasound Images by Using Deep Convolutional Neural Networks**. IEEE transactions on ultrasonics, ferroelectrics, and frequency control 2021; Pp.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33460377

ABSTRACT

Atherosclerosis is the major cause of cardiovascular diseases (CVDs). Intravascular ultrasound (IVUS) is a common imaging modality for diagnosing CVDs. However, an efficient analyzer for IVUS image segmentation is required for assisting cardiologists. In this study, an end-to-end deep-learning convolutional neural network was developed for automatically detecting media-adventitia borders, luminal regions, and calcified plaque in IVUS images. A total of 713 grayscale IVUS images from 18 patients were used as training data for the proposed deep-learning model. The model is constructed using the three modified U-Nets and combined with the concept of cascaded networks to prevent errors in the detection of calcification owing to the interference of pixels outside the plaque regions. Three loss functions (Dice, Tversky, and focal loss) with various characteristics were tested to determine the best setting for the proposed model. The efficacy of the deep-learning model was evaluated by analyzing precision-recall curve. The average precision (AP), Dice score coefficient, precision, sensitivity, and specificity of the predicted and ground truth results were then compared. All training processes were validated using leave-one-subject-out cross-validation. The experimental results showed that the proposed deep-learning model exhibits high performance in segmenting the media-adventitia layers and luminal regions for all loss functions, with all tested metrics being higher than 0.90. For locating calcified tissues, the best result was obtained when the focal loss function was applied to the proposed model, with an AP of 0.73, however, the prediction efficacy was affected by the proportion of calcified tissues within the plaque region when the focal loss function was employed. Compared with commercial software, the proposed method exhibited high accuracy in segmenting IVUS images in some special cases, such as when shadow artifacts or side vessels surrounded the target vessel.

[40] *Dahl IK, Dalgård C*. **Sami dietary habits and the risk of cardiometabolic disease: a systematic review**. International journal of circumpolar health 2021; 80:1873621.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33463398

ABSTRACT

This systematic literary review investigates if an association between Sami dietary habits and cardiometabolic outcomes exists, and examines the dietary characteristics and cardiometabolic status of the Sami population. Included were all articles assessing Sami dietary habits and cardiometabolic disease or risk factors. Embase, Medline and SweMed were searched on 26 September 2019 and articles were screened for eligibility in October 2019. Data were extracted according to Moose Guidelines and the Newcastle Ottawa Scale (NOS) was used to assess risk of bias. The initial search generated 4,195 articles in total. Nine articles met all inclusion criteria. Two were cohort studies and seven were cross-sectional. Rating by NOS ranked from 2/7 to 8/9 stars. The studies were largely descriptive and only few had results regarding a direct association between Sami dietary habits and cardiometabolic outcomes. The findings demonstrated no association between consumption of certain Sami food items and blood-lipids or mortality from CVD/CHD. A higher intake of fat, protein, reindeer-meat and coffee and a slightly lower blood pressure and mortality from CVD/CHD was seen among Sami compared with non-Sami. The limited amount and descriptive nature of the eligible articles indicate that resaerch within the fielt is limited. Thus, additional longitudinal studies are suggested.

[41] *Chua YA, Razman AZ, Ramli AS et al.* **Familial Hypercholesterolaemia in the Malaysian Community: Prevalence, Under-Detection and Under-Treatment**. Journal of atherosclerosis and thrombosis 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33455995
ABSTRACT
AIM: Familial hypercholesterolaemia (FH) is the most common autosomal dominant lipid disorder, leading to severe hypercholesterolaemia. Early detection and treatment with lipid-lowering medications may reduce the risk of premature coronary artery disease in FH patients. However, there is scarcity of data on FH prevalence, detection rate, treatment and control with lipid-lowering therapy in the Malaysian community. METHODS: Community participants (n=5130) were recruited from all states in Malaysia. Blood samples were collected for lipid profiles and glucose analyses. Personal and family medical histories were collected by means of assisted questionnaire. Physical examination for tendon xanthomata and premature corneal arcus were conducted on-site. FH were clinically screened using Dutch Lipid Clinic Network Criteria. RESULTS: Out of 5130 recruited community participants, 55 patients were clinically categorised as potential (Definite and Probable) FH, making the prevalence FH among the community as 1:100. Based on current total population of Malaysia (32 million), the estimated number of FH patients in Malaysia is 320,000, while the detection rates are estimated as 0.5%. Lipid-lowering medications were prescribed to 54.5% and 30.5% of potential and possible FH patients, respectively, but none of them achieved the therapeutic LDL-c target. CONCLUSION: Clinically diagnosed FH prevalence in Malaysian population is much higher than most of the populations in the world. At community level, FH patients are clinically under-detected, with majority of them not achieving target LDL-c level for high-risk patients. Therefore, public health measures are warranted for early detection and treatment, to enhance opportunities for premature CAD prevention.

[42] *Roghani-Shahraki H, Karimian M, Valipour S et al.* **Herbal therapy as a promising approach for regulation on lipid profiles: A review of molecular aspects**. Journal of cellular physiology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33469926
ABSTRACT
Impaired lipid profile is defined as abnormal plasma levels of low-density lipoprotein, triglycerides, and total cholesterol. This disease state is associated with the development and progression of various disorders, such as diabetes mellitus, cardiovascular diseases, and acute myocardial infarction. Globally, all of these disorders are related to a significant rate of death. Therefore, finding a suitable approach for the prevention and treatment of lipid profile-related disorders is in the spotlight. Recently, herbal therapy has been considered a promising therapeutic approach for the treatment of hyperlipidemia or its related disorders due to its safety and efficacy. Hereby, we address the potential benefits of some of these herbal compounds on different aspects of lipid profile and its abnormalities with a special focus on their underlying mechanisms. Using herbal products, such as teas and mushrooms, or their derivatives, Rosmarinus officinalis Linn, Curcuma longa, Green tea, Lippia triphylla, Lippia citriodora, Plantago asiatica L, Vine tea, and Grifola frondosa have been proved to exert several therapeutic impacts on lipid profile and its related disorders, and we would provide a brief review on them in this literature.

[43] *Kiya M, Tamura Y, Takeno K et al.* **Adipose tissue insulin resistance and decreased adiponectin are correlated with metabolic abnormalities in non-obese men**. The Journal of clinical endocrinology and metabolism 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33484562

ABSTRACT
CONTEXT: Adipose tissue dysfunction is characterized by decreased adiponectin (AN) levels and impaired adipose tissue insulin sensitivity (ATIS), and is associated with metabolic disorders. While Asians readily develop metabolic disease without obesity, it remains unclear how decreased AN level and impaired ATIS affect metabolic abnormalities in non-obese Asians. DESIGN AND SETTING: To investigate the relationships between decreased AN level, impaired ATIS, and metabolic abnormalities, we studied 94 Japanese men whose body mass index was less than 25 kg/m 2. We divided the subjects into four groups based on their median AN level and ATIS, the latter calculated as the degree of insulin-mediated suppression of free fatty acids during hyperinsulinemic euglycemic clamp, and compared the metabolic parameters in the four groups. RESULTS: The High-ATIS/High-AN group (n=29) showed similar anthropometric data to the High-ATIS/Low-AN group (n=18). In contrast, both the Low-ATIS/High-AN (n=18) and Low-ATIS/Low-AN (n=29) groups showed significantly lower muscle insulin sensitivity than the High-ATIS groups. The intrahepatic lipid level in the Low-ATIS/Low-AN group was significantly higher than that in the High-ATIS groups. In addition, the Low-ATIS/Low-AN group had a significantly higher fasting serum triglyceride level and significantly lower high-density lipoprotein cholesterol level than the other three groups. CONCLUSIONS: In non-obese Japanese men with high ATIS, the AN level was not associated with metabolic characteristics. On the other hand, subjects with low ATIS showed reduced muscle insulin sensitivity and those with a decreased AN level demonstrated multiple metabolic abnormalities, represented by fatty liver and dyslipidemia.

[44] *Tada H, Okada H, Nomura A et al.* **Prognostic impact of cascade screening for familial hypercholesterolemia on cardiovascular events**. Journal of clinical lipidology 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33461934

ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is an autosomal dominant disorder mainly caused by mutations in the low-density lipoprotein (LDL) receptor or associated genes, resulting in elevated serum cholesterol levels and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD). OBJECTIVE: We aimed to evaluate the prognostic impact of cascade screening for FH. METHODS: We retrospectively investigated the health records of 1050 patients with clinically diagnosed FH, including probands and their relatives who were cascade-screened, who were referred to our institute. We used Cox models that were adjusted for established ASCVD risk factors to assess the association between cascade screening and major adverse cardiac events (MACE). The median period of follow-up evaluating MACE was 12.3 years (interquartile ranges [IQR] = 9.1-17.5 years), and MACE included death associated with ASCVD, or acute coronary syndrome. RESULTS: During the observation period, 113 participants experienced MACE. The mean age of patients identified through cascade screening was 18-years younger than that of the probands (38.7 yr vs. 57.0 yr, $P < 0.0001$), with a lower proportion of ASCVD risk factors. Interestingly, patients identified through cascade screening under milder lipid-lowering therapies were at reduced risk for MACE (hazard ratio [HR] = 0.67; 95%CI = 0.44 to 0.90; $P = 0.0044$) when compared with the probands, even after adjusting for those known risk factors, including age, and prior ASCVD. CONCLUSIONS: The identification of patients with FH via cascade screening appeared to result in better prognosis.

[45] *Anzai T, Grandinetti A, Katz AR et al.* **Paradoxical association between atrial fibrillation/flutter and high cholesterol over age 75 years: The Kuakini Honolulu Heart Program and Honolulu-Asia Aging Study**. J Electrocardiol 2020; 65:37-44.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33482619

ABSTRACT

INTRODUCTION: Several studies have indicated high cholesterol is paradoxically associated with low prevalence of atrial fibrillation/flutter (AF). However, the etiology is uncertain. One potential explanation might be the confounding effect of age exemplifying prevalence-incidence (Neyman's) bias. However, this bias has not often been discussed in depth in the literature. Therefore, we conducted a cross-sectional analysis to test the hypothesis that there is a paradoxical association between lipid profile and AF prevalence. METHODS: This is a cross-sectional study design, using data from the Kuakini Honolulu Heart Program. Participants were 3741 Japanese-American men between 71 and 93 years old living in Hawaii. Serum total cholesterol (TC) level was measured and categorized into quartiles. AF was diagnosed by 12-lead Electrocardiogram. We categorized age into quartiles (71-74, 75-77, 78-80 and 81+ years). RESULTS: We observed opposite associations between AF and TC among different age groups. For participants age ≥75, higher TC levels were paradoxically associated with lower prevalence of AF after multivariable adjustment, i.e. the odds ratios of AF comparing the highest TC quartile with the lowest TC quartile for age 75-77, 78-80 and 81+ years were 0.17 (95% confidence interval [CI], 0.06-0.52), 0.28 (95% CI, 0.07-1.09) and 0.14 (95% CI, 0.03-0.62), respectively. Conversely, for those who were 71-74 years old, the odds ratio of AF was 2.09 (95% CI, 0.76-5.75) between the highest and the lowest TC quartiles. CONCLUSIONS: There is a paradoxical association of TC with AF in Japanese-American men age ≥75, but not <75 years. The paradox might be explained by Neyman's bias.

[46] *Dargent A, Pais de Barros JP, Saheb S et al.* **LDL apheresis as an alternate method for plasma LPS purification in healthy volunteers and dyslipidemic and septic patients**. Journal of lipid research 2020; 61:1776-1783.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33455719

ABSTRACT

Lipopolysaccharide (LPS) is a key player for innate immunity activation. It is therefore a prime target for sepsis treatment, as antibiotics are not sufficient to improve outcome during septic shock. An extracorporeal removal method by polymyxin (PMX) B direct hemoperfusion (PMX-DHP) is used in Japan, but recent trials failed to show a significant lowering of circulating LPS levels after PMX-DHP therapy. PMX-DHP has a direct effect on LPS molecules. However, LPS is not present in a free form in the circulation, as it is mainly carried by lipoproteins, including LDLs. Lipoproteins are critical for physiological LPS clearance, as LPSs are carried by LDLs to the liver for elimination. We hypothesized that LDL apheresis could be an alternate method for LPS removal. First, we demonstrated in vitro that LDL apheresis microbeads are almost as efficient as PMX beads to reduce LPS concentration in LPS-spiked human plasma, whereas it is not active in PBS. We found that PMX was also adsorbing lipoproteins, although less specifically. Then, we found that endogenous LPS of patients treated by LDL apheresis for familial hypercholesterolemia is also removed during their LDL apheresis sessions, with both electrostatic-based devices and filtration devices. Finally, LPS circulating in the plasma of septic shock and severe sepsis patients with gram-negative bacteremia was also removed in vitro by LDL adsorption. Overall, these results underline the importance of

lipoproteins for LPS clearance, making them a prime target to study and treat endotoxemia-related conditions.

[47] *Ohkawa R, Low H, Mukhamedova N et al.* **Cholesterol transport between red blood cells and lipoproteins contributes to cholesterol metabolism in blood**. Journal of lipid research 2020; 61:1577-1588.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33455704
ABSTRACT
Lipoproteins play a key role in transport of cholesterol to and from tissues. Recent studies have also demonstrated that red blood cells (RBCs), which carry large quantities of free cholesterol in their membrane, play an important role in reverse cholesterol transport. However, the exact role of RBCs in systemic cholesterol metabolism is poorly understood. RBCs were incubated with autologous plasma or isolated lipoproteins resulting in a significant net amount of cholesterol moved from RBCs to HDL, while cholesterol from LDL moved in the opposite direction. Furthermore, the bi-directional cholesterol transport between RBCs and plasma lipoproteins was saturable and temperature-, energy-, and time-dependent, consistent with an active process. We did not find LDLR, ABCG1, or scavenger receptor class B type 1 in RBCs but found a substantial amount of ABCA1 mRNA and protein. However, specific cholesterol efflux from RBCs to isolated apoA-I was negligible, and ABCA1 silencing with siRNA or inhibition with vanadate and Probucol did not inhibit the efflux to apoA-I, HDL, or plasma. Cholesterol efflux from and cholesterol uptake by RBCs from Abca1(+/+) and Abca1(-/-) mice were similar, arguing against the role of ABCA1 in cholesterol flux between RBCs and lipoproteins. Bioinformatics analysis identified ABCA7, ABCG5, lipoprotein lipase, and mitochondrial translocator protein as possible candidates that may mediate the cholesterol flux. Together, these results suggest that RBCs actively participate in cholesterol transport in the blood, but the role of cholesterol transporters in RBCs remains uncertain.

[48] *Huang SJ, Ma YH, Bi YL et al.* **Metabolically healthy obesity and lipids may be protective factors for pathological changes of Alzheimer's disease in cognitively normal adults**. Journal of neurochemistry 2021.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33460456
ABSTRACT
The associations between obesity and Alzheimer's disease (AD) at different ages have been debated. Recent evidence implied the protective effects of metabolically healthy obesity on AD. We hypothesized that obesity and lipids could mitigate the detrimental impacts of AD pathological changes among metabolically healthy individuals in late life. In this study, a total of 604 metabolically healthy participants with normal cognition were included from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) database. Multiple linear regression models were used to test the associations of body mass index (BMI) or lipids with cerebrospinal fluid (CSF) biomarkers after adjustment for age, gender, education, and Apolipoprotein E-ε4 (APOE-ε4). The results showed the lower CSF levels of total tau protein (t-tau: $p = 0.0048$) and phosphorylated tau protein (p-tau: $p = 0.0035$) in obese participants than in non-obese participants, even after correcting for covariates. Moreover, in late life, higher BMI was associated with decreased CSF t-tau (β: -0.15, $p = 0.0145$) and p-tau (β: -0.17, $p = 0.0052$). As for lipids, higher levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were associated with decreased CSF t-tau (TC: β: -0.16, $p = 0.0115$; LDL-C: β: -0.16, $p = 0.0082$) and p-tau (TC: β: -0.15, $p = 0.0177$; LDL-C: β: -0.14, $p = 0.0225$) in obese participants. Furthermore, these associations were only significant in participants with late-life obesity and APOE-

ε4 non-carriers. Overall, in a cognitively normal population, we found metabolically healthy obesity and lipids in late life might be protective factors for neurodegenerative changes.

[49] *Piko P, Dioszegi J, Sandor J, Adany R*. **Changes in the Prevalence of Metabolic Syndrome and Its Components as Well as in Relevant Preventive Medication between 2006 and 2018 in the Northeast Hungarian Population**. Journal of personalized medicine 2021; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33467044
ABSTRACT
Metabolic syndrome (MetS) is a worldwide problem with severe health consequences. In this study, we examine the changes in the prevalence of MetS and its components in two disadvantaged counties of Northeastern Hungary. Two health examination surveys were performed in the Hungarian population aged 20-64 years in 2006 (n = 450) and 2018 (n = 397) and the data were compared to each other. It was found that the prevalence of MetS increased significantly in the period examined (from 34.9% to 42.2%, p = 0.035) due to the increased prevalence of raised blood pressure (from 45.6% to 57.0%, p = 0.002) and raised fasting glucose concentration (13.2% vs. 24.8%, p < 0.001). The increase mainly affects the younger (20-34 years old) age group (12.1% in 2006 vs. 31.6% in 2018, p = 0.001). It is quite alarming that the prevalence of MetS and its components has increased significantly in the last decade, while the prevalence of preventive medication is unchanged (antihypertensive and antidiabetic treatments) or even significantly decreased (lipid-lowering medication). Consequently, the number of individuals untreated for hypertension and metabolic disturbances is severely increased. A targeted public health strategy is desperately needed to prevent further worsening the situation.

[50] *Mansour BS, Salem NA, Kader GA et al.* **Protective effect of Rosuvastatin on Azithromycin induced cardiotoxicity in a rat model**. Life sciences 2021; 269:119099.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33476632
ABSTRACT
AIMS: Azithromycin is widely used broad spectrum antibiotic recently used in treatment protocol of COVID-19 for its antiviral and immunomodulatory effects combined with Hydroxychloroquine or alone. Rat models showed that Azithromycin produces oxidative stress, inflammation, and apoptosis of myocardial tissue. Rosuvastatin, a synthetic statin, can attenuate myocardial ischemia with antioxidant and antiapoptotic effects. This study aims to evaluate the probable protective effect of Rosuvastatin against Azithromycin induced cardiotoxicity. MAIN METHOD: Twenty adult male albino rats were divided randomly into four groups, five rats each control, Azithromycin, Rosuvastatin, and Azithromycin +Rosuvastatin groups. Azithromycin 30 mg/kg/day and Rosuvastatin 2 mg/kg/day were administrated for two weeks by an intragastric tube. Twenty-four hours after the last dose, rats were anesthetized and the following measures were carried out; Electrocardiogram, Blood samples for Biochemical analysis of lactate dehydrogenase (LDH), and creatine phosphokinase (CPK). The animals sacrificed, hearts excised, apical part processed for H&E, immunohistochemical staining, and examined by light microscope. The remaining parts of the heart were collected for assessment of Malondialdehyde (MDA) and Reduced Glutathione (GSH). KEY FINDINGS: The results revealed that Rosuvastatin significantly ameliorates ECG changes, biochemical, and Oxidative stress markers alterations of Azithromycin. Histological evaluation from Azithromycin group showed marked areas of degeneration, myofibers disorganization, inflammatory infiltrate, and hemorrhage. Immunohistochemical evaluation showed significant increase in both Caspase 3 and Tumor necrosis factor (TNF) immune stain. Rosuvastatin treated group showed restoration of the cardiac muscle

fibers in H&E and Immunohistochemical results. SIGNIFICANCE: We concluded that Rosuvastatin significantly ameliorates the toxic changes of Azithromycin on the heart.

[51] *Feder S, Wiest R, Weiss TS et al.* **Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels are not associated with severity of liver disease and are inversely related to cholesterol in a cohort of thirty eight patients with liver cirrhosis**. Lipids in health and disease 2021; 20:6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33461570

ABSTRACT

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is of particular importance in cholesterol metabolism with high levels contributing to hypercholesterolemia. Cholesterol and sphingolipids are low in patients with liver cirrhosis. Purpose of this study was to find associations of plasma PCSK9 with circulating cholesterol and sphingolipid species and measures of liver disease severity in patients with liver cirrhosis. METHODS: PCSK9 protein levels were determined by ELISA in systemic vein (SVP), hepatic vein (HVP) and portal vein plasma of patients with mostly alcoholic liver cirrhosis. PCSK9 and LDL-receptor protein expression were analysed in cirrhotic and non-cirrhotic liver tissues. RESULTS: Serum PCSK9 was reduced in patients with liver cirrhosis in comparison to non-cirrhotic patients. In liver cirrhosis, plasma PCSK9 was not correlated with Child-Pugh score, Model for End-Stage Liver Disease score, bilirubin or aminotransferases. A negative association of SVP PCSK9 with albumin existed. PCSK9 protein in the liver did not change with fibrosis stage and was even positively correlated with LDL-receptor protein levels. Ascites volume and variceal size were not related to PCSK9 levels. Along the same line, transjugular intrahepatic shunt to lower portal pressure did not affect PCSK9 concentrations in the three blood compartments. Serum cholesterol, sphingomyelin and ceramide levels did not correlate with PCSK9. Stratifying patients by high versus low PCSK9 levels using the median as cut-off, several cholesteryl ester species were even low in the subgroup with high PCSK9 levels. A few sphingomyelin species were also reduced in the patients with PCSK9 levels above the median. PCSK9 is highly expressed in the liver but systemic, portal and hepatic vein levels were similar. PCSK9 was not correlated with the inflammatory proteins C-reactive protein, IL-6, galectin-3, resistin or pentraxin 3. Of note, HVP PCSK9 was positively associated with HVP chemerin and negatively with HVP adiponectin levels. CONCLUSIONS: In the cohort of patients with liver cirrhosis mostly secondary to alcohol consumption high PCSK9 was associated with low levels of certain cholesteryl ester and sphingomyelin species. Positive correlations of PCSK9 and LDL-receptor protein in the liver of patients with chronic liver injury are consistent with these findings.

[52] *Chen Z, Zhang J, Feng J et al.* **Higher serum level of Cystatin C: An additional risk factor of CAD**. Medicine (Baltimore) 2021; 100:e24269.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33466214

ABSTRACT

Cystatin C has been proposed as a useful biomarker of early impaired kidney function and a predictor of mortality risk. The present study is to investigate the association between serum Cystatin C and the severity of coronary artery lesions, Gensini score (GS), and the risk of coronary artery disease (CAD).A total of 682 CAD patients (230 females, 452 males; mean age 62.6±10.7 years, range from 31 to 86 years) and 135 controls (41 females, 94 males; mean age 58.0±10.3 years, range from 38 to 84 years) were recruited in the present study. Enzyme-linked immunosorbent assay was applied to measure serum cystatin C levels and other serum indexes. The estimated glomerular filtration rate and GS were calculated.Serum low-density lipoprotein cholesterol (LDL-C), uric acid, Cystatin C, and

homocysteine (HCY) were significantly elevated in CAD patients compared to controls. There were significant differences regarding total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, cystatin C, eGFR and GS among stable angina pectoris (SAP), unstable angina group (UAP), and acute myocardial infarction (AMI) patients. AMI group had an elevated serum Cystatin C, LDL-C, HCY, and GS than SAP and UAP patients. When stratified patient groups by the quartiles of Cystatin C, we found age, the proportion of male and patients with diabetes, HCY, and GS were increased in Q4 than in other quartile groups. Spearman correlation test revealed a positive relationship between Cystatin C, HCY, and GS. Multivariate logistic regression analysis revealed that serum Cystatin C level, presence of hypertension and diabetes, HCY, age, and male were the risk factors for coronary artery lesions.In summary, our results suggested that cystatin C is a promising clinical biomarker that provides complementary information to the established risk determinants. The serum Cystatin C level is strongly associated with GS and could be used to evaluate the severity of coronary artery lesions.

[53] *Chiti A*. **Atherosclerotic Plaque Healing**. The New England journal of medicine 2021; 384:293-294.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471989
ABSTRACT

[54] *Corrado D, Thiene G, Basso C*. **Atherosclerotic Plaque Healing**. The New England journal of medicine 2021; 384:292-293.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471987
ABSTRACT

[55] *Vergallo R, Crea F*. **Atherosclerotic Plaque Healing. Reply**. The New England journal of medicine 2021; 384:294.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471990
ABSTRACT

[56] *Wang X, Ge J*. **Atherosclerotic Plaque Healing**. The New England journal of medicine 2021; 384:293.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33471988
ABSTRACT

[57] *Velarde GP, Choudhary N, Bravo-Jaimes K et al.* **Effect of atorvastatin on lipogenic, inflammatory and thrombogenic markers in women with the metabolic syndrome**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33485731
ABSTRACT
BACKGROUND AND AIM: Specific drug therapy to target the underlying proinflammatory and prothrombotic state in patients with metabolic syndrome (MS) is lacking. We sought to study the effect of high-intensity atorvastatin on markers of lipogenesis, inflammation and thrombogenesis, in women with MS in the absence of cardiovascular disease or diabetes. METHODS AND RESULTS: This randomized double-blinded controlled trial included 88 women with MS (according to National Cholesterol Education Panel Adult Treatment Panel III criteria) and low atherosclerotic cardiovascular risk. Participants were randomized to receive atorvastatin 80 mg or matching placebo. Thrombogenic,

lipogenic and inflammatory markers were collected at the time of enrollment, after a 6-week dietary run-in phase (time of randomization), and at 6- and 12-weeks after randomization. At 6 weeks post-randomization, there was significant reduction in total cholesterol, low density lipoprotein cholesterol, triglycerides, apolipoprotein-B (Apo-B) and Apo-B/Apo-A1 ratio in the atorvastatin arm compared to placebo. This difference persisted at 12-weeks post randomization. There was no significant difference in fasting blood glucose, high-density lipoprotein cholesterol, high sensitivity C-reactive protein, serum leptin, Apo-A1, intercellular adhesion molecule 1 and platelet activity. A significant increase in vascular adhesion molecule 1 at 6 and 12 weeks was seen within the atorvastatin arm. No difference was observed in blood pressure and waist circumference. CONCLUSIONS: In conclusion, high-intensity atorvastatin has an early and significant impact on lipoproteins and apolipoproteins but did not lower inflammatory, thrombogenic or biomarkers of platelet activity and aggregation in women with MS. The use of statins for primary prevention in these patients should be further explored.

[58] *Świątkiewicz I, Woźniak A, Taub PR*. **Time-Restricted Eating and Metabolic Syndrome: Current Status and Future Perspectives**. Nutrients 2021; 13.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33466692
ABSTRACT
Metabolic syndrome (MetS) occurs in ~30% of adults and is associated with increased risk of cardiovascular disease and diabetes mellitus. MetS reflects the clustering of individual cardiometabolic risk factors including central obesity, elevated fasting plasma glucose, dyslipidemia, and elevated blood pressure. Erratic eating patterns such as eating over a prolonged period per day and irregular meal timing are common in patients with MetS. Misalignment between daily rhythms of food intake and circadian timing system can contribute to circadian rhythm disruption which results in abnormal metabolic regulation and adversely impacts cardiometabolic health. Novel approaches which aim at restoring robust circadian rhythms through modification of timing and duration of daily eating represent a promising strategy for patients with MetS. Restricting eating period during a day (time-restricted eating, TRE) can aid in mitigating circadian disruption and improving cardiometabolic outcomes. Previous pilot TRE study of patients with MetS showed the feasibility of TRE and improvements in body weight and fat, abdominal obesity, atherogenic lipids, and blood pressure, which were observed despite no overt attempt to change diet quantity and quality or physical activity. The present article aims at giving an overview of TRE human studies of individuals with MetS or its components, summarizing current clinical evidence for improving cardiometabolic health through TRE intervention in these populations, and presenting future perspectives for an implementation of TRE to treat and prevent MetS. Previous TRE trials laid the groundwork and indicate a need for further clinical research including large-scale controlled trials to determine TRE efficacy for reducing long-term cardiometabolic risk, providing tools for sustained lifestyle changes and, ultimately, improving overall health in individuals with MetS.

[59] **Correction: Cardiovascular risk and response to lipid lowering therapy in patients with HIV infection according to different recommendations**. PloS one 2021; 16:e0246176.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33481961
ABSTRACT
[This corrects the article DOI: 10.1371/journal.pone.0244675.].

[60] *Kim JB, Song WH, Park JS et al.* **A randomized, open-label, parallel, multi-center Phase IV study to compare the efficacy and safety of atorvastatin 10 and 20 mg in high-risk Asian patients with hypercholesterolemia**. PloS one 2021; 16:e0245481.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33481866

ABSTRACT

BACKGROUND: Although accumulating evidence suggests a more extensive reduction of low-density lipoprotein cholesterol (LDL-C), it is unclear whether a higher statin dose is more effective and cost-effective in the Asian population. This study compared the efficacy, safety, and cost-effectiveness of atorvastatin 20 and 10 mg in high-risk Asian patients with hypercholesterolemia. METHODS: A 12-week, open-label, parallel, multicenter, Phase IV randomized controlled trial was conducted at ten hospitals in the Republic of Korea between October 2017 and May 2019. High-risk patients with hypercholesterolemia, defined according to 2015 Korean guidelines for dyslipidemia management, were eligible to participate. We randomly assigned 250 patients at risk of atherosclerotic cardiovascular disease to receive 20 mg (n = 124) or 10 mg (n = 126) of atorvastatin. The primary endpoint was the difference in the mean percentage change in LDL-C levels from baseline after 12 weeks. Cost-effectiveness was measured as an exploratory endpoint. RESULTS: LDL-C levels were reduced more significantly by atorvastatin 20 mg than by 10 mg after 12 weeks (42.4% vs. 33.5%, $p < 0.0001$). Significantly more patients achieved target LDL-C levels (<100 mg/dL for high-risk patients, <70 mg/dL for very high-risk patients) with atorvastatin 20 mg than with 10 mg (40.3% vs. 25.6%, $p < 0.05$). Apolipoprotein B decreased significantly with atorvastatin 20mg versus 10 mg (-36.2% vs. -29.9%, $p < 0.05$). Lipid ratios also showed greater improvement with atorvastatin 20 mg than with 10 mg (total cholesterol/high-density lipoprotein cholesterol ratio, -33.3% vs. -29.4%, $p < 0.05$; apolipoprotein B/apolipoprotein A1 ratio, -36.7% vs. -31.4%, $p < 0.05$). Atorvastatin 20 mg was more cost-effective than atorvastatin 10 mg in terms of both the average and incremental cost-effectiveness ratios. Safety and tolerability of atorvastatin 20 mg were comparable to those of atorvastatin 10 mg. CONCLUSION: In high-risk Asian patients with hypercholesterolemia, atorvastatin 20 mg was both efficacious in reducing LDL-C and cost-effective compared with atorvastatin 10 mg.

[61] *Li Z, Zhao P, Zhang Y et al.* **Exosome-based Ldlr gene therapy for familial hypercholesterolemia in a mouse model**. Theranostics 2021; 11:2953-2965.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33456582

ABSTRACT

Familial hypercholesterolemia (FH), with high LDL (low-density lipoprotein) cholesterol levels, is due to inherited mutations in genes, such as low-density lipoprotein receptor (LDLR). Development of therapeutic strategies for FH, which causes atherosclerosis and cardiovascular disease, is urgently needed. Methods: Mice with low-density lipoprotein receptor (Ldlr) deletion (Ldlr (-/-) mice) were used as an FH model. Ldlr mRNA was encapsulated into exosomes by forced expression of Ldlr in the donor AML12 (alpha mouse liver) cells, and the resultant exosomes were denoted as Exo(Ldlr). In vivo distribution of exosomes was analyzed by fluorescence labeling and imaging. The delivery efficiency of Ldlr mRNA was analyzed by qPCR and Western blotting. Therapeutic effects of Exo(Ldlr) were examined in Ldlr (-/-) mice by blood lipids and Oil Red O staining. Results: The encapsulated mRNA was stable and could be translated into functional protein in the recipient cells. Following tail vein injection, exosomes were mainly delivered into the liver, producing abundant LDLR protein, resembling the endogenous expression profile in the wild-type mouse. Compared with control exosomes, Exo(Ldlr) treatment significantly decreased lipid deposition in the liver and lowered the

serum LDL-cholesterol level. Significantly, the number and size of atherosclerotic plaques and inflammation were reduced in the Exo(Ldlr)-treated mice. Conclusions: We have shown that exosome-mediated Ldlr mRNA delivery effectively restored receptor expression, treating the disorders in the Ldlr (-/-) mouse. Our study provided a new therapeutic approach for the treatment of FH patients and managing atherosclerosis.

[62] *Zhao Y, Yang YY, Yang BL et al.* **Efficacy and safety of berberine for dyslipidemia: study protocol for a randomized double-blind placebo-controlled trial**. Trials 2021; 22:85.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=33482853

ABSTRACT
BACKGROUND: Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease and a leading cause of death worldwide. The clinical utility of commonly used lipid-lowering drugs such as statins and fibrates is sometimes limited by the occurrence of various adverse reactions. Recently, berberine (BBR) has received increasing attention as a safer and more cost-effective option to manage dyslipidemia. Thus, a high-quality randomized controlled trial to evaluate the efficacy and safety of BBR in the treatment of dyslipidemia is deemed necessary. METHODS/DESIGN: This is a randomized, double-blind, and placebo-controlled clinical trial. A total of 118 patients with dyslipidemia will be enrolled in this study and randomized into two groups at a ratio of 1:1. BBR or placebo will be taken orally for 12 weeks. The primary outcome is the percentage of low-density lipoprotein cholesterol reduction at week 12. Other outcome measures include changes in other lipid profiles, high sensitivity C-reactive protein, blood pressure, body weight, Bristol Stool Chart, traditional Chinese medicine symptom form, adipokine profiles, and metagenomics of intestinal microbiota. Safety assessment includes general physical examination, blood and urine routine test, liver and kidney function test, and adverse events. DISCUSSION: This trial may provide high-quality evidence on the efficacy and safety of BBR for dyslipidemia. Importantly, the findings of this trial will help to identify patient and disease characteristics that may predict favorable outcomes of treatment with BBR and optimize its indication for clinical use. TRIAL REGISTRATION: Chinese Clinical Trial Registry ChiCTR1900021361 . Registered on 17 February 2019.