[1] *Longo A, Ribas BLP, Orlandi SP et al.* **Prevalence of metabolic syndrome and its association with risk factors in patients with established atherosclerosis disease**. An Acad Bras Cienc 2020; 92:e20180563.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32428088
ABSTRACT
Risk factors can lead to clinical conditions, like metabolic syndrome, that predisposes the development of cardiovascular diseases. The aim of this study was to describe the prevalence and which risk factors cause more impact in metabolic syndrome in patients with established atherosclerosis disease. A cross-sectional study was performed as a subanalysis of Programa Alimentacao Cardioprotetora Brasileira. Weight, height, waist circumference, blood pressure, lipid profile and fasting glucose were collected. Metabolic syndrome was defined according to the harmonized criteria. Linear regression was used to analyze the association between number of components of metabolic syndrome and risk factors. 82 patients were included and the prevalence of metabolic syndrome was 84.1%. Being overweight was associated with an increase by 0.55 point in diagnostic criteria of metabolic syndrome in crude analysis (95%CI 0.09-1.00) and 0.64 in adjusted analysis (95%CI 0.18-1.09), while former/current smoker status was responsible for raising by 0.48 the number of components of metabolic syndrome, only in adjusted analysis (95%CI 0.04-0.92). Overweight and former/current smoker status are associated with MS, increasing the probability of atherosclerotic events. A healthy lifestyle, that includes avoiding tobacco exposure and proper weight control, must be encouraged in this high-risk population.

[2] *Castano D, Rattanasopa C, Monteiro-Cardoso VF et al.* **Lipid efflux mechanisms, relation to disease and potential therapeutic aspects**. Adv Drug Deliv Rev 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32423566
ABSTRACT
Lipids are hydrophobic and amphiphilic molecules involved in diverse functions such as membrane structure, energy metabolism, immunity, and signaling. However, altered intra-cellular lipid levels or composition can lead to metabolic and inflammatory dysfunction, as well as lipotoxicity. Thus, intra-cellular lipid homeostasis is tightly regulated by multiple mechanisms. Since most peripheral cells do not catabolize cholesterol, efflux (extra-cellular transport) of cholesterol is vital for lipid homeostasis. Defective efflux contributes to atherosclerotic plaque development, impaired beta-cell insulin secretion, and neuropathology. Of these, defective lipid efflux in macrophages in the arterial walls leading to foam cell and atherosclerotic plaque formation has been the most well studied, likely because a leading global cause of death is cardiovascular disease. Circulating high density lipoprotein particles play critical roles as acceptors of effluxed cellular lipids, suggesting their importance in disease etiology. We review here mechanisms and pathways that modulate lipid efflux, the role of lipid efflux in disease etiology, and therapeutic options aimed at modulating this critical process.

[3] *Henriksbo BD, Tamrakar AK, Phulka JS et al.* **Statins activate the NLRP3 inflammasome and impair insulin signalling via p38 and mTOR**. American journal of physiology. Endocrinology and metabolism 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32421368
ABSTRACT

Statins lower cholesterol and risk of cardiovascular disease. Statins can increase blood glucose and risk of new onset diabetes. It is unclear why statins can have opposing effects on lipids versus glucose. Statins have cholesterol-independent pleiotropic effects that influence both insulin and glucose control. Statin lowering of isoprenoids required for protein prenylation promotes pancreatic beta cell dysfunction and adipose tissue insulin-resistance. Protein prenylation influences immune function and statin-mediated adipose tissue insulin resistance involves the NLRP3 inflammasome and IL-1b. However, the intracellular cues that statins engage to activate the NLRP3 inflammasome and those responsible for IL-1b-mediated insulin resistance in adipose tissue have not been identified. We hypothesized that stress kinases or components of the insulin signalling pathway mediated statin-induced insulin resistance. We tested the associations of p38, ERK, JNK, PTEN and mTOR in statin exposed adipose tissue from WT and IL-1b(-/-) mice. We found that statins increased phosphorylation of p38 in WT and IL-1b(-/-) mice. Statin activation of p38 upstream of IL-1b led to priming of this NLRP3 inflammasome effector in macrophages. We found that mTORC1 inhibition with low doses of rapamycin (2, 20 nM) lowered macrophage priming of IL-1b mRNA and secretion of IL-1b caused by multiple statins. Rapamycin (20 nM) or the rapalog, Everolimus (20 nM) prevented atorvastatin-induced lowering of insulin-mediated phosphorylation of Akt in mouse adipose tissue. These results position p38 and mTOR as mediators of statin-induced insulin resistance in adipose tissue and highlight rapalogs as candidates to mitigate the insulin resistance and glycemic side effects of statins.

[4] *Muscella A, Stefano E, Marsigliante S*. **The effects of exercise training on lipid metabolism and coronary heart disease**. American journal of physiology. Heart and circulatory physiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32442027
ABSTRACT
Blood lipoproteins are formed by various amounts of cholesterol (C), triglycerides (TG), phospholipids and apolipoproteins (Apos). Apo A1 is the major structural protein of high-density lipoprotein (HDL), accounting for approximately 70% of HDL protein, and mediates many of the anti-atherogenic functions of HDL. Conversely, Apo B is the predominant low-density lipoprotein (LDL) Apo and is a reliable indicator of circulating LDL, associated with higher coronary heart disease (CHD) risk. Furthermore, the Apo B/Apo A1 ratio is used as a surrogate marker of the risk of CHD related to lipoproteins. Elevated or abnormal levels of lipids and/or lipoproteins in the blood is a significant CHD risk factor and several studies strongly support the idea that aerobic exercise decreases CHD risk partially lowering serum TG and LDL-cholesterol (LDL-C) levels and increasing HDL-C levels. Exercise also exerts an effect on HDL-C maturation and composition and on reverse C transport from peripheral cells to the liver, in order to favor its catabolism and excretion. This process prevents atherosclerosis and several studies showed that exercise training increases heart lipid metabolism and protects against cardiovascular disease. The purpose of this review is to assess the effects of endurance training on the nontraditional lipid biomarkers including Apo B, Apo A1, Apo B/Apo A1 ratio in CHD.

[5] *Genoux A, Bastard JP*. **Effects of leptin and adiponectin on the cardiovascular system**. Annales de biologie clinique 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32420888

ABSTRACT
Elevated circulating leptin levels have been associated with an increased cardiovascular risk in humans. However, recent meta-analyses show that certain epidemiological studies did not find this association, suggesting distinct effects of leptin depending on the pathophysiological context. Studies performed in mice deficient in leptin or in leptin receptors are often contradictory, showing both protective and deleterious effects of leptin. These effects appear to vary depending on the genetic background of the animal and the doses of leptin administered, making interpretation of the results difficult. In humans, elevated adiponectinemia is associated with a favourable cardiovascular risk profile. Adiponectin exerts protective effects at all stages of development of atherosclerotic plaque. However, our knowledge of the pathophysiological mechanisms involved in these protective effects has been established from cellular models, which do not necessarily reproduce the pathology in all its complexity. In addition, mouse models have a very different lipoprotein metabolism from humans, which does not always allow extrapolation of results to humans. Finally, epidemiological studies evaluating adiponectin as a marker of cardiovascular risk show paradoxical results since a high serum adiponectin concentration has not been associated with a reduction in the number of cardiovascular events but with an increase of cardiovascular and all causes mortality in healthy subjects and coronary patients. These observations illustrate the paradox of adipokines actions and show the complexity to use these biomarkers in cardiovascular diseases. Resistance to the action of these adipokines is one of the hypotheses put forward to explain these discrepancies.

[6] *Ben Salem C, Sahnoun D, Slim R et al.* **Atorvastatin and sildenafil interaction-induced rhabdomyolysis**. The Annals of pharmacotherapy 2020:1060028020919933.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32418442
ABSTRACT

[7] *Schrottmaier WC, Mussbacher M, Salzmann M, Assinger A*. **Platelet-leukocyte interplay during vascular disease**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32439204
ABSTRACT
Vascular disease is a progressive inflammatory condition fuelled by an unhealthy lifestyle of physical inactivity, cholesterol-rich diet, and smoking. Together with endogenous factors such as age, gender, and autoimmune status, an unhealthy lifestyle fosters a pro-inflammatory and pro-thrombotic milieu, which can lead to endothelial dysfunction, atherosclerotic plaque formation and vascular obstruction or degradation of the subendothelial matrix. Platelet-leukocyte interplay represents an important feature in this context. Platelets get activated in a pro-inflammatory and pro-thrombotic microenvironment and readily interact with innate and adaptive immune cells alike. Even though platelet affinity for physical cell-cell contact is highest with monocytes/macrophages and neutrophils, platelets also avidly interact with lymphocytes by soluble mediators. Platelet-leukocyte crosstalk regulates essential immune responses, supporting leukocyte recruitment at sites of vascular insult, promoting proliferation and differentiation of leukocytes and enhancing pro-inflammatory effector functions such as cytokine and reactive oxygen production. However, under certain conditions platelet-leukocyte interplay also dampens the inflammatory process. Crosstalk of platelet and leukocytes thus represents a driving force in vascular disease. In this review, we highlight the impact of various

risk factors for vascular disease on platelet-leukocyte interactions and discuss the underlying mechanisms of platelet-mediated changes in immune responses and the effect of immune cells on the haemostatic system. As the underlying pathologies differ between vascular diseases, we summarize our current knowledge on platelet-leukocyte interplay in chronic vascular diseases such as abdominal aortic aneurysm, peripheral and coronary artery disease as well as acute vascular diseases such as ischaemic stroke and venous thromboembolism.

[8] *Kamada Y, Yamamoto A, Fujiyoshi A et al.* **Loss of core fucosylation reduces low-density lipoprotein receptor expression in hepatocytes by inducing PCSK9 production**. Biochem Biophys Res Commun 2020; 527:682-688.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32423823
ABSTRACT
Fucosylation is a type of glycosylation, a form of post-transcriptional regulation of proteins, involved in cancer and inflammation. It involves the attachment of a fucose residue to N-glycans, O-glycans, and glycolipids, which is catalyzed by a family of enzymes called fucosyltransferases (Futs). Among the many Futs, alpha-1,6-fucosyltransferase (Fut8) is the only enzyme that produces alpha-1,6-fucosylated oligosaccharides (core fucose). In the human liver, the expression and activity of Fut8 are frequently elevated during progression of chronic liver diseases. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a well-known negative regulator of the low-density lipoprotein receptor (LDLR). Here, we found that loss of core fucose in immortalized hepatocytes led to LDLR downregulation through a dramatic induction of PCSK9. We used the immortalized hepatocytes derived from Fut8 knockout mice or a Fut8 knockdown AML12 hepatocyte cell line. Using these cells, we investigated the effects of Fut8 on hepatocyte cholesterol influx. Both cell lines had reduced LDLR protein levels, resulting from marked increases in PCSK9 expression. Intracellular cholesterol levels were significantly lower and LDL cholesterol uptake was suppressed in Fut8-KO cells. Hepatocyte nuclear factor 1alpha accumulated in nuclei of Fut8-KO hepatocytes, which mediated increases in PCSK9 mRNA expression. Our findings demonstrated that loss of core fucosylation promoted degradation of LDLR and impaired cholesterol uptake, which is a novel mechanism that regulates cholesterol influx, suggesting that Fut8 might be a novel causative gene for familial hypercholesterolemia.

[9] *Alizadeh-Fanalou S, Nazarizadeh A, Alian F et al.* **Small dense low-density lipoprotein-lowering agents**. Biological chemistry 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32427116
ABSTRACT
Metabolic disorders, including obesity, diabetes, and hyperlipidemia, as well as cardiovascular diseases (CVD), particularly atherosclerosis, are still leading causes of death worldwide. Plasma levels of low-density lipoprotein (LDL) are currently being considered as a critical risk factor for the diseases mentioned above, especially atherosclerosis. Because of the heterogeneous nature of LDL, many studies have already been conducted on its subclasses, especially small dense LDL (sdLDL). According to available evidence, sdLDL levels can be considered as an ideal alternative to LDL levels for monitoring CVD and early diagnosis of atherosclerosis. Recently, several researchers have focused on factors that are able to decrease sdLDL levels and improve health quality. Therefore, the purpose of this study is to describe the production process of sdLDL particles and review the effects of pharmaceutical

and dietary agents as well as lifestyle on sdLDL plasma levels. In brief, their mechanisms of action are discussed. Apparently, cholesterol and LDL lowering compounds are also effective in the reduction of sdLDL levels. In addition, improving lipid profile, especially the reduction of triglyceride (TG) levels, appropriate regimen, and lifestyle can decrease sdLDL levels. Therefore, all the aforementioned parameters should be taken into consideration simultaneously in sdLDL levels reducing strategies.

[10] *Eltonsy S, Doiron MD, Simard P et al.* **Comparing the Effect of Combining Exercise with Rosuvastatin versus Atorvastatin on Lipid Profile and Functional Capacity: A Retrospective Cohort Study**. BioMed research international 2020; 2020:7026530.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32420363
ABSTRACT
Background: Statins and exercise are recommended for managing hypercholesterolemia. However, statin types may vary in their interaction with exercise. We compared rosuvastatin versus atorvastatin combination with exercise on lipid profile and functional capacity. Methods: A retrospective cohort study using data from a 12-week cardiovascular rehabilitation program between 2014 and 2016. Statin use was determined through prescriptions, and the average exercise minutes/week were computed from exercise logs. The outcomes were changes in total cholesterol, low- and high-density lipoproteins (LDL and HDL), triglycerides, and functional capacity (6-minute walk test (6MWT)). Directed acyclic graphs were used to identify potential confounders, accounted for using multiple linear regression modeling. Results: The cohort included 282 patients from 106 atorvastatin and 176 rosuvastatin users. The average exercise minutes/week was 109.4 +/- 66.1 among atorvastatin and 106.7 +/- 49.1 among rosuvastatin users. Interaction models suggested that a higher number of exercise minutes/week were more favorable among atorvastatin users on total cholesterol and LDL (0.004, 95% CI: 0.001, 0.008 and 0.004, 95% CI: 0.001, 0.007, respectively) but did not reach significance for HDL and triglycerides. Rosuvastatin use was associated with greater increases in 6MWT; however, we observed no between-group differences in interaction estimates by the type of statin used. Conclusion: Rosuvastatin use could blunt the beneficial effect of exercise on LDL and total cholesterol compared to atorvastatin. No significant differences were observed in triglycerides, HDL, and functional capacity levels. Additional studies are warranted with randomized treatments and larger samples. Healthcare providers should continue prescribing statins alongside recommending exercise modalities, with a careful follow-up for rosuvastatin users.

[11] *Cook S, Hopstock LA, Eggen AE et al.* **Pharmacological management of modifiable cardiovascular risk factors (blood pressure and lipids) following diagnosis of myocardial infarction, stroke and diabetes: comparison between population-based studies in Russia and Norway**. BMC cardiovascular disorders 2020; 20:234.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32430002
ABSTRACT
BACKGROUND: Cardiovascular disease (CVD) mortality is substantially higher in Russia than in neighbouring Norway. We aimed to compare blood pressure- and lipid-lowering medication use and proportion meeting treatment targets between general population samples in the two countries in those with CVD and diabetes. METHODS: The study population was adults aged 40-69 years reporting a diagnosis of myocardial infarction (MI), stroke and/or diabetes

participating in cross-sectional population-based studies in Russia (Know Your Heart (KYH) 2015-18 N = 626) and Norway (The Tromso Study 2015-16 (Tromso 7) N = 1353). Reported medications were coded according to the 2016 WHO Anatomical Therapeutic Chemical Classification system. Treatment targets were defined using the Joint European Societies guidelines for CVD prevention in clinical practice (2016). RESULTS: Age- and sex-standardized prevalence of use of lipid-lowering medications was higher in Tromso 7 for all three conditions with a disproportionately large difference in those reporting MI (+ 48% (95% CI 39, 57%)). Proportion meeting treatment targets for LDL cholesterol was poor in both studies (age- and sex-standardized prevalence of control KYH vs Tromso 7: MI 5.1% vs 10.1%; stroke 11.6% vs 5.8%; diabetes 24.9% vs 23.3%). Use of antihypertensive medication was higher in KYH for stroke (+ 40% (95% CI 30, 50%)) and diabetes (+ 27% (95% CI 19, 34%)) groups but approximately equal for the MI group (- 1% (95% CI -1, 1%)). Proportion meeting blood pressure targets was lower in KYH vs Tromso 7 (MI 51.8% vs 76.3%; stroke 49.5% vs 69.6%; diabetes 51.9% vs 63.9%). CONCLUSIONS: We identified different patterns of medication use in people with CVD and diabetes. However despite higher use of lipid-lowering medication in the Norwegian study treatment to target for total cholesterol was poor in both Russian and Norwegian studies. In contrast we found higher levels of use of antihypertensive medications in the Russian study but also that less participants met treatment targets for blood pressure. Further work should investigate what factors are responsible for this seeming paradox and how management of modifiable risk factors for secondary prevention could be improved.

[12] *Wu Z, Wu D, Jiang J et al.* **Efficacy and safety of xuezhikang once per day versus two times per day in patients with mild to moderate hypercholesterolaemia (APEX study): a protocol for a multicentre, prospective randomised controlled, open-label, non-inferiority study**. BMJ open 2020; 10:e034585.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32423930
ABSTRACT
INTRODUCTION: Reduction in low-density lipoprotein cholesterol (LDL-C) improves clinical outcomes in patients with coronary artery disease. However, rates of lipid-lowering medication adherence are far from ideal. Reducing dosage frequency from multiple dosing to once-daily dosing may improve patients' medication adherence. Xuezhikang (XZK), an extract of Chinese red yeast rice, contains a family of naturally occurring statins and is traditionally prescribed as 600 mg two times per day. A comParative Efficacy study of XZK (APEX study) is designed to test the hypothesis that XZK prescribed 1200 mg once per day (OD group) is non-inferior to 600 mg two times per day (TD group) in patients with hypercholesterolaemia. METHODS AND ANALYSIS: The APEX study is a multicentre, prospective randomised controlled, open-label, non-inferiority study. We plan to recruit 316 patients aged >/=18 years with a diagnosis of mild to moderate hypercholesterolaemia for primary prevention. Patients will be randomised (1:1) to OD group and TD group. The OD group take XZK 1200 mg once per day after dinner while TD group take a traditional dose of 600 mg, two times per day after meals. Participants will have an 8-week medication period and be followed up at weeks 0, 4 and 8. The primary end point is the mean percentage change from baseline to week 8 in serum LDL-C. Secondary end points are safety and lipid-lowering effect on other lipoproteins and compliance. Data analyses will be on the intention-to-treat principle using non-inferiority analysis. ETHICS AND DISSEMINATION: The research had been approved by the Clinical Research and Laboratory

Animal Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University ((2017)286). The results will be reported through peer-reviewed journals, seminars and conference presentations. TRIAL REGISTRATION NUMBER: ChiCTR-IIR-17013660.

[13] *Jankowski P, Kosior DA, Sowa P et al.* **Secondary prevention of coronary artery disease in Poland. Results from the POLASPIRE survey**. Cardiology journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32436589

ABSTRACT

BACKGROUND: The highest priority in preventive cardiology is given to patients with established coronary artery disease (CAD). The aim of the study was to assess the current implementation of the guidelines for secondary prevention in everyday clinical practice by evaluating control of the main risk factors and the cardioprotective medication prescription rates in patients following hospitalization for CAD. METHODS: Fourteen departments of cardiology participated in the study. Patients (aged </= 80 years) hospitalized due an acute coronary syndrome or for a myocardial revascularization procedure were recruited and interviewed 6-18 months after the hospitalization. RESULTS: Overall, 947 patients were examined 6-18 months after hospitalization. The proportion of patients with high blood pressure (>/= 140/90 mmHg) was 42%, with high low-density lipoprotein cholesterol (LDL-C >/= 1.8 mmol/L) 62%, and with high fasting glucose (>/= 7.0 mmol/L) 22%, 17% of participants were smokers and 42% were obese. The proportion of patients taking an antiplatelet agent 6-18 months after hospitalization was 93%, beta-blocker 89%, angiotensin converting enzyme inhibitor or sartan 86%, and a lipid-lowering drug 90%. Only 2.3% patients had controlled all the 5 main risk factors well (non-smoking, blood pressure < 140/90 mmHg, LDL-C < 1.8 mmol/L and glucose < 7.0 mmol/L, body mass index < 25 kg/m(2)), while 17.9% had 1 out of 5, 40.9% had 2 out of 5, and 29% had 3 out of 5 risk factors uncontrolled. CONCLUSIONS: The documented multicenter survey provides evidence that there is considerable potential for further reductions of cardiovascular risk in CAD patients in Poland. A revision of the state funded cardiac prevention programs seems rational.

[14] *Toso A, Leoncini M, Maioli M et al.* **A Prospective, Randomized, Open-Label Trial of Atorvastatin versus Rosuvastatin in the Prevention of Contrast-Induced Acute Kidney Injury, Worsened Renal Function at 30 Days, and Clinical Events After Acute Coronary Angiography: the PRATO-ACS-2 Study**. Cardiorenal Med 2020:1-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32434204

ABSTRACT

BACKGROUND/AIMS: Both high-dose atorvastatin and rosuvastatin have been shown to reduce contrast-induced acute kidney injury (AKI) occurrence and improve clinical outcomes in high-risk coronary patients undergoing angiographic procedures. However, there is a lack of head-to-head comparative studies on the effects of atorvastatin or rosuvastatin administered upon hospital admission in statin-naive patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS). METHODS: In this open-label, noninferiority study, we compared changes in renal function in 709 NSTE-ACS patients randomized to atorvastatin (80 mg upon admission followed by 40 mg/day) or rosuvastatin (40 mg upon admission followed by 20 mg/day). The primary end point was AKI (increase in serum creatinine >/=0.5 mg/dL or >/=25% above baseline within 72 h). Worsening renal function (WRF) (decrease of >/=25% in the glomerular filtration rate from baseline to 30 days), 30-day major adverse cardiovascular

events, and 12-month myocardial infarction (MI) or death were also evaluated. RESULTS: The AKI incidence was similar in the 2 groups (i.e., 8.2% with rosuvastatin and 7.6% with atorvastatin; absolute risk difference = 0.54; 90% CI -3.9 to 2.8), satisfying the noninferiority criteria. WRF occurred in 53 (7.5%) patients, 19 (34%) of whom had developed AKI. The rates of WRF and adverse events at 30 days and at 12 months did not differ significantly between the 2 groups. Both AKI and WRF were found to be closely associated with the 12-month cardiovascular outcome irrespectively of statin choice. CONCLUSIONS: High-dose rosuvastatin or atorvastatin started upon hospital admission led to similar rates of AKI, 30-day renal function changes, and 12-month death or MI in NSTE-ACS patients who underwent an early invasive strategy (clinical trial registration: https://www.clinicaltrials.gov; unique identifier: NCT01870804).

[15] *Na E, Cho S, Kim DJ et al.* **Time-varying and dose-dependent effect of long-term statin use on risk of type 2 diabetes: a retrospective cohort study**. Cardiovascular diabetology 2020; 19:67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32416728
ABSTRACT
BACKGROUND: We evaluated the effect of statin use on new-onset type 2 diabetes among individuals without atherosclerotic cardiovascular disease (ASCVD) using nationally representative South Korean claims data (2002-2013, N = 1,016,820). METHODS: A total of 13,698 patients (statin users 5273, non-statin users 5273) aged 40-74 years, newly diagnosed with dyslipidemia but without any history of diabetes or ASCVD, were selected in 2005. We followed up the final sample until 2013 and evaluated the cumulative incidence of type 2 diabetes. We used extended Cox regression models to estimate the time-varying adjusted hazard ratios of statin use on new-onset type 2 diabetes. We performed further analyses based on the cumulative defined daily dose of statin received per year to evaluate the degree of risk compared to non-statin users. RESULTS: Over the mean follow-up period of 7.1 years, 3034 patients developed type 2 diabetes; the number of statin users exceeded that of non-users, demonstrating that statin use significantly increased the risk of new-onset type 2 diabetes. The risk of new-onset type 2 diabetes differed among statin users according to cDDD per year (adjusted HR = 1.31 [95% CI 1.18-1.46] for less than 30 cDDD per year; 1.58 [1.43-1.75] for 30-120 cDDD per year; 1.83 [1.62-2.08] for 120-180 cDDD per year; and 2.83 [2.51-3.19] for more than 180 cDDD per year). The diabetogenic effect of pitavastatin was not statistically significant, but the risk was the largest for atorvastatin. Long-term exposure (>/= 5 years) to statins was associated with a statistically significant increase in the risk of new onset type 2 diabetes in all statin subtypes explored, with the highest magnitude for simvastatin (HR = 1.916, 95% CI 1.647-2.228) followed by atorvastatin (HR = 1.830, 95% CI 1.487-2.252). CONCLUSIONS: Statin use was significantly associated with an increased risk of new-onset type 2 diabetes. We also found a dose-response relationship in terms of statin use duration and dose maintenance. Periodic screening and monitoring for incident type 2 diabetes may be warranted in long-term statin users.

[16] *Bae SS, Oganesian B, Golub I, Charles-Schoeman C*. **Statin use in patients with non-HMGCR idiopathic inflammatory myopathies: A retrospective study**. Clinical cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32432360

ABSTRACT
BACKGROUND: Statins are the most widely used lipid lowering therapies which reduce cardiovascular risk, but are associated with muscular adverse events (AEs). Idiopathic inflammatory myopathies (IIM) are autoimmune diseases of the muscle with higher risk of cardiovascular disease. More data is needed regarding statin safety in patients with intrinsic muscle disease such as IIM. HYPOTHESIS: Statins are tolerated in patients with IIM without leading to significant increase in muscular AEs. METHODS: Statin use was retrospectively examined in a longitudinal IIM cohort. Safety analysis included assessment of muscular and nonmuscular AEs by chart review. IIM patients receiving a statin during the cohort follow-up period were matched to IIM patients not receiving a statin for comparative analysis of longitudinal outcomes. RESULTS: 33/214 patients had a history of statin use. 63% started for primary prevention, while others were started for clinical ASCVD events, vascular surgery, IIM related heart failure, and cardiac transplantation. A high intensity statin was used in nine patients with non-HMGCR myositis, and tolerated in 8/9 patients. Statin related muscular AE was noted in three patients. There were no cases of rhabdomyolysis, or statin related nonmuscular AEs in a median observation period of 5 years. In patients newly started on statins during cohort follow-up (n = 7) there was no change in disease activity after statin initiation. Long term outcomes were not different between statin and nonstatin IIM control groups. CONCLUSION: Statins were well tolerated in patients with non-HMGCR positive IIM. Given the accelerated atherosclerotic risk in IIM patients, further prospective studies of statin safety in IIM patients are warranted.

[17] *Biondi RB, Salmazo PS, Bazan SGZ et al.* **Cardiovascular Risk in Individuals with Inflammatory Bowel Disease**. Clin Exp Gastroenterol 2020; 13:107-113.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32425576

ABSTRACT
Background: Inflammatory bowel disease (IBD) patients present a higher risk of developing cardiovascular diseases due to the presence of chronic inflammation, which plays an essential role in atherogenesis. Therefore, the aim of the study was to evaluate the cardiovascular risk between patients with IBD and healthy control individuals. Materials and Methods: A total of 52 consecutive IBD outpatients from a tertiary hospital and 37 healthy controls were enrolled. Data collected included age, sex, smoking status, presence of comorbidities, disease activity, ongoing medical treatment, body mass index, arterial blood pressure, and cardiovascular risk. The cardiovascular risk was based on the Framingham risk score and ultrasonography variables, such as the carotid intima-media thickness and the presence of atherosclerotic plaque in the carotid. Multivariate logistic regression or multiple linear regression analysis was performed at a significance level of 5%. Results: No differences were observed between groups with regard to age, sex, smoking status, comorbidities, blood pressure, body mass index, lipid profile, and Framingham risk score. In the IBD group, fasting glucose [95 (86.2-107.3) mg/dL vs 86 (79-100) mg/dL, p=0.041], carotid intima-media thickness (0.69+/-0.12 mm vs 0.63+/-0.12 mm, p=0.031), and atherosclerotic carotid plaque (25% vs 5.4%, p=0.032) were higher compared with those in the control group. Multivariate logistic regression analysis showed that patients with IBD presented a 6.45-fold higher risk of carotid atherosclerotic plaque (odds ratio: 6.45; 95% confidence interval: 1.035-40.216; p<0.046). Conclusion: Patients with IBD are at an increased risk of atherosclerosis and, consequently, an increased risk for cardiovascular diseases.

[18] *Broch K, Gude E, Karason K et al.* **Cholesterol-lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients: Design of the randomized controlled EVOLVD trial**. Clinical transplantation 2020:e13984.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32445429
ABSTRACT
BACKGROUND: Cardiac allograft vasculopathy (CAV) is characterized by diffuse thickening of the arterial intima. Statins reduce the incidence of CAV, but despite the use of statins, CAV remains one of the leading causes of long-term death after heart transplant. Inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9) substantially reduce cholesterol levels but have not been tested in heart transplant recipients. METHODS: The Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients (EVOLVD) trial (ClinicalTrials.gov Identifier: NCT03734211) is a randomized, double-blind trial designed to test the effect of the PCSK9 inhibitor evolocumab on coronary intima thickness in heart transplant recipients. Adults who have received a cardiac transplant within the past 4 - 8 weeks are eligible. Exclusion criteria include an estimated glomerular filtration rate < 20 mL/min/1.73 m(2) , renal replacement therapy, or contraindications to coronary angiography with intravascular ultrasound. 130 patients will be randomized (1:1) to 12-months' treatment with evolocumab or matching placebo. The primary endpoint is the coronary artery intima thickness as measured by intravascular ultrasound. CONCLUSION: The EVOLVD trial is a randomized clinical trial designed to show whether treatment with the PCSK9 inhibitor evolocumab can ameliorate CAV over the first year after heart transplant.

[19] *Bagias C, Xiarchou A, Bargiota A, Tigas S*. **Familial Partial Lipodystrophy (FPLD): Recent Insights**. Diabetes, metabolic syndrome and obesity : targets and therapy 2020; 13:1531-1544.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32440182
ABSTRACT
Lipodystrophies are a heterogeneous group of congenital or acquired disorders, characterized by partial or generalized loss of adipose tissue. Familial partial lipodystrophy (FPLD) presents with genetic and phenotypic variability with insulin resistance, hypertriglyceridemia and hepatic steatosis being the cardinal metabolic features. The severity of the metabolic derangements is in proportion with the degree of lipoatrophy. The underpinning pathogenetic mechanism is the limited capacity of adipose tissue to store lipids leading to lipotoxicity, low-grade inflammation, altered adipokine secretion and ectopic fat tissue accumulation. Advances in molecular genetics have led to the discovery of new genes and improved our knowledge of the regulation of adipose tissue biology. Diagnosis relies predominantly on clinical findings, such as abnormal fat tissue topography and signs of insulin resistance and is confirmed by genetic analysis. In addition to anthropometry and conventional imaging, new techniques such as color-coded imaging of fat depots allow more accurate assessment of the regional fat distribution and differentiation of lipodystrophic syndromes from common metabolic syndrome phenotype. The treatment of patients with lipodystrophy has proven to be challenging. The use of a human leptin analogue, metreleptin, has recently been approved in the management of FPLD with evidence suggesting improved metabolic profile, satiety, reproductive function and self-perception. Preliminary data on the use of glucagon-like peptide 1 receptor agonists (GLP1 Ras) and sodium-glucose co-transporter 2 (SGLT2) inhibitors in cases of FPLD have shown

promising results with reduction in total insulin requirements and improvement in glycemic control. Finally, investigational trials for new therapeutic agents in the management of FPLD are underway.

[20] *Reda A, Elserafy AS, Farag E et al.* **Egyptian Association of Vascular Biology and Atherosclerosis (EAVA) consensus on the usage of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors**. The Egyptian heart journal : (EHJ) : official bulletin of the Egyptian Society of Cardiology 2020; 72:23.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32424543
ABSTRACT
BACKGROUND: The current expert view of the PCSK9 inhibitors' use in Egypt is still ambiguous. MAIN BODY: Hyperlipidemia is an important, if not the most important, risk factor for the occurrence of atherosclerosis worldwide. Egypt is the most populous country in the Middle East and North Africa and has > 15% of the cardiovascular deaths in the region. The burden of dyslipidemia as seen in the recently published CardioRisk project conducted throughout Egypt shows a high prevalence of dyslipidemia as a risk factor that is still reaching up to 71% in female participants. Reaching the targets for LDL lowering, and thus control of hyperlipidemia, is quite often very difficult especially with the update of the last ESC guidelines. With the advent of PCSK9 inhibitors, the control rate of patients, reduction of cardiac major adverse events, and mortality have been improved. However, Egypt is not considered a rich country on the grounds of annual income, and this raises a concern on which patients would benefit from these expensive medications. Revising the randomized control trials, we analyzed the data that would enable us to control LDL in those patients, at risk, to obtain simple clear indications for the use of these rather expensive medications. CONCLUSION: We recommend the use of PCSK9 inhibitors in addition to statins +/- ezetimibe in patients with ASCVD, by definition at very high risk; patients with ASCVD at very high risk who do not tolerate appropriate doses of at least three statins; and familial hypercholesterolaemia patients with clinically diagnosed ASCVD, at very high cardiovascular risk.

[21] *Chen K, Ma Z, Yan X et al.* **Investigation of the Lipid-Lowering Mechanisms and Active Ingredients of Danhe Granule on Hyperlipidemia Based on Systems Pharmacology**. Frontiers in pharmacology 2020; 11:528.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32435189
ABSTRACT
Objective: Investigate the active ingredients and underlying hypolipidemic mechanisms of Danhe granule (DHG). Methods: The lipid-lowering effect of DHG was evaluated in hyperlipidemic hamsters induced by a high-fat diet. The ingredients absorbed into the blood after oral administration of DHG in hamsters were identified by ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-Q-TOF/MS). A systems pharmacology approach incorporating target prediction and network construction, gene ontology (GO) enrichment and pathway analysis was performed to predict the active compounds and map the compounds-targets-disease network. Real-time polymerase chain reaction (RT-PCR) and Western blot were utilized to analyze the mRNA and protein expression levels of predicted targets. Results: DHG remarkably lowered the levels of serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), and arteriosclerosis index (AI), at the same time, elevated the levels of serum high-density

lipoprotein cholesterol (HDL-c) and HDL-c/TC ratio in hyperlipidemic hamsters. Sixteen ingredients absorbed into blood after oral administration of DHG were identified as the possible components interacted with targets. Moreover, 65 potential targets were predicted after targets intersection and compounds-targets-disease network mapping. Then, compounds-targets-pathways network mapping revealed that six active compounds (emodin, naringenin, etc.) compounds could interact with 10 targets such as sterol regulatory element binding protein (SREBP) 1c, SREBP-2 and peroxisome proliferation-activated receptor (PPAR) alpha, regulate three lipid metabolism-related pathways including SREBP control of lipid synthesis pathway, PPAR signaling pathway and nuclear receptors in lipid metabolism and toxicity pathway, and further affect lipid metabolic processes including fatty acid biosynthesis, low-density lipoprotein receptor (LDLR)-mediated cholesterol uptake, bile acid biosynthesis, and cholesterol efflux. Experimental results indicated that DHG significantly increased SREBP-2, LDLR, PPARalpha, liver X receptor alpha (LXRalpha), cholesterol 7alpha-hydroxylase (CYP7A1), and ATP binding cassette subfamily A member 1 (ABCA1) mRNA and protein expressions while decreased SREBP-1c and fatty acid synthase (FAS) mRNA, and protein expressions. Conclusion: DHG possessed a good hypolipidemic effect that may be through affecting the mRNA and protein expressions of SREBP-1c, FAS, SREBP-2, LDLR, PPARalpha, LXRalpha, CYP7A1, and ABCA1, involving in fatty acid synthesis, LDLR-mediated cholesterol uptake, bile acid biosynthesis, and cholesterol efflux. This study further provided experimental evidence about its practical application for treating hyperlipidemia and its complications.

[22] *Nambi V, Hussain A, Stein JH*. **Safety of Evolocumab in People Living With HIV Infection: An Important First Step**. Journal of the American College of Cardiology 2020; 75:2585-2587.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32439007
ABSTRACT

[23] *Fujisue K, Yamanaga K, Nagamatsu S et al.* **Effects of Statin Plus Ezetimibe on Coronary Plaques in Acute Coronary Syndrome Patients with Diabetes Mellitus: Sub-Analysis of PRECISE-IVUS Trial**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32435011
ABSTRACT
AIM: Coronary plaque regression is weak in acute coronary syndrome (ACS) patients with diabetes mellitus (DM). We evaluated whether dual lipid-lowering therapy (DLLT) with ezetimibe and atorvastatin attenuates coronary plaques in ACS patients with DM. METHODS: The prospective, randomized controlled, multicenter PRECISE-IVUS (Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial assigned 246 patients undergoing percutaneous coronary intervention to DLLT or atorvastatin monotherapy and evaluated IVUS-derived changes in percent atheroma volume (DeltaPAV), at baseline and 9-12-month follow-up, in 126 ACS cases, including 25 DM patients. The atorvastatin dose was up-titrated to achieve low-density lipoprotein cholesterol (LDL-C) 70 mg/dL. RESULTS: In DM patients, the monotherapy group (n=13) and the DLLT group (n=12) showed a similar prevalence of coronary risks and baseline lipid profiles. During the study, the change in LDL-C level was similar between DM and non-DM patients. Compared with non-DM patients, DM patients showed weaker regression of DeltaPAV by DLLT than those who underwent monotherapy (DM: -2.77+/-3.47% vs. -0.77+/-2.51%, P=0.11;

non-DM: -2.01+/-3.36% vs. -0.08+/-2.66%, P=0.008). The change in LDL-C level was not correlated with DeltaPAV in non-DM patients, but there was significant correlation between the change in LDL-C level and DeltaPAV in DM patients (r=0.52, P=0.008). CONCLUSIONS: ACS patients with DM showed weaker coronary plaque regression than their counterparts. A significant correlation between the change in LDL-C level and DeltaPAV in DM patients suggested that more intensive lipid-lowering therapy is required in ACS patients with DM.

[24] *Masuda D, Kiyosue A, Hirayama A et al.* **Evolocumab Effects on Lipoproteins, Measured by High-Performance Liquid Chromatography**. Journal of atherosclerosis and thrombosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32435010
ABSTRACT
AIMS: Profiling of lipoproteins can predict risk of cardiovascular disease; gel permeation high-performance liquid chromatography (HPLC) improves prediction accuracy by providing detailed data for specific lipoprotein subclasses. This study applied HPLC to examine the effects of evolocumab, which effectively treats hyperlipidemia and mixed dyslipidemia, on lipoprotein subclasses, specifically the number and size of lipoprotein particles. METHODS: This post-hoc analysis used patient blood samples from YUKAWA-2, a phase 3 trial evaluating the efficacy of evolocumab in Japanese adult patients with hyperlipidemia or mixed dyslipidemia and at high risk for cardiovascular disease. We used HPLC to assess observed values and percent change from baseline in cholesterol and triglyceride (TG) concentrations, number of particles in lipoprotein subclasses to week 12, and mean observed values and mean percent change from baseline in variables to weeks 10 and 12. HPLC was also compared with conventional methods in assessing low-density lipoprotein (LDL) cholesterol (LDL-C) values. RESULTS: Data for all 404 patients were analyzed. Evolocumab significantly decreased cholesterol and TG concentrations, and total particle count, in very low-density lipoprotein (VLDL) and LDL subclasses. Particle size increased slightly in LDL, high-density lipoprotein (HDL), and VLDL, but data varied widely. At very low LDL-C, HPLC measurements were higher than those from conventional methods. CONCLUSION: This research used HPLC to assess the effects of evolocumab in 20 lipid subclasses. By lowering lipid content and improving the lipid profile, evolocumab may reduce atherogenicity. This reduction is better quantified by HPLC than by conventional methods in the very low LDL-C range.

[25] *Nakamura A, Kanazawa M, Kagaya Y et al.* **Plasma kinetics of mature PCSK9, furin-cleaved PCSK9, and Lp(a) with or without administration of PCSK9 inhibitors in acute myocardial infarction**. J Cardiol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32439340
ABSTRACT
BACKGROUND: There are two types of circulating proprotein convertase subtilisin/kexin type 9 (PCSK9), mature and furin-cleaved. Most types of lipoprotein(a) [Lp(a)], an independent risk factor of cardiovascular events, bind to mature PCSK9. OBJECTIVE: This study examined the effects of monoclonal anti-PCSK9 antibody on plasma PCSK9 and Lp(a) levels in acute myocardial infarction (MI). METHODS: Acute MI patients (n=36) were randomly divided into evolocumab (140mg; n=17) and non-evolocumab (n=19) groups. Changes in plasma PCSK9 and Lp(a) levels were monitored before and 1, 3, 5, 10, and 20 days after evolocumab administration. RESULTS: In the non-evolocumab group, plasma levels of mature PCSK9,

furin-cleaved PCSK9, and Lp(a) (236.4+/-57.3ng/mL, 22.4+/-5.8ng/mL, and 19.2.+/-16.5mg/dL, respectively) significantly increased by day 3 (408.8+/-77.1ng/mL, p<0.001; 47.2+/-15.7ng/mL, p<0.001; and 39.7+/-21.3mg/dL, p<0.005, respectively) and returned to the baseline by day 10 or 20. In the evolocumab group, mature PCSK9 significantly increased by >1000ng/mL with a simultaneous decline of furin-cleaved PCSK9 below the measurement sensitivity level after day 3. The incremental area under the curve for plasma Lp(a) levels was significantly smaller in the evolocumab group compared with the non-evolocumab group (p=0.038). CONCLUSION: Mature and furin-cleaved PCSK9 are transiently upregulated after MI onset. Evolocumab significantly increases mature PCSK9 and decreases furin-cleaved PCSK9 and might inhibit transient increase of plasma Lp(a) in acute MI.

[26] *Chiu SW, Pratt CM, Feinn R, Chatterjee S*. **Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors and Ezetimibe on Risk of New-Onset Diabetes: A Systematic Review and Meta-Analysis of Large, Double-Blinded Randomized Controlled Trials**. Journal of cardiovascular pharmacology and therapeutics 2020:1074248420924983.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32419478
ABSTRACT
BACKGROUND: Previous meta-analyses have shown that statins may cause incident diabetes. This article reviews randomized controlled trials using proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i) or ezetimibe on the risk of new-onset diabetes. METHODS: Eight trials involving PCSK9i and 3 trials of ezetimibe were selected for review. PubMed, Cochrane Central Register of Controlled Trials, and Clinicaltrials.gov were thoroughly searched for relevant trials. Inclusion criteria included at least 100 patients per treatment arm, follow-up of at least 52 weeks, and at least double-blinded study design. Exclusion criteria included patients with previously diagnosed diabetes, nonrandomized, placebo-controlled, open-label, and crossover trials. The primary outcome was the number of incident diabetes cases. A random effects model was used. Heterogeneity in effect sizes was measured with I (2) parameter and the Q statistic was used to test for excessive between-study heterogeneity. RESULTS: A total of 52 214 participants for the PCSK9i and a total of 20 084 for the ezetimibe meta-analyses were included. Participants randomized to PCSK9i did not differ from the control patients in diabetes incidence (risk ratio [RR] = 0.99, P = .87, 95% CI = 0.92-1.07). Participants randomized to ezetimibe did not differ from the control patients in diabetes incidence (RR = 1.05, P = .37, 95% CI = 0.95-1.15). DISCUSSION: The use of PCSK9i and ezetimibe does not appear to impact the risk of incident diabetes mellitus when added to guideline-directed medical therapy.

[27] *Gencer B, Mach F, Murphy SA et al.* **Efficacy of Evolocumab on Cardiovascular Outcomes in Patients With Recent Myocardial Infarction: A Prespecified Secondary Analysis From the FOURIER Trial**. JAMA cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32432684
ABSTRACT
Importance: The 2018 American Heart Association/American College of Cardiology Multisociety Guideline on the Management of Blood Cholesterol identified patients with recent (past 12 months) myocardial infarction (MI) as very high risk, in whom a PCSK9 inhibitor is reasonable to add to maximally tolerated statin combined with ezetimibe if their low-density lipoprotein cholesterol level is 70 mg/dL or greater or non-high-density lipoprotein cholesterol

level is 100 mg/dL or greater. Objective: To examine the clinical efficacy of evolocumab in patients with recent MI. Design, Setting, and Participants: This was a prespecified secondary analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, in which 27 564 patients with atherosclerotic cardiovascular disease treated with a statin were randomized to evolocumab vs placebo. Patients with prior MI with a known date (n = 22320) were stratified as having a recent MI (within 12 months of randomization) or a remote MI (more than 12 months prior to randomization). Per protocol, patients with MI within 4 weeks prior to randomization were excluded from the FOURIER trial. Data were collected from February 2013 to November 2016, and data were analyzed from May 2019 to February 2020. Main Outcomes and Measures: The primary composite end point was cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary composite end point was cardiovascular death, MI, or stroke. Results: Of 22320 included patients, 17516 (78.5%) were male, and the mean (SD) age was 62.2 (9.0) years. Compared with 16609 patients with a remote MI, 5711 patients with a recent MI were younger and more likely to be treated with high-intensity statin (77.3% [4415] vs 69.3% [11506]). In the placebo arm, the 3-year Kaplan-Meier rate for the primary end point was 17.2% in patients with recent MI compared with 14.4% in those with remote MI (adjusted HR, 1.45; 95% CI, 1.29-1.64; P < .001). Similarly, the 3-year Kaplan-Meier rates for the key secondary end point was also higher in those with recent MI (10.9% vs 9.5%; adjusted HR, 1.45; 95% CI, 1.24-1.69; P < .001). In patients with a recent MI, evolocumab reduced the risk of the primary and key secondary end points by 19% (hazard ratio [HR], 0.81; 95% CI, 0.70-0.93) and 25% (HR, 0.75; 95% CI, 0.62-0.91), respectively. In patients with a remote MI, evolocumab reduced the risk of the primary and key secondary end points by 8% (HR, 0.92; 95% CI, 0.84-1.01; P for interaction = .13) and 15% (HR, 0.85; 95% CI, 0.76-0.96; P for interaction = .24), respectively. Given the higher event rates in patients with a recent MI, the absolute risk reductions over 3 years with evolocumab were 3.7% in those with recent MI vs 1.1% in those with remote MI for the primary end point and 3.2% vs 1.3%, respectively, for the key secondary end point. Conclusions and Relevance: Patients with a recent MI were at higher risk of cardiovascular events and tended to experience greater absolute risk reductions with evolocumab than those with remote MIs. These findings support the concept in US and European guidelines to aggressively lower low-density lipoprotein cholesterol levels in very high-risk patients, such as those with a recent MI. Trial Registration: ClinicalTrials.gov Identifier: NCT01764633.

[28] *Khan SU, Khan MZ, Raghu Subramanian C et al.* **Participation of Women and Older Participants in Randomized Clinical Trials of Lipid-Lowering Therapies: A Systematic Review**. JAMA network open 2020; 3:e205202.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32437574
ABSTRACT
Importance: Randomized clinical trials (RCTs) of lipid-lowering therapies form the evidence base for national and international guidelines. However, concerns exist that women and older patients are underrepresented in RCTs. Objective: To determine the trends of representation of women and older patients (>/=65 years) in RCTs of lipid-lowering therapies from 1990 to 2018. Data Sources: The electronic databases of MEDLINE and ClinicalTrials.gov were searched from January 1990 through December 2018. Study Selection: RCTs of lipid-lowering therapies with sample sizes of at least 1000 patients and follow-up periods of at least 1 year

were included. Data Extraction and Synthesis: Two independent investigators abstracted the data on a standard data collection form. Main Outcomes and Measures: Patterns of representation of women and older adults were examined overall in lipid-lowering RCTs and according to RCT-level specific characteristics. The participation-to-prevalence ratio (PPR) metric was used to estimate the representation of women compared with their share of disease burden. Results: A total of 60 RCTs with 485409 participants were included. The median (interquartile range) number of participants per trial was 5264 (1062-27564). Overall, representation of women was 28.5% (95% CI, 24.4%-32.4%). There was an increase in the enrollment of women from the period 1990 to 1994 (19.5%; 95% CI, 18.4%-20.5%) to the period 2015 to 2018 (33.6%; 95% CI, 33.4%-33.8%) (P for trend = .01). Among common limiting factors were inclusion of only postmenopausal women or surgically sterile women (28.3%; 95% CI, 18.5%-40.7%) or exclusion of pregnant (23.3%; 95% CI, 14.4%-35.4%) and lactating (16.6%; 95% CI, 9.3%-28.1%) women. Women were underrepresented compared with their disease burden in lipid RCTs of diabetes (PPR, 0.74), heart failure (PPR, 0.27), stable coronary heart disease (PPR, 0.48), and acute coronary syndrome (PPR, 0.51). Only 23 RCTs with 263628 participants reported the proportion of older participants. Overall representation of older participants was 46.7% (95% CI, 46.5%-46.9%), which numerically increased from 31.6% (95% CI, 30.8%-32.3%) in the period 1995 to 1998 to 46.2% (95% CI, 46.0%-46.5%) in the period 2015 to 2018 (P for trend = .43). A total of 53.0% (95% CI, 41.8%-65.3%) and 36.6% (95% CI, 25.6% to 49.3%) trials reported outcomes according to sex and older participants, respectively, which did not improve over time. Conclusions and Relevance: In this systematic review of RCTs of lipid-lowering therapies, the enrollment of women and older participants increased over time, but women and older participants remained consistently underrepresented. This limits the evidence base for efficacy and safety in these subgroups.

[29] *Mickiewicz A, Futema M, Cwiklinska A et al.* **Higher Responsiveness to Rosuvastatin in Polygenic versus Monogenic Hypercholesterolaemia: A Propensity Score Analysis**. Life (Basel) 2020; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32443900
ABSTRACT
Background: The monogenic defect in familial hypercholesterolemia (FH) is detected in approximately 40% of cases. The majority of mutation-negative patients have a polygenic cause of high LDL-cholesterol (LDL-C). We sought to investigate whether the underlying monogenic or polygenic defect is associated with the response to rosuvastatin. METHODS: FH Individuals were tested for mutations in LDLR and APOB genes. A previously established LDL-C-specific polygenic risk score (PRS) was used to examine the possibility of polygenic hypercholesterolemia in mutation-negative patients. All of the patients received rosuvastatin and they were followed for 8 +/- 2 months. A propensity score analysis was performed to evaluate the variables associated with the response to treatment. RESULTS: Monogenic subjects had higher mean (+/-SD) baseline LDL-C when compared to polygenic (7.6 +/- 1.5 mmol/L vs. 6.2 +/- 1.2 mmol/L; $p < 0.001$). Adjusted model showed a lower percentage of change in LDL-C after rosuvastatin treatment in monogenic patients vs. polygenic subjects (45.9% vs. 55.4%, $p < 0.001$). The probability of achieving LDL-C targets in monogenic FH was lower than in polygenic subjects (0.075 vs. 0.245, $p = 0.004$). Polygenic patients were more likely to achieve LDL-C goals, as compared to those monogenic (OR 3.28; 95% CI: 1.23-8.72). CONCLUSION: Our findings indicate an essentially higher responsiveness to

rosuvastatin in FH patients with a polygenic cause, as compared to those carrying monogenic mutations.

[30] *Kruse AB, Kowalski CD, Leuthold S et al.* **What is the impact of the adjunctive use of omega-3 fatty acids in the treatment of periodontitis? A systematic review and meta-analysis**. Lipids in health and disease 2020; 19:100.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32438906
ABSTRACT
BACKGROUND: Host modulation therapy has gained increasing interest in periodontal therapy. This systematic review aimed to evaluate the effects of adjunctive administration of omega-3 fatty acids in periodontal therapy. METHODS: The search strategy was determined using the "patient, intervention, comparison, outcome" model. A resulting search term was generated using keywords, and the databases were fed. The databases PubMed, Cochrane Library, and LIVIVO were used. Studies were selected for the literature review based on previously specified inclusion and exclusion criteria. Randomized, controlled, blinded studies, longitudinal studies, comparative studies, and clinical studies were included in the review. Additionally, they used omega-3 fatty acids in the treatment of periodontitis. The following parameters were observed: clinical attachment level (CAL), probing depth (PD), gingival index (GI), bleeding on probing (BOP) and plaque index (PI). A meta-analysis was performed for PD and CAL after 3 months. By analyzing the risk of bias, the validity of the results of each study was demonstrated, and its credibility and quality were assessed. RESULTS: Of 14 studies found, six were included. The results showed a significant reduction in PD and CAL compared to that in the placebo groups in four out of six involved studies, which was confirmed by the meta-analysis. In one study, a significant reduction in BOP was found. GI was significantly reduced in three included studies. PI also showed a significant reduction in three studies. CONCLUSIONS: Within the study limitations, omega-3 fatty acids appear to have a positive effect on periodontal wound healing with regard to reduction in CAL and PD. Based on the results, patients receiving periodontal treatment might benefit from nutritional counseling.

[31] *Wei CJ, Zou CY, Wang ZM, Jiang YJ*. **Association between serum lipoprotein levels and cognitive impairment in acute cerebral infarction: A protocol for systematic review and meta-analysis**. Medicine (Baltimore) 2020; 99:e20178.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32443336
ABSTRACT
BACKGROUND: The objective of this study is to examine the association between serum lipoprotein levels (SLL) and cognitive impairment (CI) in patients with acute cerebral infarction (ACI). METHODS: All published studies will be searched from the following electronic databases: PubMed, EMBASE, Cochrane Library, PsycINFO, Web of Science, WANGFANG, and China National Knowledge Infrastructure from inauguration of each electronic database up to March 1, 2020. In addition, we will also search other sources, such as dissertations, Google scholar, conference proceedings, and reference lists of relevant reviews. We will not apply any language restrictions to the electronic databases. Two researchers will independently carry out literature selection, data collection, and methodological quality. A third researcher will help to solve any divergences by discussion. The RevMan 5.3 software will be employed to pool the collected data and to analyze the outcome data. RESULTS: This study will scrutinize the association between SLL and CI in patients with ACI. CONCLUSIONS: The results of this

study will present helpful evidence of the association between SLL and CI in patients with ACI.Registration number: INPLASY202040018.

[32] *Alkhalil M*. **Lipoprotein(a) Reduction in Persons with Cardiovascular Disease**. The New England journal of medicine 2020; 382:e65.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32433851
ABSTRACT

[33] *Andreotti F, Maggioni AP*. **Lipoprotein(a) Reduction in Persons with Cardiovascular Disease**. The New England journal of medicine 2020; 382:e65.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32433852
ABSTRACT

[34] *Creager MA*. **A Bon VOYAGER for Peripheral Artery Disease**. The New England journal of medicine 2020; 382:2047-2048.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32433842
ABSTRACT

[35] *Ferro CJ, Sarafidis P, Ortiz A*. **Lipoprotein(a) Reduction in Persons with Cardiovascular Disease**. The New England journal of medicine 2020; 382:e65.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32433853
ABSTRACT

[36] *Tsimikas S, Karwatowska-Prokopczuk E, Xia S*. **Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. Reply**. The New England journal of medicine 2020; 382:e65.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32433854
ABSTRACT

[37] *Johnson EL, Heaver SL, Waters JL et al.* **Sphingolipids produced by gut bacteria enter host metabolic pathways impacting ceramide levels**. Nature communications 2020; 11:2471.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32424203
ABSTRACT
Gut microbes are linked to host metabolism, but specific mechanisms remain to be uncovered. Ceramides, a type of sphingolipid (SL), have been implicated in the development of a range of metabolic disorders from insulin resistance (IR) to hepatic steatosis. SLs are obtained from the diet and generated by de novo synthesis in mammalian tissues. Another potential, but unexplored, source of mammalian SLs is production by Bacteroidetes, the dominant phylum of the gut microbiome. Genomes of Bacteroides spp. and their relatives encode serine palmitoyltransfease (SPT), allowing them to produce SLs. Here, we explore the contribution of SL-production by gut Bacteroides to host SL homeostasis. In human cell culture, bacterial SLs are processed by host SL-metabolic pathways. In mouse models, Bacteroides-derived lipids transfer to host epithelial tissue and the hepatic portal vein. Administration of B. thetaiotaomicron to mice, but not an SPT-deficient strain, reduces de novo SL production and increases liver ceramides. These results indicate that gut-derived bacterial SLs affect host lipid metabolism.

[38] *Adorni MP, Zimetti F, Lupo MG et al.* **Naturally Occurring PCSK9 Inhibitors**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32429343
ABSTRACT
Genetic, epidemiological and pharmacological data have led to the conclusion that antagonizing or inhibiting Proprotein convertase subtilisin/kexin type 9 (PCSK9) reduces cardiovascular events. This clinical outcome is mainly related to the pivotal role of PCSK9 in controlling low-density lipoprotein (LDL) cholesterol levels. The absence of oral and affordable anti-PCSK9 medications has limited the beneficial effects of this new therapeutic option. A possible breakthrough in this field may come from the discovery of new naturally occurring PCSK9 inhibitors as a starting point for the development of oral, small molecules, to be used in combination with statins in order to increase the percentage of patients reaching their LDL-cholesterol target levels. In the present review, we have summarized the current knowledge on natural compounds or extracts that have shown an inhibitory effect on PCSK9, either in experimental or clinical settings. When available, the pharmacodynamic and pharmacokinetic profiles of the listed compounds are described.

[39] *Meng H, Zhu L, Kord-Varkaneh H et al.* **Effects of intermittent fasting and energy-restricted diets on lipid profile: A systematic review and meta-analysis**. Nutrition 2020; 77:110801.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32428841
ABSTRACT
OBJECTIVES: To the best of our knowledge, no systematic review and meta-analysis has evaluated the cholesterol-lowering effects of intermittent fasting (IF) and energy-restricted diets (ERD) compared with control groups. The aim of this review and meta-analysis was to summarize the effects of controlled clinical trials examining the influence of IF and ERD on lipid profiles. METHODS: A systematic review of four independent databases (PubMed/Medline, Scopus, Web of Science and Google Scholar) was performed to identify clinical trials reporting the effects of IF or ERD, relative to non-diet controls, on lipid profiles in humans. A random-effects model, employing the method of DerSimonian and Laird, was used to evaluate effect sizes, and results were expressed as weighted mean difference (WMD) and 95% confidence intervals (CIs). Heterogeneity between studies was calculated using Higgins I(2), with values >/=50% considered to represent high heterogeneity. Subgroup analyses were performed to examine the influence of intervention type, baseline lipid concentrations, degree of energy deficit, sex, health status, and intervention duration. RESULTS: For the outcomes of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triacylglycerols (TG), there were 34, 33, 35, and 33 studies meeting all inclusion criteria, respectively. Overall, results from the random-effects model indicated that IF and ERD interventions resulted significant changes in TC (WMD, -6.93 mg/dL; 95% CI, -10.18 to -3.67; P < 0.001; I(2) = 78.2%), LDL-C (WMD, -6.16 mg/dL; 95% CI, -8.42 to -3.90; P < 0.001; I(2) = 52%), and TG concentrations (WMD, -6.46 mg/dL; 95% CI, -10.64 to -2.27; P = 0.002; I(2) = 61%). HDL-C concentrations did not change significantly after IF or ERD (WMD, 0.50 mg/dL; 95% CI, -0.69 to 1.70; P = 0.411; I(2) = 80%). Subgroup analyses indicated potentially differential effects between subgroups for one or more lipid parameters in the majority of analyses. CONCLUSIONS: Relative to a non-diet control, IF and ERD are effective

for the improvement of circulating TC, LDL-C, and TG concentrations, but have no meaningful effects on HDL-C concentration. These effects are influenced by several factors that may inform clinical practice and future research. The present results suggest that these dietary practices are a means of enhancing the lipid profile in humans.

[40] *Abdelwahed KS, Siddique AB, Mohyeldin MM et al.* **Pseurotin A as a novel suppressor of hormone dependent breast cancer progression and recurrence by inhibiting PCSK9 secretion and interaction with LDL receptor**. Pharmacological research : the official journal of the Italian Pharmacological Society 2020; 158:104847.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32438039
ABSTRACT
Hypercholesterolemia has been documented to drive hormone-dependent breast cancer (BC) progression and resistance to hormonal therapy. Proprotein convertase subtilisin/kexin type-9 (PCSK9) regulates cholesterol metabolism through binding to LDL receptor (LDLR) and targeting the receptor for lysosomal degradation. Inhibition of PCSK9 is an established strategy to treat hypercholesterolemia. Pseurotin A (PS) is a unique spiro-heterocyclic gamma-lactam alkaloid isolated from the fungus Aspergillus fumigatus. Preliminary studies indicated that PS lowered PCSK9 secretion in cultured HepG2 hepatocellular carcinoma cells, with an IC50 value of 1.20 muM. Docking studies suggested the ability of PS to bind at the PCSK9 narrow interface pocket that accommodates LDLR. Surface plasmon resonance (SPR) showed PS ability to inhibit the PCSK9-LDLR interaction at a concentration range of 10-150 muM. PS showed in vitro dose-dependent reduction of PCSK9, along with increased LDLR levels in hormone-dependent BT-474 and T47D breast cancer (BC) cell lines. In vivo, daily oral 10 mg/kg PS suppressed the progression of the hormone-dependent BT-474 BC cells in orthotopic nude mouse xenograft model. Immunohistochemistry (IHC) investigation of BT-474 breast tumor tissue proved the PS ability to reduce PCSK9 expression. PS also effectively suppressed BT-474 BC cells locoregional recurrence after primary tumor surgical excision. Western blot analysis showed decreased PCSK9 expression in liver tissues of PS-treated mice compared to vehicle-treated control group. PS treatment significantly reduced PCSK9 expression and normalized LDLR levels in collected primary and recurrent breast tumors at the study end. PS-treated mice showed reduced plasma cholesterol and 17beta-estradiol levels. Inhibition of tumor recurrence was associated with significant reductions in plasma level of the human BC recurrence marker CA 15-3 in treated mice at the study end. Histopathological examination of various PS-treated mice organs indicated lack of metastatic tumor cells and any pathological changes. The results of this study provide the first evidence for the suppression of the hormone-dependent breast tumor progression and recurrence by targeting the PCSK9-LDLR axis. PS is a novel first-in-class PCSK9-targeting lead appropriate for the use to control hormone-dependent BC progression and recurrence.

[41] *Ruscica M, Corsini A, Ferri N et al.* **Clinical approach to the inflammatory etiology of cardiovascular diseases**. Pharmacological research : the official journal of the Italian Pharmacological Society 2020:104916.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32445957
ABSTRACT
Inflammation is an obligatory marker of arterial disease, both stemming from the inflammatory activity of cholesterol itself and from well-established molecular mechanisms. Raised

progenitor cell recruitment after major events and clonal hematopoiesis related mechanisms have provided an improved understanding of factors regulating inflammatory phenomena. Trials with inflammation antagonists have led to an extensive evaluation of biomarkers such as the high sensitivity C reactive protein (hsCRP), not exerting a causative role, but frequently indicative of the individual cardiovascular (CV) risk. Aim of this review is to provide indication on the anti-inflammatory profile of agents of general use in CV prevention, i.e. affecting lipids, blood pressure, diabetes as well nutraceuticals such as n-3 fatty acids. A crucial issue in the evaluation of the benefit of the anti-inflammatory activity is the frequent discordance between a beneficial activity on a major risk factor and associated changes of hsCRP, as in the case of statins vs PCSK9 antagonists. In hypertension, angiotensin converting enzyme inhibitors exert an optimal anti-inflammatory activity, vs the case of sartans. The remarkable preventive activity of SLGT-2 inhibitors in heart failure is not associated with a clear anti-inflammatory mechanism. Finally, icosapent ethyl has been shown to reduce the CV risk in hypertriglyceridemia, with a 27% reduction of hsCRP. The inflammation-based approach to arterial disease has considerably gained from an improved understanding of the clinical diagnostic strategy and from a better knowledge on the mode of action of numerous agents, including nutraceuticals.

[42] *Roy D, Mahapatra T, Manna K et al.* **Comparing effectiveness of high-dose Atorvastatin and Rosuvastatin among patients undergone Percutaneous Coronary Interventions: A non-concurrent cohort study in India**. PloS one 2020; 15:e0233230. **PM:** http://www.ncbi.nlm.nih.gov/pubmed/?term=32428019

ABSTRACT

INTRODUCTION: Atorvastatin-80mg/day and Rosuvastatin-40mg/day are the commonest high-dose statin (3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors) regimes for post-PCI (Percutaneous Coronary Interventions) patients to lower (by >/=50%) blood low-density-lipoprotein cholesterol (LDL-C). Dearth of conclusive evidence from developing world, regarding overall safety, tolerability and comparative effectiveness (outcome/safety/tolerability/endothelial inflammation control) of Rosuvastatin over Atorvastatin in high-dose, given its higher cost, called for an overall and comparative assessment among post-PCI patients in a tertiary cardiac-care hospital of Kolkata, India. METHODS: A record-based non-concurrent cohort study was conducted involving 942 post-PCI patients, aged 18-75 years, on high-dose statin for three months and followed up for >/=one year. Those on Atorvastatin-80mg (n = 321) and Rosuvastatin-40mg (n = 621) were compared regarding outcome (death/non-fatal myocardial infarction: MI/repeated hospitalization/target-vessel revascularisation/control of LDL and high-sensitivity C-reactive protein: hsCRP), safety (transaminitis/myopathy/myalgia/myositis/rhabdomyolysis), tolerability (gastroesophageal reflux disease: GERD/gastritis) and inflammation control adjusting for socio-demographics, tobacco-use, medications and comorbidities using SAS-9.4. RESULTS: Groups varied minimally regarding distribution of age/gender/tobacco-use/medication/comorbidity/baseline (pre-PCI) LDL and hs-CRP level. During one-year post-PCI follow up, none died. One acute MI and two target vessel revascularizations occurred per group. Repeated hospitalization for angina/stroke was 2.18% in Atorvastatin group vs. 2.90% in Rosuvastatin group. At three-months follow up, GERD/Gastritis (2.18% vs 4.83%), uncontrolled hs-CRP (22.74% vs 31.08%) and overall non-tolerability (4.67% vs. 8.21%) were lower for Atorvastatin group. Multiple logistic regression did show that compared to Atorvastatin-80mg, Rosuvastatin-40mg

regime had poorer control of hs-CRP (A3OR = 1.45,p = 0.0202), higher (A3OR = 2.07) adverse effects, poorer safety profile (A3OR = 1.23), higher GERD/Gastritis (A3OR = 1.50) and poorer overall tolerability (A3OR = 1.50). CONCLUSION: Post-PCI high dose statins were effective, safe and well-tolerated. High dose Rosuvastatin as compared to high dose Atorvastatin were similar in their clinical efficacy. Patients treated with Atrovastatin had significantly lower number of patients with hs-CRP (high-sensitivity C-reactive protein)/C-reactive protein (CRP) level beyond comparable safe limit and relatively better tolerated as opposed to Rosuvastatin-40mg.Thus given the lower price, Atorvastatin 80mg/day appeared to be more cost-effective. A head-to-head cost-effectiveness as well as efficacy trial may be the need of the hour.

[43] *Munoz-Cabrejas A, Espina Cadena S, Arbones-Mainar JM, Moreno-Franco B*. **[Lipid metabolism alterations produced by hepatitis C virus in patients with chronic infection.]**. Rev Esp Salud Publica 2020; 94.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32419698

ABSTRACT
BACKGROUND: Chronic infection with the hepatitis C virus (HCV) is known to generate an apparently favorable lipid profile. Paradoxically, these patients present an increase in concomitant cardiovascular events. The objectives of the present review were to analyze and synthesize studies that inquired into the changes produced by hepatitis C virus (HCV) in the lipid metabolism of patients with chronic infection, and about whether these modifications can be associated with subsequent episodes of cardiovascular diseases. METHODS: A bibliographic search was carried out in the Medline and Scopus databases of the articles published from January 2008 to February 2019. A total of 901 publications were identified, of which 10 studies that fulfilled the inclusion and exclusion criteria were reviewed. RESULTS: It was found that the levels of total cholesterol and its lipid fractions were decreased in patients with chronic HCV infection. There was no clear association with triglyceride levels. In addition, there seemed to be an association between chronic HCV infection and an increased risk of developing atherosclerosis and cardiovascular diseases. CONCLUSIONS: Chronic HCV infection has a lipid-lowering effect and increases cardiovascular risk. Prospective studies are needed to analyze the effect of new therapies with direct-acting antivirals on lipid metabolism and cardiovascular risk.