Literature update week 51 (2019)

[1] *Descamps OS, Verhaegen A, Demeure F et al.* **Evolving concepts on the management of dyslipidaemia**. Acta clinica Belgica 2019:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31846601
ABSTRACT
It has been well established that low-density lipoproteins (LDL) and other apolipoprotein B-containing lipoproteins are causally related to atherosclerotic cardiovascular disease (ASCVD) and that lowering these lipoproteins reduces the risk of ASCVD. By lowering LDL particles as much as possible, ASCVD can be prevented. There seems to be no LDL-cholesterol (LDL-C) threshold below which no further ASCVD prevention can be achieved. Furthermore, a low (an even very low) LDL-C appears to be safe. The new ESC/EAS guidelines based on these concepts are a step towards a benefit-based strategy by focusing on the clinical benefit that can be achieved by treating the cause of ASCVD. It is recommended to lower LDL-C as much as possible to prevent ASCVD, especially in high and very high-risk patients. With these new recommendations come recognition of the importance of combination therapies in high and very high-risk patients, first with statins and ezetimibe, and if needed with a PCSK9 inhibitor. The present paper is a review of some new concepts arising during the past 10 years in the field of lipidology and the description of what is new in the 2019 EAS/ESC guidelines.

[2] *Boccara F, Kumar P, Caramelli B et al.* **Evolocumab treatment in patients with HIV and hypercholesterolemia/mixed dyslipidemia: BEIJERINCK study design and baseline characteristics**. American heart journal 2019; 220:203-212.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31841795
ABSTRACT
BACKGROUND: People living with human immunodeficiency virus (PLHIV) are at higher risk of atherosclerotic cardiovascular disease (ASCVD) due to traditional and HIV- or antiretroviral treatment (ART)-related risk factors. The use of high-intensity statin therapy is often limited by comorbidities and drug-drug interactions with ART. Herein, we present the design and baseline characteristics of the BEIJERINCK study, which will assess the safety and efficacy of evolocumab in PLHIV and hypercholesterolemia/mixed dyslipidemia. METHODS: Randomized, double-blind, placebo-controlled, multinational trial that investigates monthly subcutaneous evolocumab 420 mg versus placebo in PLHIV with hypercholesterolemia/mixed dyslipidemia who are treated with maximally-tolerated statin therapy. The primary outcome is the baseline to week 24 percent change in low density lipoprotein cholesterol (LDL-C). Secondary outcomes include achievement of LDL-C<70 mg/dL and percent change in other plasma lipid and lipoprotein levels. Safety will also be examined. RESULTS: This study enrolled and dosed 464 patients who had a mean age of 56.4 years and were mostly male (82.5%). Mean duration with HIV was 17.4 years, and, by design, HIV viral load at screening was </=50 copies/mL. ASCVD was documented in 35.6% of patients. Mean LDL-C of enrolled patients at baseline was 133.3 mg/dL. Statin use was prevalent (79.3% overall) with 74.6% receiving moderate or high-intensity statins. In total, 20.7% of patients did not receive statins due to intolerance/contraindications. CONCLUSIONS: The BEIJERINCK study is the first clinical trial to examine the lipid-lowering efficacy and safety of a fully human PCSK9 monoclonal antibody inhibitor in a moderate/high cardiovascular risk population of PLHIV.

[3] *Go AS, Ambrosy AP, Kheder K et al.* **Statin Therapy and Risk of Incident Diabetes Mellitus in Adults With Cardiovascular Risk Factors**. The American journal of cardiology 2019.

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PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31848029

ABSTRACT

The association between statins and diabetes mellitus (DM) remains controversial. The Kaiser Permanente CHAMP Study identified adults without DM who had cardiovascular (CV) risk factors and no previous lipid lowering therapy (LLT) between 2008 and 2010. The CV risk factors included known atherosclerotic CV disease (ASCVD), elevated low-density lipoprotein cholesterol >/=190 mg/dl, or a low-density lipoprotein cholesterol between 70 and 189 mg/dl and an estimated 10-year ASCVD risk >/=7.5%. Incident DM was defined as >/=2 abnormal tests (i.e., A1C >/=6.5% or a fasting blood glucose >/=126 mg/dl) or >/=1 abnormal test result plus a new diagnostic code or medication for DM. Among 213,289 eligible adults, 28,149 patients initiating statins were carefully matched to an equal number of patients who remained off LLT during follow-up. Compared with matched patients not receiving statins, those initiating statin therapy had the same mean age (67.9 +/- 9.4 years) and gender (42.8% women). The crude rate (per 100 person-years) of incident DM was low (0.55, 95% confidence interval [CI] 0.52 to 0.59) but was marginally higher in patients who were treated with a statin (0.69, 95% CI 0.64 to 0.74) versus no LLT (0.42, 95% CI 0.38 to 0.46). After additional adjustment, statin therapy was associated with a modestly increased risk of incident DM (adjusted hazard ratio 1.17, 95% CI 1.02 to 1.34). In conclusion, in adults without DM at increased ASCVD risk, initiation of statin therapy was independently associated with a modestly higher risk of incident DM.

[4] *Koutsos A, Riccadonna S, Ulaszewska MM et al.* **Two apples a day lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic adults: a randomized, controlled, crossover trial**. The American journal of clinical nutrition 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31840162

ABSTRACT

BACKGROUND: Apples are rich in bioactive polyphenols and fiber. Evidence suggests that consumption of apples or their bioactive components is associated with beneficial effects on lipid metabolism and other markers of cardiovascular disease (CVD). However, adequately powered randomized controlled trials are necessary to confirm these data and explore the mechanisms. OBJECTIVE: We aimed to determine the effects of apple consumption on circulating lipids, vascular function, and other CVD risk markers. METHODS: The trial was a randomized, controlled, crossover, intervention study. Healthy mildly hypercholesterolemic volunteers (23 women, 17 men), with a mean +/- SD BMI 25.3 +/- 3.7 kg/m2 and age 51 +/- 11 y, consumed 2 apples/d [Renetta Canada, rich in proanthocyanidins (PAs)] or a sugar- and energy-matched apple control beverage (CB) for 8 wk each, separated by a 4-wk washout period. Fasted blood was collected before and after each treatment. Serum lipids, glucose, insulin, bile acids, and endothelial and inflammation biomarkers were measured, in addition to microvascular reactivity, using laser Doppler imaging with iontophoresis, and arterial stiffness, using pulse wave analysis. RESULTS: Whole apple (WA) consumption decreased serum total (WA: 5.89 mmol/L; CB: 6.11 mmol/L; P = 0.006) and LDL cholesterol (WA: 3.72 mmol/L; CB: 3.86 mmol/L; P = 0.031), triacylglycerol (WA: 1.17 mmol/L; CB: 1.30 mmol/L; P = 0.021), and intercellular cell adhesion molecule-1 (WA: 153.9 ng/mL; CB: 159.4 ng/mL; P = 0.028), and increased serum uric acid (WA: 341.4 mumol/L; CB: 330 mumol/L; P = 0.020) compared with the CB. The response to endothelium-dependent microvascular vasodilation was greater after the apples [WA: 853 perfusion units (PU), CB: 760 PU; P = 0.037] than after the CB. Apples had no effect on blood pressure or other CVD markers. CONCLUSIONS: These data support beneficial hypocholesterolemic and vascular effects of the daily consumption of PA-rich apples

by mildly hypercholesterolemic individuals.This trial was registered at clinicaltrials.gov as NCT01988389.

[5] *Fatehi Hassanabad A, Mina F*. **Targeting the Mevalonate Pathway for Treating Lung Cancer**. American journal of clinical oncology 2020; 43:69-70.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31842152
ABSTRACT
The mevalonate (MVA) pathway is a key metabolic pathway involved in various important cellular functions. Its downstream products are critical for cell-signaling, cell membrane integrity, protein synthesis, and cellular respiration. The rate-limiting enzyme of this pathway is targeted by statins, a class of medications best known for their lipid-lowering effects. Many studies have shown that a variety of cancerous cells have a dysregulated MVA pathway. Lung cancer is responsible for a third of all cancer-related deaths worldwide. As our understanding of the molecular mechanisms driving the pathogenesis of lung cancer improves, newer therapeutics have been proposed. However, these medications have not had the expected benefits for all subtypes of lung cancer. Therefore, there exists a significant role in identifying medications with safe profiles, which can potentially be used in managing various types of lung cancer. Herein, we review whether there is a role in utilizing statins to target the MVA pathway in treating lung cancer.

[6] *Kazakov, II, Iakovlev AO*. **[Surgical policy of managing patients with concomitant atherosclerotic lesions of the internal and common carotid arteries]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2019; 25:124-130.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31855209
ABSTRACT
AIM: The purpose of this study was to investigate the natural course of stenosis of the common carotid artery (CCA) after carotid endarterectomy, as well as the long-term outcomes of various methods of reconstruction of the internal carotid artery (ICA) in patients with extended atherosclerotic lesions. PATIENTS AND METHODS: Presented herein are the remote retrospective and prospective results of carotid endarterectomy in a total of 78 patients with concomitant atherosclerotic lesions of carotid arteries. Depending on the degree of CCA stenosis, the patients were divided into 2 groups. Group One (n=25): stenosis of the internal carotid artery (ICA) of more than 70% and haemodynamically insignificant (30-35% stenosis) but extended (from 3.0 to 5.0 cm (Q1, Me, Q3); 3.5 cm, 4.0 cm, 5.0 cm) stenosis of the CCA. These patients underwent carotid endarterectomy (CEA) from the ostium of the ICA, during which an atherosclerotic plaque was not completely removed from the CCA because the stenosis was extended but haemodynamically insignificant. Group Two (n=53): stenosis of the ICA of more than 70% and haemodynamically significant, extended (from 7.0 to 10.0 cm (Q1, Me, Q3); 7.5 cm, 8.0 cm, 9.0 cm) stenosis of the CCA. The patients of this group were subjected to various methods of operative intervention on the ICA and CCA: carotid endarterectomy (ECA) combined with open endarterectomy from the CCA with plasty using the primary suture (n=23); carotid endarterectomy and alloreconstruction of the CCA (n=10); simultaneous eversion endarterectomy from the ICA and CCA (n=20). The remote period of follow up of patients ranged from 14 to 24 months ((Q1, Me, Q3; 19 months, 22 months, 24 months). The differences were statistically insignificant (Mann-Whitney U-test, p=0.881). RESULTS: In the remote postoperative period, 32% of Group One patients after previously performed carotid endarterectomy were found to have an increase in the degree of stenosis of the

CCA up to a haemodynamically significant one (70% and more), thus suggesting progression of the atherosclerotic process. In Group Two patients, after plasty of the CCA with the primary suture, 21.7% of patients were diagnosed as having restenosis of the reconstruction zone up to 30%, with no neurological deficit. 20% of patients after carotid endarterectomy and alloreconstruction of the CCA were diagnosed as having restenosis of the reconstruction zone more than 70% and acute impairment of cerebral circulation with a lethal outcome. The patients after simultaneous eversion endarterectomy form the ICA and CCA in the intraoperative and postoperative periods had neither restenosis of the reconstruction zone nor neurological deficit. CONCLUSION: 32% of patients after previously performed carotid endarterectomy with the presence of extended, but haemodynamically insignificant stenosis of the CCA (30-35% stenosis) in the postoperative period were found to have progression of the atherosclerotic lesion in the form of an increased degree of stenosis up to haemodynamically significant (more than 70%), thus requiring repeat reconstructive operation. Therefore, in patients presenting with concomitant atherosclerotic lesions of the carotid arteries it is appropriate to carry out operative intervention simultaneously on the ICA and CCA, which would make it possible to considerably improve the remote postoperative results of reconstructive interventions on the carotid basin in this cohort of patients. A comparative study of the outcomes of various methods of reconstruction of carotid arteries in patients with concomitant atherosclerotic lesions of the ICA and CCA demonstrated that simultaneous eversion endarterectomy from the ICA and CCA resulted in good postoperative parameters: absence of restenosis and neurological deficit in the remote period of follow up.

[7] *Tanashian MM, Medvedev RB, Gemdzhian EG et al.* **[Predictors of acute cerebral embolic lesions during carotid artery stenting]**. Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery 2019; 25:83-90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31855204
ABSTRACT
The authors carried out a prospective study aimed at revealing predictors of acute embolic lesions of cerebral vessels during angioplasty with stenting of the internal carotid artery. The study enrolled a total of 54 patients who between May 2015 and December 2018 underwent carotid angioplasty with stenting performed at the Department of Vascular and Endovascular Surgery of the Research Centre of Neurology. The procedure of internal carotid artery stenting may be accompanied by intraoperative acute embolic lesions. In order to reveal intraoperative acute embolic lesions of cerebral vessels all patients before and 24 hours after the intervention were subjected to diffusion-weighted magnetic resonance imaging. Thirty-six patients received classical carotid stents (Xact and Acculink) and 18 patients received Casper stents. The patients of both groups were comparable by 24 characteristics studied, including the incidence of intraoperative acute cerebral embolic lesions (18/36 for the classical stents and 10/18 for the Casper stent), which made it possible to unite them into one group in order to increase the power of the study. All acute embolic lesions detected by the diffusion-weighted magnetic resonance imaging (prior to stenting and 24 hours thereafter) were clinically, asymptomatic with no perioperative stroke observed. In order to reveal predictors of intraoperative acute embolic lesions of cerebral vessels we analysed 22 characteristics of the patients, with the obtained findings demonstrating the following signs: a low-intensity (below 20 dB) ultrasonographic signal reflected from fragments of an atherosclerotic plaque during ultrasound examination prior to stenting (p=0.001) - a sign strongly associated with acute embolic lesions (sensitivity - 75%, specificity - 92%); symptomatic

stenosis according to the anamnestic data (p=0.02) - a sign significantly associated with acute embolic lesions; female gender (p=0.06) - a sign moderately associated with acute embolic lesions; a history previously endured (according to the anamnestic data) operations on coronary and/or carotid arteries (p=0.09) - a sign weakly associated with acute embolic lesions. Based on the obtained findings we proposed a prognostic scale to assess the risk of acute embolic lesions of cerebral vessels during internal carotid artery stenting. Knowing the factors associated with intraoperative acute embolic lesions will allow the endovascular surgeon to single out the patients at increased risk of acute embolic lesions.

[8] *Zhang S, Xu W, Gao P et al.* **Construction of dual nanomedicines for the imaging and alleviation of atherosclerosis**. Artificial cells, nanomedicine, and biotechnology 2020; 48:169-179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31852323
ABSTRACT
Magnetic resonance imaging (MRI) is an essential tool for the diagnosis of atherosclerosis, a chronic cardiovascular disease. MRI primarily uses superparamagnetic iron oxide (SPIO) as a contrast agent. However, SPIO integrated with therapeutic drugs has rarely been studied. In this study, we explored biocompatible paramagnetic iron-oxide nanoparticles (NPs) in a complex with low pH-sensitive cyclodextrin for the diagnostic imaging and treatment of atherosclerosis. The NPs were conjugated with profilin-1 antibody (PFN1) to specifically target vascular smooth muscle cells (VSMCs) in the atherosclerotic plaque and integrated with the anti-inflammatory drug, rapamycin. The PFN1-CD-MNPs were easily binded to the VSMCs, indicating their good biocompatibility and low renal toxicity over the long term. Ex vivo near-infrared fluorescence (NIRF) imaging and in vivo MRI indicated the accumulation of PFN1-CD-MNPs in the atherosclerotic plaque. The RAP@PFN1-CD-MNPs alleviated the progression of arteriosclerosis. Thus, PFN1-CD-MNPs served not only as multifunctional imaging probes but also as nanovehicles for the treatment of atherosclerosis.

[9] *Duan JN, Du W, Hou RH et al.* **[Progressive necrosis of lipid: A case report]**. Beijing Da Xue Xue Bao Yi Xue Ban 2019; 51:1182-1184.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31848527
ABSTRACT
A 61-year-old woman was referred to our department with a 11-year-erythra. In the anterior tibia of both lower extremities, we could see large dark red infiltrating erythema, waxy luster, clear boundary, slight central atrophy, depression and capillary dilatation. He was diagnosed with "dermatitis contusiformis" in local hospitals, but the treatment of traditional Chinese medicine and external drugs was not effective. She had normal laboratory findings for blood routine test, biochemical indexes, C reactive protein(CRP) and erythrocyte sedimentation rate(ESR)Furthermore, autoimmune antibodies were all negative. The skin pathology showed degeneration and necrosis of collagen fibers, chronic granulomatous inflammation in the dermis, and there were more acute and chronic inflammatory cell infiltration around the small vessels and in the wall of the tube. We eventually diagnosed it as necrobiosis lipoidica (NL) according to the history, erythra morphology and skin pathology. After treatment of low dose hormone and thalidomide for 1 year, the color and range of skin lesions gradually alleviated. NL was a rare chronic granulomatous inflammatory disease. There appeared to be a predominance in females. The incidence of NL was higher in patients with diabetes mellitus, although this asscoiation was currently questioned. NL might also be connected with autoimmune diseases, such

as rheumatoid arthritis, sarcoidosis, ulcerative colitis and Crohn's disease. The pathological changes of the tissue were mainly in the dermis, including necrotic type, granulomatous type or mixed type. NL typically presented on the pretibial surface of lower extremities. Less typical locations included the face, scalp, vulva and upper limbs. Leisions usually began with small papules and nodules that gradually infiltrated into browndouble ended arrowyellow patches and developed central wax-like atrophy. The diagnosis is often based on clinical examination and skin biopsy. NL is rare and easy to be misdiagnosed. For rheumatologists, we should carefully compare with the nodular erythema, the microscopic polyangitis and allergic purpura. It is significant for differential diagnosis to perform skin biopsy. Lacking of randomized controlled trials, no specific treatment has proven to be the gold standard. First-line therapy mainly consists of intralesional and systemic corticosteriods. Additionally, other reported treatment options include immunomodulator, biological agent, antiplatelet aggregation drug and plateletdouble ended arrowrich plasma. These patients need long term follow up continuously for progression of the disease, ulcerations, and possibility of malignant tranformation.

[10] *Nishida S, Horinouchi A, Higashimura Y et al.* **Cholestyramine, a bile acid sequestrant, increases cecal short chain fatty acids and intestinal immunoglobulin A in mice**. Biological & pharmaceutical bulletin 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31852854
ABSTRACT
Bile acid sequestrants are used as medicinal drugs to treat dyslipidemia and type 2 diabetes. We found that cholestyramine, a bile acid sequestrant, increases cecal short-chain fatty acid (SCFA) production and intestinal immunoglobulin A (IgA) in C57BL/6J mice. In a 12-week high-fat diet study, feeding cholestyramine (2% w/w) significantly promoted C2-C4 SCFAs in the cecum by ~1.6-fold and fecal IgA by 1.8-fold. In an 8-week normal-fat diet study, feeding cholestyramine (1% and 2%) increased the cecal propionic acid content by ~2.0-fold. Fecal IgA was also significantly increased at 4 weeks (1%: 1.7-fold; 2%: 2.1-fold) and 8 weeks (1%: 1.8-fold; 2%: 2.0-fold) in the normal-fat diet study. These results indicate that bile acid sequestrants may exert their physiological functions, such as intestinal IgA production, through SCFA-dependent signaling pathways.

[11] *Gaviria-Mendoza A, Machado-Duque ME, Machado-Alba JE*. **Lipid-lowering drug prescriptions in a group of Colombian patients**. Biomedica : revista del Instituto Nacional de Salud 2019; 39:759-768.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31860186
ABSTRACT
INTRODUCTION: Lipid-lowering drugs, especially statins, have shown great relevance in preventing and treating cardiovascular diseases. OBJECTIVE: To determine the prescription patterns of lipid-lowering drugs and the variables associated with their use in a Colombian population. MATERIALS AND METHODS: This is a cross-sectional descriptive study. From a drug dispensing database of approximately 4.5 million Colombian health system affiliates, patients of all ages and both sexes treated with lipid-lowering agents (statins, fibrates, ezetimibe) were identified between January and March, 2017. Demographic, pharmacological and co-medication variables were included. RESULTS: In total, 103,624 patients were identified as being treated with lipid-lowering agents. The average age was 67.5 years, and 49.8% were 65 years or older. Women comprised 58.0% of the patients. Statins were the most used (n=96,910; 93.5%), and atorvastatin (n=80,812; 78.0%) and lovastatin (n=12,621; 12.2%) were the most frequent. The mean atorvastatin dose was 30.3 mg/day, and 49.9% of its users

received presentations of 40 mg or more. A total of 9,258 (8.9%) patients received fibrates, and only 780 (0.8%) were taking ezetimibe. Of this population, 94.9% were treated with lipid-lowering monotherapy, and 97.3% (n=100,813) had co-medication for their comorbidities, with the most frequent being antihypertensive (89.1%), antiplatelet (57.8%), antidiabetic (31.5%) and antiulcerative agents (34.2%). CONCLUSIONS: Atorvastatin is currently the most frequently used lipid-lowering drug in this group of Colombian patients, especially in monotherapy and at doses close to the defined daily dose. Only half received high-intensity doses. New studies are required to verify the efficacy of these therapies.

[12] *Guo M, Zhao J, Zhai Y et al.* **A prospective study of hepatic safety of statins used in very elderly patients**. BMC geriatrics 2019; 19:352.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31842780
ABSTRACT
BACKGROUND: Statins play an important role in the care of patients with cardiovascular disease and have a good safety record in clinical practice. Hepatotoxicity is a barrier that limits the ability of primary care physicians to prescribe statins for patients with elevated liver transaminase values and/or underlying liver disease. However, limited population-based data are available on the use of statin therapy and on the hepatotoxicity of statins in very elderly patients. This prospective study evaluated the liver enzyme elevation during statin therapy in very elderly patients (>/=80 years old). METHODS: Patients with hypercholesterolemia (LDL-C levels >/=3.4 and < 5.7 mmol/L), atherosclerosis, coronary heart disease (CHD), or a CHD-risk equivalent were enrolled and received once-daily statin treatment. Multivariate logistic regression models were used to study the impact of age, gender, hepatitis B infection, fatty liver disease, biliary calculus, other chronic diseases, drug kinds, alcohol abuse, statin variety, and statin dose variables. RESULTS: A total of 515 consecutive patients ranging from 80 to 98 years old were included in the analysis. These patients were treated with simvastatin, fluvastatin, pravastatin, rosuvastatin, or atorvastatin. Twenty-four patients (4.7, 95% CI 2.7-6.6) showed an increase in their hepatic aminotransferase levels. No significant difference of hepatic aminotransferase elevation rates was observed in different statin treatment groups. The incidence of mild, moderate, and severe elevation of aminotransferase levels was 62.5% (15/24), 29.2% (7/24), and 8.3% (2/24), respectively. None of the patients developed hepatic failure. Nine patients with moderate or severe aminotransferase elevations discontinued therapy. The time of onset of hepatic aminotransferase elevation ranged from 2 weeks to 6 months after statin treatment. The onset of hepatic aminotransferase elevation was within 1 month for 70.8% of patients. The patients took 2 weeks to 3 months to recover their liver function after statin therapy cessation. Multivariate analysis identified chronic hepatitis B infection and alcohol consumption as independent factors associated with the hepatic response to statins: OR, 12.83; 95% CI (4.36-37.759) and OR, 2.736; 95% CI (1.373-5.454), respectively. CONCLUSION: The prevalence of elevated transaminases was higher than published data in very elderly patients. Overall, statin treatment is safe for patients >/=80 years old.

[13] *Trebaticky B, Muchova J, Ziaran S et al.* **Natural polyphenols improve erectile function and lipid profile in patients suffering from erectile dysfunction**. Bratislavske lekarske listy 2019; 120:941-944.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31855055
ABSTRACT

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OBJECTIVES: Erectile dysfunction (ED) is characterised as the inability to achieve or maintain an erection to complete sexual intercourse. ED may be considered as an early complication of diabetes mellitus (DM). The aim of this study was to assess the effect of registered food supplement, natural polyphenolic extract from the French maritime pine bark, Pycnogenol (PYC) on erectile function and lipid profile in ED patients. METHODS: 53 patients with ED were divided into two groups (32 with DM, 21 non-DM) in randomised, blinded and placebo-controlled study. During 3-month intervention with PYC or placebo and one month after the end of the intervention patients were investigated for ED with validated questionnaire International Index of Erectile Function-5 (IIEF-5); lipid profile, glycaemia was analysed in each group. RESULTS: In a randomised, blinded and placebo-controlled study, we found that natural polyphenolic extract, Pycnogenol improved erectile function in DM group by 45 % compared to the NDM group, where the improvement was also significant, but only by 22 %. Total cholesterol, LDL-cholesterol and glucose level was lowered by PYC in patients with DM. Glucose level was not affected by PYC in non-DM. Placebo showed no effect on monitored parameters in both groups. CONCLUSION: Administration of Pycnogenol leads in improvement of erectile function in patients with ED and diabetes (DM group) by 45 %, in NDM group by 22 %, in lowering of total-, LDL-cholesterol by 20 % and 21 % and glycaemia by 22 % in DM (Tab. 2, Fig. 2, Ref. 19).

[14] *Langlois MR, Nordestgaard BG, Langsted A et al.* **Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM**. Clin Chem Lab Med 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31855562
ABSTRACT
The joint consensus panel of the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) recently addressed present and future challenges in the laboratory diagnostics of atherogenic lipoproteins. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), LDL cholesterol (LDLC), and calculated non-HDLC (=total - HDLC) constitute the primary lipid panel for estimating risk of atherosclerotic cardiovascular disease (ASCVD) and can be measured in the nonfasting state. LDLC is the primary target of lipid-lowering therapies. For on-treatment follow-up, LDLC shall be measured or calculated by the same method to attenuate errors in treatment decisions due to marked between-method variations. Lipoprotein(a) [Lp(a)]-cholesterol is part of measured or calculated LDLC and should be estimated at least once in all patients at risk of ASCVD, especially in those whose LDLC declines poorly upon statin treatment. Residual risk of ASCVD even under optimal LDL-lowering treatment should be also assessed by non-HDLC or apolipoprotein B (apoB), especially in patients with mild-to-moderate hypertriglyceridemia (2-10 mmol/L). Non-HDLC includes the assessment of remnant lipoprotein cholesterol and shall be reported in all standard lipid panels. Additional apoB measurement can detect elevated LDL particle (LDLP) numbers often unidentified on the basis of LDLC alone. Reference intervals of lipids, lipoproteins, and apolipoproteins are reported for European men and women aged 20-100 years. However, laboratories shall flag abnormal lipid values with reference to therapeutic decision thresholds.

[15] *Brooks DC, Schindler JL*. **Management of Hyperlipidemia After Stroke**. Current treatment options in cardiovascular medicine 2019; 21:93.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31840196

ABSTRACT
PURPOSE OF REVIEW: Hyperlipidemia is a key therapeutic target for stroke risk modification. The goal of this review is to highlight available treatment options and review their efficacy in the setting of general cardiovascular disease and after most subtypes of ischemic stroke and hemorrhagic stroke. RECENT FINDINGS: Statins remain first-line in the management of hyperlipidemia to prevent stroke. In recent trials of patients with pre-existing atherosclerotic vascular disease, new agents, most notably PCSK9 inhibitors and ezetimibe, added additional stroke risk reduction when combined with statins. Risk of stroke can be significantly reduced by understanding that hyperlipidemia is a key therapeutic target, particularly in patients with cardiovascular disease, and by identifying patients who may benefit from aggressive LDL-C reduction with statins +/- novel agents.

[16] *Chionchio A, Galmer A, Hirsh B*. **Primary and Novel Lipid-Lowering Therapies to Reduce Risk in Patients With Peripheral Arterial Disease**. Current treatment options in cardiovascular medicine 2019; 21:94.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31848747
ABSTRACT
PURPOSE OF REVIEW: The diagnosis of peripheral arterial disease (PAD) is a high-risk marker for accelerated atherosclerotic cardiovascular disease (ASCVD) and is associated with substantial morbidity and mortality. In addition to common, modifiable cardiovascular disease risk factors that contribute to PAD, which include hypertension, diabetes mellitus, and smoking, an elevation in concentrations of serum atherogenic lipoproteins (lipids) is an increasingly recognized contributor to premature atherosclerosis. RECENT FINDINGS: The recognition and inclusion of PAD as a marker of higher-cardiovascular risk demonstrates the need to aggressively reduce elevations in atherogenic lipoproteins, particularly low-density-lipoprotein cholesterol. In addition to diet, lifestyle, and statin therapy, there is evidence that novel, pharmacologic lipid-lowering treatments improve specific outcomes in patients with PAD as primary and adjunctive therapy. In this review, we discuss the efficacy and evolving roles of statin and novel nonstatin therapies on outcomes in patients with PAD.

[17] *Zijlstra L, van Velzen D, Simsek S et al.* **The kidney, subclinical thyroid disease and cardiovascular outcomes in older patients**. Endocrine connections 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31846431
ABSTRACT
OBJECTIVE: Thyroid hormones have been implicated to play a role in cardiovascular disease, along with studies linking thyroid hormone to kidney function. The aim of this study is to investigate whether kidney function modifies the association of subclinical thyroid dysfunction and the risk of cardiovascular outcomes. METHODS: Participants with normal fT4 were classified, based on TSH both at inclusion and 6 months, into 3 groups using data of 4864 patients of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER): subclinical hypothyroidism (TSH>4.5 mIU/L); euthyroidism (TSH=0.45-4.5 mIU/L); and subclinical hyperthyroidism (TSH<0.45 mIU/L). Strata of kidney function were made based on estimated glomerular filtration rate into 3 clinically relevant groups: <45; 45-60; and >60ml/min/1.73m2. The primary endpoint consists of death from coronary heart disease, non-fatal myocardial infarction and (non)fatal stroke. RESULTS: Mean age was 75.3 years and 49.0% patients were male. Mean follow-up was 3.2 years. No statistically significant relationship was found between subclinical thyroid dysfunction and primary endpoint with adjusted hazard ratios of 0.51

(0.24-1.07) comparing subclinical hyperthyroidism and 0.90 (0.58-1.39) comparing subclinical hypothyroidism with euthyroidism. Neither was this relationship present in any of the strata of kidney function, nor did kidney function interact with subclinical thyroid dysfunction in the association with primary endpoint (p-interaction=0.602 for subclinical hyperthyroidism and 0.388 for subclinical hypothyroidism). CONCLUSIONS: In this secondary analysis from PROSPER, we found no evidence that the potential association between thyroid hormones and cardiovascular disease is modified by kidney function in older patients with subclinical thyroid dysfunction.

[18] *Jiang Y, Jin M, Chen J et al.* **Discovery of a novel niacin-lipoic acid dimer N2L attenuating atherosclerosis and dyslipidemia with non-flushing effects**. European journal of pharmacology 2020; 868:172871.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31846627
ABSTRACT
Niacin has been widely used as an antihyperlipidemic drug, but the flushing effect restricted its clinical application. Here, we developed novel niacin-lipoic acid dimers which lead to better lipid modulation, higher synergistic effects and less side effects. We utilized molecular docking simulation to design a novel series of niacin-lipoic acid dimers. The compound N-(2-(5-(1,2-dithiolan-3-yl)pentanamido)ethyl)nicotinamide (N2L) was selected for the in vitro and in vivo evaluation, including the agonist activity in CHO-hGPR109A cells, cell protective effects in HT22 and HUVECs cells, flushing effect in guinea pigs and rats, lipid modulation in C57BL/6 mice and high fat diet-rats and atherosclerotic lesions regulation in apolipoprotein E null mice. N2L worked as potent and selective agonists for the high affinity niacin receptor GPR109A. N2L retained antioxidation and cytoprotection of lipoic acid. In addition, N2L displayed a good therapeutic index regarding lipid modulation and atherosclerotic lesions regulation, and minimized niacin-induced vasodilation (flushing) effect in vivo. N2L showed effective treatment regarding to lipid regulation and atherosclerosis inhibition effects, also with excellent antioxidant effects, safety profiles and non-flushing. All these results suggest N2L promising application prospects in the drug development for the treatment of atherosclerosis.

[19] *Wang YY, Cheng XD, Jiang H*. **Effect of atorvastatin on pulmonary arterial hypertension in rats through PI3K/AKT signaling pathway**. European review for medical and pharmacological sciences 2019; 23:10549-10556.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31841211
ABSTRACT
OBJECTIVE: The aim of this study was to investigate the effect of atorvastatin on pulmonary arterial hypertension (PAH) in rats and to observe its specific regulatory mechanism through the phosphatidylinositol 3-hydroxy kinase/protein kinase B (PI3K/AKT) signaling pathway. MATERIALS AND METHODS: The model of PAH was successfully established in rats via hypoxia feeding. All rats were divided into three groups, including Control group (n=15), PAH model group (Model group, n=15) and atorvastatin treatment group (Ator group, n=15). Tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and nitric oxide (NO) were detected via enzyme-linked immunosorbent assay (ELISA). Right ventricular systolic pressure (RVSP) and right ventricular hypertrophy index (RVHI) in each group were determined as well. Meanwhile, the pathological changes in lung tissues of rats were detected via hematoxylin-eosin (HE) staining. Furthermore, the apoptosis level of lung tissues in each group was detected via terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) staining.

In addition, the expression levels of PI3K/AKT signaling pathway and apoptotic genes in lung tissues were detected via quantitative Polymerase Chain Reaction (qPCR). RESULTS: In Model group, the levels of TNF-alpha and IL-6 increased significantly, while the level of NO decreased. Both RVSP and RVHI in Model group were significantly higher than those of Control group and Ator group ($p<0.05$). The results of HE staining revealed that Model group showed significantly severe lung tissue injury ($p<0.05$). According to the results of TUNEL staining, the number of apoptotic cells in lung tissues in Model group was significantly smaller than that of Ator group ($p<0.05$). Meanwhile, the expression level of cysteinyl aspartate-specific proteinase-3 (Caspase-3) in Model group was markedly lower than that of Ator group ($p<0.05$). However, the expression level of B-cell lymphoma-2 (Bcl-2) in Model group was markedly higher than that of Ator group ($p<0.05$). In Ator group, the expression levels of PI3K and AKT in lung tissues were remarkably higher than those of Model group ($p<0.05$). All the above results indicated that atorvastatin could effectively up-regulate the expressions of PI3K and AKT ($p<0.05$). CONCLUSIONS: Atorvastatin regulates the symptoms of PAH in rats through activating the PI3K/AKT signaling pathway.

[20] *Josse G, Mias C, Le Digabel J et al.* **High bacterial colonization and lipase activity in microcomedones**. Experimental dermatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31863492
ABSTRACT
BACKGROUND: Although Acne Vulgaris has a multifactorial etiology, comedogenesis and bacteria colonization of the pilosebaceous unit are known to play a major role in the onset of inflammatory acne lesions. However, many aspects remain poorly understood such as: Where and when is the early stage of the Propionibacterium acnes colonization in follicular unit? Our research aimed at providing a precise analysis of microcomedone's structure to better understand the interplay between Propionibacterium acnes and follicular units, and therefore the role of its interplay in the formation of acne lesions. METHODS: Microcomedones were sampled using cyanoacrylate skin surface stripping (CSSS). Their morphology was investigated with multiphoton imaging and their ultrastructure with Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Bacterial lipase activity in the microcomedones was quantified using a dedicated enzymatic test as well as a Fourier Transform Infra-Red (FTIR) analysis. The porphyrin produced by bacteria were analysed with HPTLC and fluorescence spectroscopy. RESULTS: The imaging analysis showed that microcomedones' structure resembles a pouch, whose interior is mostly composed of lipids with clusters of bacteria and whose outer shell is made up of corneocyte layers. The extensive bacteria colonization is clearly visible using TEM. Even after sampling, clear lipase activity was still seen in the microcomedone. A high correlation, $r=0.85$, was observed between porphyrin content measured with HPTLC and with fluorescence spectroscopy. These observations show that microcomedones, which are generally barely visible clinically, already contains a bacterial colonization.

[21] *Morelli MB, Chavez C, Santulli G*. **Angiopoietin-like proteins as therapeutic targets for cardiovascular disease: focus on lipid disorders**. Expert opinion on therapeutic targets 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31856617
ABSTRACT
Introduction: Angiopoietin-like (ANGPTL) proteins belong to a family of eight secreted factors that are structurally related to proteins that modulate angiogenesis; these are commonly known as

angiopoietins. Angiopoietin-like proteins, ANGPTL3, ANGPTL4, and ANGPTL8 (the "ANGPT L3-4-8 triad"), have surfaced as principal regulators of plasma lipid metabolism by functioning as potent inhibitors of lipoprotein lipase. The targeting of these proteins may open up future therapeutic avenues for metabolic and cardiovascular disease.Areas covered: This article systematically summarizes the compelling literature that describes the mechanistic roles of ANGPTL3, 4, and 8 in lipid metabolism; this emphasizes their importance in determining the risk of cardiovascular disease. We shed light on population-based studies linking loss-of-function variations in ANGPTL3, 4, and 8 with decreased risk of metabolic conditions and cardiovascular disorders. We also discuss how the targeting of the ANGPT L3-4-8 triad could one day offer therapeutic benefit.Expert opinion: Monoclonal antibodies and antisense oligonucleotides that target ANGPTL3, 4, and 8 are potentially an efficient therapeutic strategy for hypertriglyceridemia and cardiovascular risk reduction, especially in patients with limited treatment options. These innovative therapeutical approaches are at an embryonic stage in development and hence further investigations are necessary for eventual use in humans.

[22] *Provenzano M, Coppolino G, De Nicola L et al.* **Unraveling Cardiovascular Risk in Renal Patients: A New Take on Old Tale**. Frontiers in cell and developmental biology 2019; 7:314.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31850348

ABSTRACT

Chronic kidney disease (CKD), defined by an estimated glomerular filtration rate <60 ml/min/1.73 m(2) and/or an increase in urine protein excretion (i.e., albuminuria), is an important public health problem. Prevalence and incidence of CKD have risen by 87 and 89%, worldwide, over the last three decades. The onset of either albuminuria and eGFR reduction has found to predict higher cardiovascular (CV) risk, being this association strong, independent from traditional CV risk factors and reproducible across different setting of patients. Indeed, this relationship is present not only in high risk cohorts of CKD patients under regular nephrology care and in those with hypertension or type 2 diabetes, but also in general, otherwise healthy population. As underlying mechanisms of damage, it has hypothesized and partially proved that eGFR reduction and albuminuria can directly promote endothelial dysfunction, accelerate atherosclerosis and the deleterious effects of hypertension. Moreover, the predictive accuracy of risk prediction models was consistently improved when eGFR and albuminuria have been added to the traditional CV risk factors (i.e., Framingham risk score). These important findings led to consider CKD as an equivalent CV risk. Although it is hard to accept this definition in absence of additional reports from scientific Literature, a great effort has been done to reduce the CV risk in CKD patients. A large number of clinical trials have tested the effect of drugs on CV risk reduction. The targets used in these trials were different, including blood pressure, lipids, albuminuria, inflammation, and glucose. All these trials have determined an overall better control of CV risk, performed by clinicians. However, a non-negligible residual risk is still present and has been attributed to: (1) missed response to study treatment in a consistent portion of patients, (2) role of many CV risk factors in CKD patients not yet completely investigated. These combined observations provide a strong argument that kidney measures should be regularly included in individual prediction models for improving CV risk stratification. Further studies are needed to identify high risk patients and novel therapeutic targets to improve CV protection in CKD patients.

[23] *Albany CJ, Trevelin SC, Giganti G et al.* **Getting to the Heart of the Matter: The Role of Regulatory T-Cells (Tregs) in Cardiovascular Disease (CVD) and Atherosclerosis**. Frontiers in immunology 2019; 10:2795.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31849973
ABSTRACT
Cardiovascular diseases (CVD) are the leading cause of mortality worldwide. Atherosclerosis is directly associated with CVD and is characterized by slow progressing inflammation which results in the deposition and accumulation of lipids beneath the endothelial layer in conductance and resistance arteries. Both chronic inflammation and disease progression have been associated with several risk factors, including but not limited to smoking, obesity, diabetes, genetic predisposition, hyperlipidemia, and hypertension. Currently, despite increasing incidence and significant expense on the healthcare system in both western and developing countries, there is no curative therapy for atherosclerosis. Instead patients rely on surgical intervention to avoid or revert vessel occlusion, and pharmacological management of the aforementioned risk factors. However, neither of these approaches completely resolve the underlying inflammatory environment which perpetuates the disease, nor do they result in plaque regression. As such, immunomodulation could provide a novel therapeutic option for atherosclerosis; shifting the balance from proatherogenic to athero-protective. Indeed, regulatory T-cells (Tregs), which constitute 5-10% of all CD4(+) T lymphocytes in the peripheral blood, have been shown to be athero-protective and could function as new targets in both CVD and atherosclerosis. This review aims to give a comprehensive overview about the roles of Tregs in CVD, focusing on atherosclerosis.

[24] *Gomez-Alvarez E, Verdejo J, Ocampo S et al.* **Reaching blood pressure guideline targets with the CNIC polypill in patients with a previous cardiovascular event in Mexico: a post hoc analysis of the SORS study**. Future cardiology 2020; 16:53-60.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31850802
ABSTRACT
Aim: To determine the effectiveness of Centro Nacional de Investigaciones Cardiovasculares (CNIC)-polypill (acetylsalicylic acid 100 mg, ramipril 5/10 mg, simvastatin 40 mg) in achieving blood pressure (BP) goals. Patients & methods: A multicenter, observational, one cohort, prospective study. BP targets were analyzed in patients with cardiovascular disease after 12-months treatment with the CNIC polypill. Results: A total of 572 patients (59.4 +/- 13.9 years, 57.3% men) were analyzed. At baseline, BP was 147.1 +/- 18.1/88.3 +/- 10.6 mmHg, 97.1% of patients were taken renin-angiotensin system inhibitors, 5.4% calcium antagonists, 1.9% diuretics and 13.1% beta-blockers. The proportion of patients who achieved BP targets increased from 20.1 to 55.4% ($p < 0.001$). Conclusion: In routine practice, switching from usual care to the CNIC-polypill in patients with cardiovascular disease could facilitate achieving BP goals.

[25] *Heinzl MW, Resl M, Klammer C et al.* **Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is not induced in artificial human inflammation and is not correlated with inflammatory response**. Infection and immunity 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31843964
ABSTRACT

Background: Lipoproteins as well as Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) have been shown to play a key role in the innate immune response. However, knowledge about the role and kinetics of PCSK9 in human inflammation is currently insufficient. The aim of this study was to investigate the interaction between inflammation and lipid metabolism including the possible role of PCSK9.Methods: A single-blinded, placebo-controlled cross-over study using the Human Endotoxin Model was performed. Ten healthy men received lipopolysaccharide (LPS) or placebo on two different study days after overnight fasting. Lipoproteins as well as PCSK9 were measured repetitively over 48 hours.Results: PCSK9 plasma concentrations were not induced by LPS infusion and no correlation between PCSK9 plasma concentrations and the degree of inflammation could be identified. The observed LDL response to inflammation was more complex than anticipated, especially in the very early phase after the inflammatory stimulus. Baseline concentrations of LDL as well as HDL correlated negatively with inflammatory response.Conclusions: Our data suggest that the lipoprotein response to inflammation seems to be independent of PCSK9. The proposed elevations of PCSK9 and suspected correlations between PCSK9 levels and inflammatory response are not supported by our data.Clinical Trial Registration: URL: https://www.clinicaltrials.gov Unique identifier: NCT03392701.

[26] *Maalouly G, Hajal J, Saliba Y et al.* **Beneficial role of simvastatin in experimental autoimmune myositis**. Int Immunopharmacol 2019; 79:106051.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31863923
ABSTRACT
OBJECTIVE: Statins have immunomodulatory potential in autoimmune diseases but had not been studied as a disease-modifying agent in inflammatory myopathies. The objective of this study is to assess the effect of simvastatin in an experimental model of autoimmune myositis in mice on muscle strength and histopathology. METHODS: Four groups of mice (n = 5 per group) were selected for experimentally induced myositis. Mice were immunized with 1.5 mg myosin in complete Freund's adjuvant weekly for two times and injected with 500 ng pertussis toxin twice immediately after each immunization. From day 1 before immunization to 10 days after the last immunization, mice were treated with oral simvastatin (10 or 20 or 40 mg/kg) diluted in DMSO. The control group mice were injected with complete Freund's adjuvant weekly for two times and did not receive treatment. Non-immunized mice (n = 5 per group) were treated either with simvastatin (5 mg/kg or 20 mg/kg or 40 mg/kg of simvastatin diluted in DMSO) or with DMSO. RESULTS: Inflammation was observed in myositis groups with positive myositis-specific antibodies. Muscle strength dropped significantly after immunization. Immunized simvastatin 20 mg/kg treated group had significantly higher muscle strength versus non-treated myositis mice and versus other simvastatin doses. Besides, a trend toward higher serum Th17 percentage population was found in immunized non-treated mice, versus immunized simvastatin- treated mice, without significant difference. CONCLUSION: Simvastatin at 20 mg/kg decreases the severity of myositis in experimental autoimmune myositis and is a candidate of being a disease-modifying agent in inflammatory myopathies.

[27] *Gencer B, Carballo D, Nanchen D et al.* **Intensified lipid lowering using ezetimibe after publication of the IMPROVE-IT trial: A contemporary analysis from the SPUM-ACS cohort**. International journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31859113
ABSTRACT

BACKGROUND: The relevance of the IMPROVE-IT trial on real-life practice has not been explored in patients with ACS. METHODS: A prospective Swiss cohort of 6266 patients hospitalized for ACS between 2009 and 2017 with a one-year follow-up. The primary endpoints were the ezetimibe use overall or in combination with high-intensity statin at discharge and at one year after ACS. Secondary endpoint was LDL-C target achievement at one year in a subsample of 2984 patients. Relative Ratios (RR) were used to assess changes in primary endpoints before and after the publication of IMPROVE-IT, adjusting for age, sex, diabetes, prior myocardial infarction, LDL-C and attendance to cardiac rehabilitation. RESULTS: The period following the publication of the IMPROVE-IT trial was associated with a steady increase in the use of ezetimibe at discharge (from 1.8% to 3.8%, P < 0.001, adjusted RR 2.85, 95% CI 1.90-4.25) and at one year (from 5.0% to 13.8%, P < 0.001, adjusted RR 3.00, 95% CI 2.40-3.75). The combination of high-intensity statin and ezetimibe rose from 0.9% to 2.1% at discharge (P < 0.001, adjusted RR 3.35, 95% CI 1.90-5.89) and from 2.1% to 7.8% at one year (P < 0.001, adjusted RR 3.98, 95% CI 2.90-5.47). The period following the publication of the IMPROVE-IT trial was associated with an improvement of LDL-C target <1.8 mmol/L (adjusted RR 1.37, 95% CI 1.12-1.68). CONCLUSIONS: After the publication of the IMPROVE-IT trial, the use of ezetimibe was increased by three-fold in a large contemporary cohort of ACS patients, concomitant with an improved LDL-C target achievement.

[28] *Visconti MJ, Bashyam AM, Jorizzo JL*. **Statin-induced dermatomyositis for the practicing dermatologist: a review of the literature**. International journal of dermatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31840246
ABSTRACT
Statins cause a spectrum of muscle-related adverse events, including autoimmune myopathies such as dermatomyositis (DM). This review aims to describe the events of statin-induced DM and amyopathic dermatomyositis (ADM) to increase awareness for practicing dermatologists about harmful interactions with the most commonly prescribed lipid-lowering medication. PubMed was searched for relevant literature related to statin-induced DM and ADM. Numerous cases of statin-induced DM have been reported in individuals with no history of DM or other autoimmune conditions. Statins also cause ADM, although this is a rare association. Because of the widespread use of statins worldwide for atherosclerotic disease prevention, it may be of benefit to practicing dermatologists and all clinicians to assess for a history of DM when prescribing statins and inquire if patients with a DM-like presentation are taking or have taken a statin medication.

[29] *Chou CC, Lee HL, Huang YC et al.* **Single Bolus Rosuvastatin Accelerates Calcium Uptake and Attenuates Conduction Inhomogeneity in Failing Rabbit Hearts With Regional Ischemia-Reperfusion Injury**. Journal of cardiovascular pharmacology 2020; 75:64-74.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31842025
ABSTRACT
Acute statin therapy reduces myocardial ischemia/reperfusion (IR) injury-induced ventricular fibrillation (VF), but the underlying electrophysiological mechanisms remain unclear. This study sought to investigate the antiarrhythmic effects of a single bolus rosuvastatin injection in failing rabbit hearts with IR injury and to unveil the underlying molecular mechanisms. Rabbits were divided into rosuvastatin, rosuvastatin + L-NAME, control, and L-NAME groups. Intravenous bolus rosuvastatin (0.5 mg/kg) and/or L-NAME (10 mg/kg) injections were administered 1 hour and 15 minutes before surgery,

respectively. Heart failure was induced using rapid ventricular pacing. Under general anesthesia with isoflurane, an IR model was created by coronary artery ligation for 30 minutes, followed by reperfusion for 15 minutes. Plasma NO end product levels were measured during IR. Then, hearts were excised and Langendorff-perfused for optical mapping studies. Cardiac tissues were sampled for Western blot analysis. Rosuvastatin increased plasma NO levels during IR, which was abrogated by L-NAME. Spontaneous VF during IR was suppressed by rosuvastatin ($P < 0.001$). Intracellular calcium (Cai) decay and conduction velocity were significantly slower in the IR zone. Rosuvastatin accelerated Cai decay, ameliorated conduction inhomogeneity, and reduced the inducibility of spatially discordant alternans and VF significantly. Western blots revealed significantly higher expression of enhancing endothelial NO-synthase and phosphorylated enhancing endothelial NO-synthase proteins in the Rosuvastatin group. Furthermore, SERCA2a, phosphorylated connexin43, and phosphorylated phospholamban were downregulated in the IR zone, which was attenuated or reversed by rosuvastatin. Acute rosuvastatin therapy before ischemia reduced IR-induced VF by improving SERCA2a function and ameliorating conduction disturbance in the IR zone.

[30] *Higgins V, Omidi A, Tahmasebi H et al.* **Marked influence of adiposity on laboratory biomarkers in a healthy cohort of children and adolescents**. The Journal of clinical endocrinology and metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31845996
ABSTRACT
BACKGROUND: The prevalence of pediatric obesity is increasing worldwide and strongly associates with metabolic abnormalities, including inflammation, insulin resistance and dyslipidemia. This study assessed the influence of three measures of adiposity on levels of routinely assessed biochemical markers in apparently healthy children and adolescents. METHODS: The influence of adiposity on 35 biochemical markers were examined in the CALIPER (Canadian Laboratory Initiative on Pediatric Reference Intervals) cohort of healthy children and adolescents by comparing serum biomarker levels between subjects with a normal weight, overweight, and obese BMI. The cohort was comprised of 1,332 subjects ages 5.1-19.0 years with BMI ranging from 13.4-65.0 kg/m2. The association between each biochemical marker and BMI, WC and WHtR z-scores was assessed, while adjusting for age and sex. Reference intervals were established for all biochemical markers before and after removing overweight/obese subjects. RESULTS: In children and adolescents, levels of 13 routinely assessed biochemical markers, including ALT, apoB, C3, C4, ChE, hsCRP, GGT, haptoglobin, HDL-C, iron, transferrin, triglycerides, and uric acid, were significantly differed between BMI categories. BMI, WC, and/or WHtR significantly associated with serum concentration of 24 of the 35 markers examined, after adjusting for age and sex. CONCLUSIONS: Excess adiposity significantly influences circulating levels of routinely assessed laboratory markers, most notably liver enzymes, lipids/lipoproteins, inflammatory markers and uric acid, in children and adolescents. While it is unknown whether altered biochemical marker levels in subjects with overweight/obesity reflect health or indolent disease, clinicians should be aware of the effect of weight status on several laboratory tests.

[31] *Wen J, Dong Q, Liu G et al.* **Improvement of oxidative stress status by lipoprotein apheresis in Chinese patients with familial hypercholesterolemia**. Journal of clinical laboratory analysis 2019:e23161.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31859412

ABSTRACT
BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) characterized by severe high blood cholesterol levels usually presents an imbalance of systemic oxidative stress (OS). Lipoprotein apheresis (LA), which is the most effective therapy to reduce cholesterol levels, remains unclear in altering OS and scarce in Chinese patient studies. Our study aims to assess the impact of LA on OS status in Chinese patients with FH. METHODS: About 31 patients (22 males, age: 12-69 years) with FH and receiving LA treatment were consecutive enrolled. Free oxygen radicals test (FORT) and free oxygen radicals defense (FORD) values were determined using the free oxygen radical monitor and kit immediately before and after LA, while blood samples were collected to measure plasma lipid levels and hs-CRP by conventional methods. Data were analyzed by paired t test or rank sum test and Spearman-rho correlation analysis. RESULTS: Besides plasma lipid levels, the OS status showed that FORTs were significantly decreased and FORD values significantly enhanced immediately after LA treatment compared with before (both P < .01). In addition, the correlation analysis showed that the removal rates (big up tri, open%) of TC were positively related to the increased rates (big up tri, open%) of FORD value (rho = 0.513, P = .003); LDL-C to FORD (rho = 0.39, P = .03); Lp(a) to FORD (rho = 0.473, P = .007); and non-HDL-C to FORD (rho = 0.46, P = .009). However, no significant difference in hsCRP was found. CONCLUSIONS: The present study indicated, besides effectively lowering plasma lipid levels, LA could significantly improve OS status in Chinese patients with FH.

[32] *Marco-Benedi V, Laclaustra M, Casado-Dominguez JM et al.* **Aortic Valvular Disease in Elderly Subjects with Heterozygous Familial Hypercholesterolemia: Impact of Lipid-Lowering Therapy**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31847331

ABSTRACT
Hypercholesterolemia and statins are risk factors for aortic stenosis (AS) and vascular calcification, respectively. Whether heterozygous subjects with familial hypercholesterolemia (HeFH) treated with statins are at risk of AS is unknown. We study the prevalence of AS, aortic valve calcification (AoVC), and aortic sclerosis (ASc) in elderly subjects with HeFH in a prolonged statin treatment. Case-control study, cases were adults >/=65 years of age with a genetic diagnosis of HeFH, LDLc >220 mg/dl, and statin treatment >/=5 years. Controls were relatives of HeFH patients, with LDLc <190 mg/dl. Participants underwent a cardiac ultrasound for aortic valve analysis. We studied 205 subjects, 112 HeFH and 93 controls, with mean age 71.8(6.5) years and 70.0(7.3) years, respectively. HeHF, with respect to controls, presented greater gradients of aortic transvalvular pressure, 7.4(7.3) mmHg versus 5.0(2.8) mmHg, and maximum aortic velocity, 1.7(0.7) m/s versus 1.5(0.4) m/s, and lower aortic valve opening area, 2.0(0.7) cm(2) versus 2.4(0.6) cm(2) (all p < 0.05). AoVC and ASc were also more prevalent in HeFH (p < 0.05 between groups). Moderate/severe AS prevalence was higher among HeFH: 7.1% versus 1.1% (age- and sex-adjusted odds ratio (OR) 8.33, p = 0.03). Independent risk factors for aortic valve disease in HeFH were age and LDLc before treatment. The number of years under statin treatment was not associated with any aortic valve measurement. Subjects >/=65 years with HeFH in prolonged statin treatment show more aortic valvular disease and higher frequency of AS than controls. Life-long elevated LDLc exposure, rather than time of exposure to statins, explains this higher risk.

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[33] *Shirke PY, Kolte AP, Kolte RA, Bawanakar PV*. **Evaluation of the clinical efficacy of 1.2% atorvastatin in the treatment of periodontal intraosseous defects by CBCT: A randomized controlled clinical trial**. Journal of dental research, dental clinics, dental prospects 2019; 13:183-191.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31857864
ABSTRACT
Background. Atorvastatin (ATV), which belongs to the statin class of drugs, is the formidable inhibitor of 3-hydroxy-2- methyl-glutaryl coenzyme A reductase. This clinical trial evaluated and compared the clinical and radiographic changes in chronic periodontitis (CP) patients, obtained through 1.2% ATV as an adjunct to scaling and root planing (SRP) in the treatment of intraosseous defects. Methods. Twenty CP patients, with a minimum of one pair of bilateral intraosseous, were randomly selected for this splitmouth study. Group 1 included 20 sites treated with SRP and subgingival delivery of a placebo gel, whereas an equal number of sites in group 2 were treated by SRP along with subgingival delivery of 1.2% ATV gel. The plaque index (PI), modified sulcus bleeding index (mSBI), probing pocket depth (PPD) and clinical attachment level (CAL) were evaluated at baseline and 3- and 6-month intervals, while the intraosseous defect was assessed at baseline and 6-month interval using cone-beam computed tomography (CBCT). Paired t-test was used to determine statistical significance. Results. A greater reduction in the mean PPD and gain in CAL was found in group 2 compared to group 1 at 3- and 6-month intervals. Furthermore, a significantly greater bone fill was obtained in group 2 (1.70+/-0.54 mm) compared to group 1 (0.22+/-0.43 mm) after six months. Conclusion. ATV, as an adjunct to SRP, enhanced periodontal regeneration, as a noninvasive way to treat periodontal intraosseous defects.

[34] *Lin Z, Wang SH, Wei DY et al.* **PCSK9 E670G polymorphism increases risk of coronary artery disease in a Chinese Han population**. J Int Med Res 2019:300060519892177.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31840538
ABSTRACT

[35] *Baass A, Paquette M, Bernard S, Hegele RA*. **Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridaemia**. Journal of internal medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31840878
ABSTRACT
Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive disorder of chylomicron metabolism causing severe elevation of triglyceride (TG) levels (>10 mmol L(-1)). This condition is associated with a significant risk of recurrent acute pancreatitis (AP). AP caused by hypertriglyceridaemia (HTG) has been associated with a worse prognosis and higher mortality rates compared to pancreatitis of other aetiology. Despite its association with poor quality of life and increased lifelong risk of HTG-AP, few healthcare providers are familiar with FCS. Because this condition is under-recognized, the majority of FCS patients are diagnosed after age 20 often after consulting several physicians. Although other forms of severe HTG such as multifactorial chylomicronemia have been associated with high atherosclerotic cardiovascular disease (ASCVD) risk and metabolic abnormalities, ASCVD and metabolic syndrome are not usually observed in FCS patients. Because FCS is a genetic condition, the optimal diagnosis strategy remains genetic testing. The presence of bi-allelic pathogenic mutations in LPL, APOC2, GPIHBP1, APOA5 or LMF1 genes confirms the diagnosis. However, some cases of FCS caused by autoantibodies against LPL or GPIHBP1 proteins have also been reported. Furthermore, a clinical score for the diagnosis of FCS has been proposed but

needs further validation. Available treatment options to lower triglycerides such as fibrates or omega-3 fatty acids are not efficacious in FCS patients. Currently, the cornerstone of treatment remains a lifelong very low-fat diet, which prevents the formation of chylomicrons. Finally, inhibitors of apo C-III and ANGPTL3 are in development and may eventually constitute additional treatment options for FCS patients.

[36] *Vuorio A, Watts GF, Schneider WJ et al.* **Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities**. Journal of internal medicine 2020; 287:2-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31858669
ABSTRACT
There is compelling evidence that the elevated plasma lipoprotein(a) [Lp(a)] levels increase the risk of atherosclerotic cardiovascular disease (ASCVD) in the general population. Like low-density lipoprotein (LDL) particles, Lp(a) particles contain cholesterol and promote atherosclerosis. In addition, Lp(a) particles contain strongly proinflammatory oxidized phospholipids and a unique apoprotein, apo(a), which promotes the growth of an arterial thrombus. At least one in 250 individuals worldwide suffer from the heterozygous form of familial hypercholesterolemia (HeFH), a condition in which LDL-cholesterol (LDL-C) is significantly elevated since birth. FH-causing mutations in the LDL receptor gene demonstrate a clear gene-dosage effect on Lp(a) plasma concentrations and elevated Lp(a) levels are present in 30-50% of patients with HeFH. The cumulative burden of two genetically determined pro-atherogenic lipoproteins, LDL and Lp(a), is a potent driver of ASCVD in HeFH patients. Statins are the cornerstone of treatment of HeFH, but they do not lower the plasma concentrations of Lp(a). Emerging therapies effectively lower Lp(a) by as much as 90% using RNA-based approaches that target the transcriptional product of the LPA gene. We are now approaching the dawn of an era, in which permanent and significant lowering of the high cholesterol burden of HeFH patients can be achieved. If outcome trials of novel Lp(a)-lowering therapies prove to be safe and cost-effective, they will provide additional risk reduction needed to effectively treat HeFH and potentially lower the CVD risk in these high-risk patients even more than currently achieved with LDL-C lowering alone.

[37] *Pouwer MG, Pieterman EJ, Worms N et al.* **Alirocumab, evinacumab, and atorvastatin triple therapy regresses plaque lesions and improves lesion composition in mice**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31843957
ABSTRACT
Atherosclerosis-related cardiovascular disease causes nearly 20 million deaths annually. Most patients are treated after plaques develop, so therapies must regress existing lesions. Current therapies reduce plaque volume, but targeting all apoB-containing lipoproteins with intensive combinations that include alirocumab or evinacumab-monoclonal antibodies against cholesterol-regulating PCSK9 and ANGPTL3-may provide more benefit. We investigated the effect of such lipid-lowering interventions on atherosclerosis in APOE*3-Leiden.CETP mice, a well-established model for hyperlipidemia. Mice were fed a Western-type diet for 13 weeks and thereafter matched into a baseline group (sacrificed at 13 weeks) and five groups that received diet alone (control) or with treatment-atorvastatin; atorvastatin and alirocumab; atorvastatin and evinacumab; or atorvastatin, alirocumab, and evinacumab (triple therapy)-for 25 weeks. We measured effects on cholesterol levels, plaque composition and

morphology, monocyte adherence, and macrophage proliferation. All interventions reduced plasma total cholesterol (37% with atorvastatin to 80% with triple treatment; all p < 0.001). Triple treatment decreased non-HDL cholesterol to 1.0 mmol/L (91% difference from control; p < 0.001). Atorvastatin reduced atherosclerosis progression by 28% versus control (p < 0.001); double treatment completely blocked progression and diminished lesion severity. Triple treatment regressed lesion size versus baseline in the thoracic aorta by 50% and the aortic root by 36% (both p < 0.05 vs baseline); decreased macrophage accumulation through reduced proliferation; and abated lesion severity. Thus, high-intensive cholesterol-lowering triple treatment targeting all apoB-containing lipoproteins regresses atherosclerotic lesion area and improves lesion composition in mice, making it a promising potential approach for treating atherosclerosis.

[38] *Cucuruz B, Kopp R, Pfister K et al.* **Risk and protective factors for post-thrombotic syndrome after deep venous thrombosis**. Journal of vascular surgery. Venous and lymphatic disorders 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31843481
ABSTRACT
OBJECTIVE: The most frequent complication of deep venous thrombosis (DVT) is post-thrombotic syndrome (PTS). We recently showed inhibition of varicose vein development by atorvastatin and rosuvastatin. The aim of this study was to test the influence of lipid-lowering therapy with statins on PTS development. METHODS: All patients between January 2002 and June 2018 with diagnosed DVT were enrolled in this study and analyzed retrospectively. Documentation was performed using the standardized system M1 (CompuGroup Medical, Koblenz, Germany) throughout the observation period. Patients received therapeutic anticoagulation and compression stockings. In case of recurrent DVT, patients received lifelong therapeutic anticoagulation. All patients received clinical examination and duplex ultrasound evaluation 3 to 6 months after primary diagnosis and annually thereafter. RESULTS: A total of 579 patients with DVT were enrolled in this study. Of these patients, 414 (71%) developed PTS (337/414 [81%] presented with the mild version; mean Villalta score, 5.79). Risk factors for PTS development were recurrent DVT (P = .001) and malignant disease (P = .001). Protective factors were therapy with platelet aggregation inhibitors (P = .049) and lipid-lowering therapy with statins (P = .001). After multivariable analysis, the only risk factor was recurrent DVT (P = .001), and the only protective factor was lipid-lowering therapy (P = .001). CONCLUSIONS: Post-thrombotic changes might be reduced by lipid-lowering therapy.

[39] *Tmoyan NA, Afanasieva OI, Ezhov MV et al.* **[Lipoprotein(small a, Cyrillic) Level, Apolipoprotein(small a, Cyrillic) Polymorphism small a, Cyrillicnd Autosmall a, Cyrillicntibodies Against Lipoprotein(small a, Cyrillic) in Patients with Stenotic Csmall a, Cyrillicrotid Atherosclerosis]**. Kardiologiia 2019; 59:20-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31849309
ABSTRACT
capital A, Cyrillicim. Comparative assessment of respiratory indicators according to multifunctional monitoring (PFM) with the recommended standard for a complete polysomnographic study and an assessment of the effect of blood pressure (BP) measurements in PFM on sleep quality. Trismall a, Cyrillicls on the small a, Cyrillicssocismall a, Cyrilliction of Lp(small a, Cyrillic) and csmall a, Cyrillicrotid small a, Cyrillictherosclerosis small a, Cyrillicre limited. The small a, Cyrillicim of the study wsmall a, Cyrillics to investigsmall a, Cyrillicte the small a, Cyrillicssocismall a, Cyrilliction of Lp(small a, Cyrillic),

small a, Cyrillicpolipoprotein(small a, Cyrillic) [apo(small a, Cyrillic)] polymorphism small a, Cyrillicnd small a, Cyrillicutosmall a, Cyrillicntibodies to Lp(small a, Cyrillic) with stenotic (>/=50%) csmall a, Cyrillicrotid small a, Cyrillictherosclerosis in dependence on CHD presence. Materials and methods. The study included 785 psmall a, Cyrillictients small a, Cyrillict the small a, Cyrillicge from 21 to 92 with dsmall a, Cyrillictsmall a, Cyrillic of instrumentsmall a, Cyrillicl exsmall a, Cyrillicmination of coronsmall a, Cyrillicry, csmall a, Cyrillicrotid small a, Cyrillicnd lower limbs small a, Cyrillicrteries. Stenotic csmall a, Cyrillicrotid small a, Cyrillictherosclerosis wsmall a, Cyrillics dismall a, Cyrillicgnosed in 447 psmall a, Cyrillictients who were divided into two groups depending on presence (n=344) or small a, Cyrillicbsence (n=103) of CHD. The control group comprised of 338 psmall a, Cyrillictients without stenotic small a, Cyrillictherosclerosis of coronsmall a, Cyrillicry, csmall a, Cyrillicrotid small a, Cyrillicnd lower limbs small a, Cyrillicrteries. In the blood serum of psmall a, Cyrillictients levels of Lp(small a, Cyrillic), small a, Cyrillicutosmall a, Cyrillicntibodies to Lp(small a, Cyrillic) were determined small a, Cyrillicnd small a, Cyrilliclso small a, Cyrillicpo(small a, Cyrillic) phenotyping wsmall a, Cyrillics conducted. Results. There were more msmall a, Cyrillicles, higher small a, Cyrillicversmall a, Cyrillicge small a, Cyrillicge small a, Cyrillicnd frequency of hypertension, type 2 dismall a, Cyrillicbetes mellitus, smoking, Lp(small a, Cyrillic) concentrsmall a, Cyrilliction (medismall a, Cyrillicn [interqusmall a, Cyrillicrtile rsmall a, Cyrillicnge]): 30 [11; 63] vs. 14 [5; 30] mg/dl, p<0.01) in the group with stenotic csmall a, Cyrillicrotid small a, Cyrillictherosclerosis in compsmall a, Cyrillicrison with control group. Besides, Lp(small a, Cyrillic) level wsmall a, Cyrillics higher in CHD subgroup thsmall a, Cyrillicn in psmall a, Cyrillictients with stenotic csmall a, Cyrillicrotid small a, Cyrillictherosclerosis without CHD: 32 [12; 72] vs. 24 [8; 50] mg/dl, respectively, p=0.01. Elevsmall a, Cyrillicted (>/=30 mg/dl) Lp(small a, Cyrillic) level, low moleculsmall a, Cyrillicr weight small a, Cyrillicpolipoprotein(small a, Cyrillic) [(LMW small a, Cyrillicpo(small a, Cyrillic)] phenotype were small a, Cyrillicssocismall a, Cyrillicted with stenotic csmall a, Cyrillicrotid small a, Cyrillictherosclerosis (odds rsmall a, Cyrillictio (OR) 2.9; 95% confidence intervsmall a, Cyrillicl (CI) 2.1-4.0, p<0.01 small a, Cyrillicnd OR 2.3; 95% CI 1.6-3.4, p<0.01, respectively). Logistic regression small a, Cyrillicnsmall a, Cyrilliclysis showed independent small a, Cyrillicssocismall a, Cyrilliction of elevsmall a, Cyrillicted Lp(small a, Cyrillic) level small a, Cyrillicnd LMW small a, Cyrillicpo(small a, Cyrillic) phenotype with stenotic csmall a, Cyrillicrotid small a, Cyrillictherosclerosis both in the presence small a, Cyrillicnd absence of CHD. The level of IgM small a, Cyrillicutosmall a, Cyrillicntibodies to Lp(small a, Cyrillic) wsmall a, Cyrillics higher in control group thsmall a, Cyrillicn in psmall a, Cyrillictients with stenotic csmall a, Cyrillicrotid small a, Cyrillictherosclerosis, p=0.02. Conclusion The level of Lp(a) >/=30 mg/dl and low molecular weight phenotype of aprotein(a) are predictors of stenotic atherosclerosis CA, regardless of the presence of coronary heart disease and other risk factors, while a reverse relationship was found between the level of autoantibodies of the IgM class against Lp(a) and the severity of atherosclerosis CA.

[40] *Wang N, Fulcher J, Abeysuriya N et al.* **Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants**. The lancet. Diabetes & endocrinology 2020; 8:36-49.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31862150
ABSTRACT
BACKGROUND: The benefits of LDL cholesterol-lowering treatment for the prevention of atherosclerotic cardiovascular disease are well established. However, the extent to which these effects

differ by baseline LDL cholesterol, atherosclerotic cardiovascular disease risk, and the presence of comorbidities remains uncertain. METHODS: We did a systematic literature search (MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, from inception up to June 15, 2019) for randomised controlled trials of statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors with at least 1000 patient-years of follow-up. Random-effects meta-analysis and meta-regressions were done to assess for risk of major vascular events (a composite of cardiovascular mortality, non-fatal myocardial infarction, non-fatal ischaemic stroke, or coronary revascularisation) per 1 mmol/L (38.7 mg/dL) reduction in LDL cholesterol concentrations. FINDINGS: 327 037 patients from 52 studies were included in the meta-analysis. Each 1 mmol/L reduction in LDL cholesterol was associated with a 19% relative risk (RR) reduction for major vascular events (RR 0.81 [95% CI 0.78-0.84]; p<0.0001). Similar reductions (per 1 mmol/L reduction in LDL cholesterol) were found in trials with participants with LDL cholesterol 2.60 mmol/L or lower, 2.61-3.40 mmol/L, 3.41-4.10 mmol/L, and more than 4.1 mmol/L (p=0.232 for interaction); and in a subgroup of patients who all had a baseline LDL cholesterol less than 2.07 mmol/L (80 mg/dL; RR 0.83 [95% CI 0.75-0.92]; p=0.001). We found greater RR reductions in patients at lower 10-year atherosclerotic cardiovascular disease risk (change in RR per 10% lower 10-year atherosclerotic cardiovascular disease 0.97 [95% CI 0.95-0.98]; p<0.0001) and in patients at younger age across a mean age of 50-75 years (change in RR per 10 years younger age 0.92 [0.83-0.97]; p=0.015). We found no difference in RR reduction for participants with or without diabetes (p=0.878 for interaction) and chronic kidney disease (p=0.934 for interaction). INTERPRETATION: For each 1 mmol/L LDL cholesterol lowering, the risk reduction of major vascular events is independent of the starting LDL cholesterol or the presence of diabetes or chronic kidney disease. Patients at lower cardiovascular risk and younger age might have a similar relative reduction in risk with LDL-cholesterol lowering therapies and future studies should investigate the potential benefits of earlier intervention. FUNDING: None.

[41] *Yalcinkaya A, Unal S, Oztas Y*. **Altered HDL particle in sickle cell disease: decreased cholesterol content is associated with hemolysis, whereas decreased Apolipoprotein A1 is linked to inflammation**. Lipids in health and disease 2019; 18:225.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31861992
ABSTRACT
BACKGROUND: Hypocholesterolemia is the most frequently encountered lipid abnormality in sickle cell disease (SCD). We enrolled pediatric patients to determine the relationships between lipid profile and parameters of hemolysis, oxidative stress and chronic inflammation in SCD. METHODS: The study involved 35 pediatric SCD patients and 19 healthy controls. Patients were crisis-free and had not received transfusions for the last 3 months. Total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C, apolipoprotein A1, apolipoprotein B, LCAT, LDH, bilirubin, haptoglobin, iron, ferritin, hemin, serum amyloid A (SAA), myeloperoxidase (MPO), uric acid, ALT and GGT levels were evaluated in patients' blood. RESULTS: Patients had hypocholesterolemia depicted by lower levels of total cholesterol, HDL-C, LDL-C, as well as Apolipoprotein A1 and Apolipoprotein B compared to controls. The chronic hemolysis of SCD was evident in patients by higher LDH and bilirubin and almost undetectable haptoglobin levels. Hemin levels (as a measure of oxidized heme) were significantly increased in patients with SCD. Inflammation markers, SAA and MPO, were significantly increased in the patients as well. There were negative correlations between HDL-C and LDH, and Apo A1 and SAA. Hemin was positively correlated to MPO. CONCLUSION: Hemolysis was associated with decreased HDL -C, and Inflammation was linked

to decreased apolipoprotein A1 levels in our SCD patients. Therefore, we suggest that the HDL particle is altered during the course of the disease. The altered HDL in SCD may become dysfunctional and result with a slowing down of the reverse cholesterol transport.

[42] *Hyun MH, Jang JW, Choi BG et al.* **The low-density lipoprotein cholesterol lowering is an ineffective surrogate marker of statin responsiveness to predict cardiovascular outcomes: The 10-year experience of matched population (a STROBE-compliant article)**. Medicine (Baltimore) 2019; 98:e18510.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31861037
ABSTRACT
Statins therapy decrease both low-density lipoprotein cholesterol (LDL-C) levels and the risk of atherosclerotic cardiovascular disease (ASCVD) with considerable individual variability. Whether the amount of LDL-C lowering is a surrogate maker of statin responsiveness to ASCVD prevention has not been fully investigated. Among 2352 eligible patients with statin prescriptions in a cardiovascular center between January 2005 and February 2014, one-third of patients (33%) on statin therapy failed to achieve effective reductions in LDL-C (LDL-C level reduction of less than 15%). By using, propensity-score matched population (480 pairs, n = 960), the 5-year cumulative incidences of total major adverse cardiac events (MACE) were evaluated. The 5-year total MACE did not differ between normal cholesterol responders and non-responders (15.4% vs 16.1%, respectively; P = .860). In the subgroup analysis, male sex, older age, percutaneous coronary intervention, and heart failure were positive predictors, and dyslipidemia at the beginning of statin therapy was the only negative predictor of MACE in the 5-year follow-up (all P value < .05). However, cholesterol responsiveness after statin therapy did not influence the incidence of MACE (P = .860). The amount of LDL-C lowering did not predict beneficial effect on clinical outcomes of ASCVD after statin therapy. This result supports that given statin therapy, total ASCVD risk reduction should be tailored, which may not dependent to adherence to degree of LDL-C lowering or LDL-C goal based treatment.

[43] *Fernandez-Ruiz I*. **GPR146 is a potential new therapeutic target for lipid lowering**. Nature reviews. Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31848468
ABSTRACT

[44] *Alwhaibi M, Altoaimi M, AlRuthia Y et al.* **Adherence to Statin Therapy and Attainment of LDL Cholesterol Goal Among Patients with Type 2 Diabetes and Dyslipidemia**. Patient preference and adherence 2019; 13:2111-2118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31853174
ABSTRACT
Background: Statins are widely utilized antidyslipidemics with a proven track record of safety and efficacy. However, the efficacy of these therapeutic agents hinges on patients' adherence to their prescribed statins. Objective: The primary objectives of this study were to examine the relationship between adherence to prescribed statins and its impact on the low-density lipoprotein (LDL) level, and to explore the factors that influence patient adherence to statins among patients with diabetes and dyslipidemia. Methods: This was a retrospective, cross-sectional study using the electronic health records data of adults (>/=18 years) with type 2 diabetes and dyslipidemia visiting outpatient clinics at

a university-affiliated tertiary care center. Adherence to statin therapy was estimated using the proportion of days covered (PDC). Patients with diabetes were considered adherent to statins if they had a PDC of >/=80%. Treatment success was considered if the LDL level of < 2.6 mmol/L. Results: Out of 10,226 of patients with diabetes, 1532 met the inclusion criteria and were included in the study. Seventy-nine percent of the patients with diabetes were on atorvastatin and 21% were on simvastatin. The vast majority of the patients with diabetes (77%) were considered adherent and about 42% achieved LDL-cholesterol goal < 2.6 mmol/L. No association between adherence to statin therapy and LDL goal attainment was observed. Women had lower odds of being adherent to statin therapy (AOR=0.66, 95% CI: 0.49-0.87) compared to men. Further, young adults (18-44 years) had lower odds of being adherent to statin therapy (AOR=0.58, 95% CI: 0.32-0.97) compared to older adults (age>65 years). Conclusion: The findings of this study highlight the need to examine the impact of adherence to statins on healthcare services utilization due to different complications of uncontrolled dyslipidemia.

[45] *Heine GH, Eller K, Stadler JT et al.* **Lipid-modifying therapy in chronic kidney disease: Pathophysiological and clinical considerations**. Pharmacology & therapeutics 2019:107459.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31863818
ABSTRACT
Chronic kidney disease (CKD), which affects >10% of the population worldwide, is associated with a dramatically increased rate of cardiovascular disease (CVD). More people with CKD will die from CVD than develop end-stage renal disease with dialysis-dependency. However, the contribution of classical atherosclerotic cardiovascular risk factors is less evident than in the general population. Particularly, the relationship between dyslipidemia and CVD morbidity and mortality in CKD patients is not as evident as in the general population. While LDL cholesterol-lowering drugs such as statins significantly reduce the rate of cardiovascular events in the general population, their role in patients with end-stage renal disease has been questioned. This could be caused by a shift from atherosclerotic to non-atherosclerotic CVD in patients with advanced CKD, which cannot be effectively prevented by lipid-lowering drugs. In addition, many lines of evidence suggest that impaired renal function directly affects the metabolism, composition and functionality of lipoproteins, which may affect their responsiveness to pharmacological interventions. In this review, we highlight the challenges for the therapeutic application of lipid-lowering treatment strategies in CKD and discuss why treatment strategies used in the general population cannot be applied uncritically to CKD patients.

[46] *Can L, Junxiong Z, Bao H et al.* **"Single intraosseous injection of simvastatin promotes endothelial progenitor cell mobilization, neovascularization, and wound healing in diabetic rats"**. Plastic and reconstructive surgery 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31842119
ABSTRACT
BACKGROUND: This study explored the effect of a single local intraosseous application of a small dose simvastatin on the wound healing process in type 1 diabetic rats and related mechanisms. METHODS: We chose the streptozotocin-induced type 1 diabetic rat to establish a full thickness dermal wound using a 12-mm diameter sterile disposable punch. The rats (n=32) were randomly divided into four groups: (1) Normal control rats, (2) type 1 diabetic rats with an intraosseous injection of hydrogel vehicle or (3) simvastatin (0.5 mg), and (4) with intragastric administration of simvastatin (20 mg/kg.d). Wound closure was followed by digital planimetry. Mobilization of endothelial progenitor cells into

circulatory system was studied using fluorescence activated cell sorter (FACS). Neovasculization was analyzed with immunofluorescence histochemical staining. The relative levels of adiponectin and stromal cell-derived factor 1 (SDF-1) in serum, bone and wound tissues were examined via ELISA and western blot. RESULTS: Diabetic rats exhibited impaired wound healing. Intraosseous administration of simvastatin accelerated wound healing beginning at day 4 and angiogenesis was more obvious than in the control group. ELISA revealed that adiponectin concentrations in T1DM+SIM 0.5 mg group were significantly higher compared with the T1DM group beginning at day 4. Intraosseous administration of simvastatin decreased the expression of adiponectin (APN) and SDF-1 in bone tissue but enhanced the expression of APN in wounded skin. CONCLUSIONS: A single local intraosseous application of simvastatin promotes wound healing in type 1 diabetic rat. The underlying mechanisms may be attributed to the regulation of the APN/SDF-1 pathway, which plays a pivotal role in endothelial progenitor cell mobilization and angiogenesis.

[47] *Kettunen J, Holmes MV, Allara E et al.* **Lipoprotein signatures of cholesteryl ester transfer protein and HMG-CoA reductase inhibition**. PLoS biology 2019; 17:e3000572.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31860674
ABSTRACT
Cholesteryl ester transfer protein (CETP) inhibition reduces vascular event risk, but confusion surrounds its effects on low-density lipoprotein (LDL) cholesterol. Here, we clarify associations of genetic inhibition of CETP on detailed lipoprotein measures and compare those to genetic inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). We used an allele associated with lower CETP expression (rs247617) to mimic CETP inhibition and an allele associated with lower HMGCR expression (rs12916) to mimic the well-known effects of statins for comparison. The study consists of 65,427 participants of European ancestries with detailed lipoprotein subclass profiling from nuclear magnetic resonance spectroscopy. Genetic associations were scaled to 10% reduction in relative risk of coronary heart disease (CHD). We also examined observational associations of the lipoprotein subclass measures with risk of incident CHD in 3 population-based cohorts totalling 616 incident cases and 13,564 controls during 8-year follow-up. Genetic inhibition of CETP and HMGCR resulted in near-identical associations with LDL cholesterol concentration estimated by the Friedewald equation. Inhibition of HMGCR had relatively consistent associations on lower cholesterol concentrations across all apolipoprotein B-containing lipoproteins. In contrast, the associations of the inhibition of CETP were stronger on lower remnant and very-low-density lipoprotein (VLDL) cholesterol, but there were no associations on cholesterol concentrations in LDL defined by particle size (diameter 18-26 nm) (-0.02 SD LDL defined by particle size; 95% CI: -0.10 to 0.05 for CETP versus -0.24 SD, 95% CI -0.30 to -0.18 for HMGCR). Inhibition of CETP was strongly associated with lower proportion of triglycerides in all high-density lipoprotein (HDL) particles. In observational analyses, a higher triglyceride composition within HDL subclasses was associated with higher risk of CHD, independently of total cholesterol and triglycerides (strongest hazard ratio per 1 SD higher triglyceride composition in very large HDL 1.35; 95% CI: 1.18-1.54). In conclusion, CETP inhibition does not appear to affect size-specific LDL cholesterol but is likely to lower CHD risk by lowering concentrations of other atherogenic, apolipoprotein B-containing lipoproteins (such as remnant and VLDLs). Inhibition of CETP also lowers triglyceride composition in HDL particles, a phenomenon reflecting combined effects of circulating HDL, triglycerides, and apolipoprotein B-containing particles and is associated with a lower CHD risk in

observational analyses. Our results reveal that conventional composite lipid assays may mask heterogeneous effects of emerging lipid-altering therapies.

[48] *Unger AL, Eckstrom K, Jetton TL, Kraft J*. **Colonic bacterial composition is sex-specific in aged CD-1 mice fed diets varying in fat quality**. PloS one 2019; 14:e0226635.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31851713
ABSTRACT
Evidence suggests that sex influences the effect of diet on the gut bacterial composition, yet, no studies have been performed assessing dietary fatty acid composition (i.e., fat quality) in this context. This study examined the effect of dietary fat quality on colonic bacterial composition in an aged, genetically-diverse mouse population. CD-1 mice were fed isoenergetic diets consisting of (1) control fat (CO; "Western-style" fat blend), (2) CO supplemented with 30% fish oil, (3) CO supplemented with 30% dairy fat, or (4) CO supplemented with 30% echium oil. Fecal samples were collected at mid-life and aged (reproductively senescent) time points. Overall, the abundance of Bacteroidetes was greater in mice fed echium oil compared to mice fed the control fat. Examination of colonic bacterial relative abundance also revealed sex differences, with 73 bacterial taxa being differentially expressed in males and females. Notably, results showed a strong interactive effect among the diet, sex, and age of mice which influenced colonic bacterial relative abundance and alpha diversity. In males, supplementation of the diet with dairy fat or echium oil caused the abundance of Bacteroidetes and Bacteroides to change with age. Additionally, supplementation of the diet with fish oil induced sex-dependent changes in the alpha diversity of aged mice compared to mid-life. This work supports that sex is a critical factor in colonic bacterial composition of an aged, genetically-heterogenous population. Moreover, this study establishes that the effectiveness of dietary interventions for health maintenance and disease prevention via direct or indirect manipulation of the gut microbiota is likely dependent on an individual's sex, age, and genetic background.

[49] *DeMizio DJ, Geraldino-Pardilla LB*. **Autoimmunity and Inflammation Link to Cardiovascular Disease Risk in Rheumatoid Arthritis**. Rheumatology and therapy 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31853784
ABSTRACT
Rheumatoid arthritis (RA) patients have a 50% increased risk of cardiovascular (CV)-related morbidity and mortality. This excess CV risk is closely linked to RA disease severity and chronic inflammation, hence is largely underestimated by traditional risk calculators such as the Framingham Risk Score. Epidemiological studies have shown that patients with RA are more likely to have silent ischemic heart disease, develop heart failure, and experience sudden death compared with controls. Elevations in pro-inflammatory cytokines, circulating autoantibodies, and specific T cell subsets, are believed to drive these findings by promoting atherosclerotic plaque formation and cardiac remodeling. Current European League Against Rheumatism (EULAR) guidelines state that rheumatologists are responsible for the assessment and coordination of CV disease (CVD) risk management in patients with RA, yet the optimal means to do so remain unclear. While these guidelines focus on disease activity control to mitigate excess CV risk, rather than providing a precise algorithm for choice of therapy, studies suggest a differential impact on CV risk of non-biologic disease-modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, and small molecule-based therapy. In this review, we explore the mechanisms

linking the pathophysiologic intrinsic features of RA with the increased CVD risk in this population, and the impact of different RA therapies on CV outcomes.

[50] *Gobbi G, Carubbi C, Tagliazucchi GM et al.* **Sighting acute myocardial infarction through platelet gene expression**. Scientific reports 2019; 9:19574.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31863085
ABSTRACT
Acute myocardial infarction is primarily due to coronary atherosclerotic plaque rupture and subsequent thrombus formation. Platelets play a key role in the genesis and progression of both atherosclerosis and thrombosis. Since platelets are anuclear cells that inherit their mRNA from megakaryocyte precursors and maintain it unchanged during their life span, gene expression profiling at the time of an acute myocardial infarction provides information concerning the platelet gene expression preceding the coronary event. In ST-segment elevation myocardial infarction (STEMI), a gene-by-gene analysis of the platelet gene expression identified five differentially expressed genes: FKBP5, S100P, SAMSN1, CLEC4E and S100A12. The logistic regression model used to combine the gene expression in a STEMI vs healthy donors score showed an AUC of 0.95. The same five differentially expressed genes were externally validated using platelet gene expression data from patients with coronary atherosclerosis but without thrombosis. Platelet gene expression profile highlights five genes able to identify STEMI patients and to discriminate them in the background of atherosclerosis. Consequently, early signals of an imminent acute myocardial infarction are likely to be found by platelet gene expression profiling before the infarction occurs.

[51] *Kim Y, Yoon S, Choi Y et al.* **Influence of OATP1B1 and BCRP polymorphisms on the pharmacokinetics and pharmacodynamics of rosuvastatin in elderly and young Korean subjects**. Scientific reports 2019; 9:19410.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31857620
ABSTRACT
A lack of information regarding whether genetic polymorphisms of SLCO1B1 and ABCG2 affect the pharmacokinetics (PKs)/pharmacodynamics (PDs) of rosuvastatin in elderly subjects prevents optimal individualized pharmacotherapy of rosuvastatin in clinical settings. This study aimed to investigate the effect of age and genetic polymorphisms and possible differences in genetic effects on the PKs/PDs of rosuvastatin between elderly and young subjects. Two separate clinical studies designed as open-label, one-sequence studies with multiple-dose administration for elderly (n = 20) and young (n = 32) subjects were conducted. All subjects received 20 mg of rosuvastatin once daily for 21 days. The exposure to rosuvastatin, characterized by the area under the time curve (AUC), increased by 23% in the elderly subjects compared with that of young subjects, which was not significant. When compared to the subjects with breast cancer resistance protein (BCRP) normal function, the exposure to rosuvastatin increased by 44% in young subjects ($p = 0.0021$) with BCRP intermediate function (IF) and by 35% and 59% ($p > 0.05$ for both) in elderly subjects with BCRP IF and low function, respectively. SLCO1B1 521T > C was also partially associated with a higher AUC of rosuvastatin in young subjects and a less pronounced increasing trend in elderly subjects ($p > 0.05$ for both). The lipid-lowering effect of rosuvastatin was less pronounced in the elderly subjects than in the young subjects, and genetic polymorphisms of neither SLCO1B1 nor ABCG2 significantly affected the PDs of rosuvastatin. The ABCG2 421C > A polymorphism was associated with the PKs of rosuvastatin and was identified as a

more important determinant than the SLCO1B1 521T > C polymorphism in both elderly and young subjects.

[52] *Mozetic V, Leonel L, Leite Pacheco R et al.* **Reporting quality and adherence of randomized controlled trials about statins and/or fibrates for diabetic retinopathy to the CONSORT checklist**. Trials 2019; 20:729.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31842982
ABSTRACT
BACKGROUND: A considerable amount of randomized controlled trials (RCTs) have been published on statins and/or fibrates for diabetic retinopathy, a clinical condition associated with high social and economic burden. Adherence to the CONSORT statement items is imperative to ensure transparency and reproducibility in clinical research. The aim of this study is to assess the reporting quality and the adherence to CONSORT of RCTs assessing statins and/or fibrates for diabetic retinopathy. METHODS: We conducted a critical appraisal study at Discipline of Evidence-based Medicine, Escola Paulista de Medicina, Universidade Federal de Sao Paulo (Unifesp). A sensitive literature search was performed to identify all relevant RCTs, with no time or language limits. Two authors independently evaluated the reporting quality of the selected RCTs using the CONSORT statement as a standard. RESULTS: Thirteen reports of RCTs were included in this study. The adherence of the reports to CONSORT items ranged from 24% to 68%. The median score was 11 (interquartile range (IQR) 8 to 13). When analyzed separately, the methods sections of the reports had a median of three items (IQR 2 to 4) judged adherent to the methods items of CONSORT (items 3 to 12). The most underreported items were those related to trial design, title and abstract, allocation concealment, implementation of the randomization sequence, and blinding. Other important items, such as the one related to the description of the inclusion criteria, also had low adherence. CONCLUSIONS: The overall adherence to the CONSORT checklist items was poor, especially in the items related to the methods section. RCT reports on statins and/or fibrates for diabetic retinopathy must be optimized to avoid reporting biases and to improve transparency and reproducibility.

[53] *Zebrowski P, Kaszynska M*. **[Ezetimibe as a treatment for dyslipidaemia in CKD]**. Wiadomosci lekarskie (Warsaw, Poland : 1960) 2019; 72:2210-2213.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31860838
ABSTRACT
Cardiovascular disease is the leading cause of death among patients with chronic kidney disease (CKD). Primary and secondary prevention of cardiovascular events is one of the major CKD patients' treatment targets. Dyslipidaemia is the important modifiable risk factor in general population. Each 1.0 mmol reduction in LDL cholesterol with statins reduces annual rate of heart attack, coronary revascularization or ischemic stroke by 20% leading to 10% reduction of all-cause mortality. Adding ezetimibe, an inhibitor of intestinal lipids absorption, further reduces LDL cholesterol by 20%. Optimal lipid lowering treatment for CKD patients remains unclear. Cardiovascular risk reduction observed with statins therapy decreases together with a progression of the disease, moreover patients with advanced CKD treated with high doses of statins have an increased risk of adverse events. These patients might benefit from adding ezetimibe to moderate dose statin therapy for prevention of cardiovascular events.

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