Literature update week 14 (2020)

[1] *Shao C, Wang J, Tian J, Tang YD*. **Coronary Artery Disease: From Mechanism to Clinical Practice**. Advances in experimental medicine and biology 2020; 1177:1-36.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32246442
ABSTRACT
In most developed countries, coronary artery disease (CAD), mostly caused by atherosclerosis of coronary arteries, is one of the primary causes of death. From 1990s to 2000s, mortality caused by acute MI declined up to 50%. The incidence of CAD is related with age, gender, economic, etc. Atherosclerosis contains some highly correlative processes such as lipid disturbances, thrombosis, inflammation, vascular smooth cell activation, remodeling, platelet activation, endothelial dysfunction, oxidative stress, altered matrix metabolism, and genetic factors. Risk factors of CAD exist among many individuals of the general population, which includes hypertension, lipids and lipoproteins metabolism disturbances, diabetes mellitus, chronic kidney disease, age, genders, lifestyle, cigarette smoking, diet, obesity, and family history. Angina pectoris is caused by myocardial ischemia in the main expression of pain in the chest or adjoining area, which is usually a result of exertion and related to myocardial function disorder. Typical angina pectoris would last for minutes with gradual exacerbation. Rest, sit, or stop walking are the usual preference for patients with angina, and reaching the maximum intensity in seconds is uncommon. Rest or nitroglycerin usage can relieve typical angina pectoris within minutes. So far, a widely accepted angina pectoris severity grading system included CCS (Canadian Cardiovascular Society) classification, Califf score, and Goldman scale. Patients with ST-segment elevated myocardial infarction (STEMI) may have different symptoms and signs of both severe angina pectoris and various complications. The combination of rising usage of sensitive MI biomarkers and precise imaging techniques, including electrocardiograph (ECG), computed tomography, and cardiac magnetic resonance imaging, made the new MI criteria necessary. Complications of acute myocardial infarction include left ventricular dysfunction, cardiogenic shock, structural complications, arrhythmia, recurrent chest discomfort, recurrent ischemia and infarction, pericardial effusion, pericarditis, post-myocardial infarction syndrome, venous thrombosis pulmonary embolism, left ventricular aneurysm, left ventricular thrombus, and arterial embolism.

[2] *Wan Q, Qian S, Huang Y et al.* **Drug Discovery for Coronary Artery Disease**. Advances in experimental medicine and biology 2020; 1177:297-339.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32246449
ABSTRACT
Cardiovascular disease is the number one cause of human morbidity and mortality worldwide. Although cholesterol-lowering drugs, including statins and recently approved PCSK9 inhibitors, together with antithrombotic drugs have been historically successful in reducing the occurrence of coronary artery disease (CAD), the high incidence of CAD remains imposing the largest disease burden on our healthcare systems. We reviewed cardiovascular drugs recently approved or under clinical development, with a particular focus on their pharmacology and limitations. New agents targeting cholesterol/triglyceride lowering bear promise of further cardiovascular risk reduction. Some new antidiabetic agents show cardiovascular benefit in patients with diabetes. Improved antithrombotic agents with diminished bleeding risk are in clinical development. The recent clinical success of the IL-1beta antibody in reducing atherothrombosis opens a new era of therapeutic discovery that targets inflammation. Chinese traditional medicine and cardiac regeneration are also discussed. Human genetics studies of CAD and further delineation of key determinants/pathways underlying the residual

risk of CAD under current standard therapy will continue to fuel the pipeline of cardiovascular drug discovery.

[3] *Xu RX, Wu YJ*. **Lipid-Modifying Drugs: Pharmacology and Perspectives**. Advances in experimental medicine and biology 2020; 1177:133-148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32246446
ABSTRACT
Coronary artery disease (CAD) is one of the leading causes of death worldwide. It is well known that dyslipidemia is a major pathogenic risk factor for atherosclerosis and CAD, which results in cardiac ischemic injury and myocardial infarction. Lipid-modifying drugs can effectively improve lipid abnormalities including reducing low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) or increasing high-density lipoprotein cholesterol (HDL-C), and eventually decrease the incidence of cardiovascular events. This chapter will review basic principles of lipid metabolism and focus on the therapeutic strategies of lipids modifying drugs (statins, proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe, niacin, polyunsaturated fatty acids, and so on) in patients with arteriosclerotic cardiovascular disease. Meanwhile, the challenges and perspectives of the lipid-lowering agents currently in clinical practice as well as their limitations will be outlined.

[4] *Reda A, Almahmeed W, Dobrecky-Mery I et al.* **A Narrative Review and Expert Panel Recommendations on Dyslipidaemia Management After Acute Coronary Syndrome in Countries Outside Western Europe and North America**. Adv Ther 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32227306
ABSTRACT
Patients who have experienced an acute coronary syndrome (ACS) are at very high risk of recurrent atherosclerotic cardiovascular disease (CVD) events. Dyslipidaemia, a major risk factor for CVD, is poorly controlled post ACS in countries outside Western Europe and North America, despite the availability of effective lipid-modifying therapies (LMTs) and guidelines governing their use. Recent guideline updates recommend that low-density lipoprotein cholesterol (LDL-C), the primary target for dyslipidaemia therapy, be reduced by >/= 50% and to < 1.4 mmol/L (55 mg/dL) in patients at very high risk of CVD, including those with ACS. The high prevalence of CVD risk factors in some regions outside Western Europe and North America confers a higher risk of CVD on patients in these countries. ACS onset is often earlier in these patients, and they may be more challenging to treat. Other barriers to effective dyslipidaemia control include low awareness of the value of intensive lipid lowering in patients with ACS, physician non-adherence to guideline recommendations, and lack of efficacy of currently used LMTs. Lack of appropriate pathways to guide follow-up of patients with ACS post discharge and poor access to intensive medications are important factors limiting dyslipidaemia therapy in many countries. Opportunities exist to improve attainment of LDL-C targets by the use of country-specific treatment algorithms to promote adherence to guideline recommendations, medical education and greater prioritisation by healthcare systems of dyslipidaemia management in very high risk patients.

[5] *Dixon DL*. **Catch of the Day: Icosapent Ethyl for Reducing Cardiovascular Risk**. The American journal of medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32243872

ABSTRACT
For decades, omega-3 fatty acids (O3FA) have been used for their cardioprotective effects. Although several prescription products are available, icosapent ethyl (IPE) is the lone pure, eicosapentaenoic acid (EPA)-only, O3FA product. Initially approved by the Food and Drug Administration (FDA) to reduce triglyceride (TG) levels in patients with TG levels >/=500 mg/dL, the Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT) demonstrated that IPE reduces cardiovascular events in patients with either established atherosclerotic cardiovascular disease (ASCVD) or diabetes plus >/=2 ASCVD risk factors, a TG level between 135 mg/dL and 499 mg/dL, and who were taking a statin. IPE is generally well tolerated, but caution is advised if used in patients taking antiplatelet or anticoagulant therapies because of an increased risk of bleeding. Based on the REDUCE-IT trial, the Food and Drug Administration granted IPE an indication for ASCVD risk reduction, making it the first O3FA product to receive such an indication. IPE is a cost-effective approach to reducing residual cardiovascular risk in high risk patients treated with statins.

[6] *Moffa S, Mazzuccato G, De Bonis M et al.* **Identification of two novel LDLR variants by Next Generation Sequencing**. Ann Ist Super Sanita 2020; 56:122-127.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32242544
ABSTRACT
INTRODUCTION: Familial hypercholesterolemia (FH) is an autosomal dominant inherited disease characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C). Targeted Next Generation Sequencing (NGS) is a new opportunity to expand the existing pathogenic variants (PVs) spectrum associated to FH. Our aim was to report a diagnostic NGS-based approach to detect variants associated to FH. METHODS: We report two patients: a 48-year-old Asian woman, without known history of hypercholesterolemia and a 46-year-old Caucasian man, with childhood hypercholesterolemia. RESULTS: An effective NGS-based pipeline, FH-Devyser kit/Amplicon Suite, beginning from sequencing to data analysis, did not identify known PVs in the LDLR, APOB, APOE, LDLRAP1, STAP1 and PCSK9 genes, but revealed two novel LDLR variants (c.1564A>T, p.Ile522Phe and c.1688C>T, p.Pro563Leu). DISCUSSION AND CONCLUSIONS: This study showed that an effective NGS-based pipeline led to a definitive diagnosis in two FH families, allowing to plan their therapeutic treatment. Although the functional consequence of the two LDLR variants needs to be assessed in vitro, the in silico analysis and high preservation of the two amino acid positions observed in the LDLR protein, across different animal species, suggest that both variants are deleterious.

[7] *Das UN*. **Can Bioactive Lipids Inactivate Coronavirus (COVID-19)?** Arch Med Res 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32229155
ABSTRACT
SARS-CoV-2, SARS and MERS are all enveloped viruses that can cause acute respiratory syndrome. Arachidonic acid (AA) and other unsaturated fatty acids (especially eicosapentaenoic acd, EPA and docosahexaenoic acid DHA) are known to inactivate enveloped viruses and inhibit proliferation of various microbial organisms. The pro-inflammatory metabolites of AA and EPA such as prostaglandins, leukotrienes and thromboxanes induce inflammation whereas lipoxins, resolvins, protectins and maresins derived from AA, EPA and DHA not only suppress inflammation but also enhance would healing and augment phagocytosis of macrophages and other immunocytes and decrease microbial load. In view of these actions, it is suggested that AA and other unsaturated fatty acids and their

metabolites may serve as endogenous anti-viral compounds and their deficiency may render humans susceptible to SARS-CoV-2, SARS and MERS and other similar viruses' infections. Hence, oral or intravenous administration of AA and other unsaturated fatty acids may aid in enhancing resistance and recovery from SARS-CoV-2, SARS and MERS infections.

[8] *Li B, Luo YR, Tian F et al.* **Sitagliptin attenuates the progression of coronary atherosclerosis in patients with coronary disease and type 2 diabetes**. Atherosclerosis 2020; 300:10-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32247073

ABSTRACT

BACKGROUND AND AIMS: Type 2 diabetes mellitus (T2DM) is a well-recognized independent risk factor for ASCVD, the aim of this study was to investigate the effects of a dipeptidyl peptidase-4 inhibitor, sitagliptin, on prevention of progression of coronary atherosclerosis assessed by three-dimensional quantitative coronary angiography (3D-QCA) in T2DM patients with coronary artery disease (CAD). METHODS: This was a prospective, randomized, double-center, open-label, blinded end point, controlled 18-month study in patients with CAD and T2DM. A total of 149 patients, who had at least 1 atherosclerotic plaque with 20%-80% luminal narrowing in a coronary artery, and had not undergone intervention during a clinically indicated coronary angiography or percutaneous coronary intervention, were randomized to sitagliptin group (n = 74) or control group (n = 75). Atherosclerosis progression was measured by repeat 3D-QCA examination in 88 patients at study completion. The primary outcome was changes in percent atheroma volume (PAV) from baseline to study completion measured by 3D-QCA. Secondary outcomes included change in 3D-QCA-derived total atheroma volume (TAV) and late lumen loss (LLL). RESULTS: The primary outcome of PAV increased of 1.69% (95%CL, -0.8%-4.2%) with sitagliptin and 5.12% (95%CL, 3.49%-6.74%) with the conventional treatment (p = 0.023). The secondary outcome of change in TAV in patients treated with sitagliptin increased of 6.45 mm(3) (95%CL,-2.46 to 6.36 mm(3)) and 9.45 mm(3) (95%CL,-4.52 to 10.14 mm(3)) with conventional treatment (p = 0.023), however, no significant difference between groups was observed (p = 0.175). Patients treated with sitagliptin had similar LLL as compared with conventional antidiabetics (-0.06, 95%CL, -0.22 to 0.03 vs. -0.08, -0.23 to -0.03 mm, p = 0.689). CONCLUSIONS: In patients with type 2 diabetes and coronary artery disease, treatment with sitagliptin resulted in a significantly lower rate of progression of coronary atherosclerosis compared with conventional treatment.

[9] *Tsimikas S, Stroes ESG*. **The dedicated "Lp(a) clinic": A concept whose time has arrived?** Atherosclerosis 2020; 300:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32234580

ABSTRACT

The emergence of pathophysiological, epidemiologic, and genetic data strongly supports the causality for lipoprotein(a) [Lp(a)] in cardiovascular disease (CVD) and calcific aortic valve disease (CAVD). In parallel, novel Lp(a) lowering approaches have been developed that have re-invigorated clinical interest in Lp(a). Because Lp(a) is the most prevalent monogenetic lipid disorder globally, with prevalence of Lp(a) > 50 mg/dL estimated at >1.4 billion people, the rationale for diagnosing and managing Lp(a)-mediated risk is now stronger than ever. Patients with elevated Lp(a) are significantly under-diagnosed and the diagnosis is frequently made ad hoc rather than systematically. Elevated Lp(a) levels are associated with atherothrombotic risk and patients present with varied clinical phenotypes, ranging from stroke in pediatric age groups, to ST-segment elevation myocardial

infarction in young males, to CAVD in elderly individuals. A new clinical care paradigm of a dedicated "Lp(a) Clinic" would serve to evaluate and manage such patients who have elevated Lp(a) as the pathophysiological etiology. Such a clinic would include multidisciplinary expertise in lipid metabolism, clinical cardiology, vascular medicine, valvular disease, thrombosis, and pediatric aspects of clinical care. This viewpoint argues for the rationale of an Lp(a) outpatient clinic where patients with elevated Lp(a) and their affected relatives can be referred, evaluated, managed and followed, to ultimately reduce Lp(a)-mediated CVD and CAVD risk.

[10] *Hosseinzadeh A, Goudarzi M, Fatemi I et al.* **Gemfibrozil attenuates doxorubicin induced toxicity in renal tissues of male rats by reducing the oxidative insult and inflammation**. Biotechnic & histochemistry : official publication of the Biological Stain Commission 2020:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32242747
ABSTRACT
Nephrotoxicity is a significant side effect of doxorubicin (DXN) treatment. We investigated the protective effect of gemfibrozil (GEM) co-administration with DXN on DXN induced nephrotoxicity. We divided 28 male Wistar rats into four groups of seven. Group 1 received normal saline for 2 weeks. Group 2 received 15 mg/kg DXN for 2 weeks. Group 3 received DXN + GEM for 2 weeks. Group 4 received GEM for 2 weeks. On day 15 of the experiment, blood samples were collected, animals were sacrificed and kidneys were excised for biochemical and histological evaluation. We measured serum creatinine, blood urine nitrogen, renal malondialdehyde, nitric oxide, glutathione, superoxide dismutase, glutathione peroxidase, catalase, tumor necrosis factor-alpha and interleukin-1beta. GEM administration mitigated DXN induced nephrotoxicity. GEM co-administered with DXN attenuated the inflammatory and oxidative responses associated with DXN induced nephrotoxicity.

[11] *Ge L, Sadeghirad B, Ball GDC et al.* **Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials**. Bmj 2020; 369:m696.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32238384
ABSTRACT
OBJECTIVE: To determine the relative effectiveness of dietary macronutrient patterns and popular named diet programmes for weight loss and cardiovascular risk factor improvement among adults who are overweight or obese. DESIGN: Systematic review and network meta-analysis of randomised trials. DATA SOURCES: Medline, Embase, CINAHL, AMED, and CENTRAL from database inception until September 2018, reference lists of eligible trials, and related reviews. STUDY SELECTION: Randomised trials that enrolled adults (>/=18 years) who were overweight (body mass index 25-29) or obese (>/=30) to a popular named diet or an alternative diet. OUTCOMES AND MEASURES: Change in body weight, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, diastolic blood pressure, and C reactive protein at the six and 12 month follow-up. REVIEW METHODS: Two reviewers independently extracted data on study participants, interventions, and outcomes and assessed risk of bias, and the certainty of evidence using the GRADE (grading of recommendations, assessment, development, and evaluation) approach. A bayesian framework informed a series of random effects network meta-analyses to estimate the relative effectiveness of the diets. RESULTS: 121 eligible trials with 21 942 patients were included and reported on 14 named diets and three control diets. Compared with usual diet, low carbohydrate and low fat diets had a

similar effect at six months on weight loss (4.63 v 4.37 kg, both moderate certainty) and reduction in systolic blood pressure (5.14 mm Hg, moderate certainty v 5.05 mm Hg, low certainty) and diastolic blood pressure (3.21 v 2.85 mm Hg, both low certainty). Moderate macronutrient diets resulted in slightly less weight loss and blood pressure reductions. Low carbohydrate diets had less effect than low fat diets and moderate macronutrient diets on reduction in LDL cholesterol (1.01 mg/dL, low certainty v 7.08 mg/dL, moderate certainty v 5.22 mg/dL, moderate certainty, respectively) but an increase in HDL cholesterol (2.31 mg/dL, low certainty), whereas low fat (-1.88 mg/dL, moderate certainty) and moderate macronutrient (-0.89 mg/dL, moderate certainty) did not. Among popular named diets, those with the largest effect on weight reduction and blood pressure in comparison with usual diet were Atkins (weight 5.5 kg, systolic blood pressure 5.1 mm Hg, diastolic blood pressure 3.3 mm Hg), DASH (3.6 kg, 4.7 mm Hg, 2.9 mm Hg, respectively), and Zone (4.1 kg, 3.5 mm Hg, 2.3 mm Hg, respectively) at six months (all moderate certainty). No diets significantly improved levels of HDL cholesterol or C reactive protein at six months. Overall, weight loss diminished at 12 months among all macronutrient patterns and popular named diets, while the benefits for cardiovascular risk factors of all interventions, except the Mediterranean diet, essentially disappeared. CONCLUSIONS: Moderate certainty evidence shows that most macronutrient diets, over six months, result in modest weight loss and substantial improvements in cardiovascular risk factors, particularly blood pressure. At 12 months the effects on weight reduction and improvements in cardiovascular risk factors largely disappear. SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42015027929.

[12] *Evans NR, Tarkin JM, Le EP et al.* **Integrated cardiovascular assessment of atherosclerosis using PET/MRI**. Br J Radiol 2020:20190921.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32238077
ABSTRACT
Atherosclerosis is a systemic inflammatory disease typified by the development of lipid-rich atheroma (plaques), the rupture of which are a major cause of myocardial infarction and stroke. Anatomical evaluation of the plaque considering only the degree of luminal stenosis overlooks features associated with vulnerable plaques, such as high-risk morphological features or pathophysiology, and hence risks missing vulnerable or ruptured non-stenotic plaques. Consequently, there has been interest in identifying these markers of vulnerability using either MRI for morphology, or positron emission tomography (PET) for physiological processes involved in atherogenesis. The advent of hybrid PET/MRI scanners offers the potential to combine the strengths of PET and MRI to allow comprehensive assessment of the atherosclerotic plaque. This review will discuss the principles and technical aspects of hybrid PET/MRI assessment of atherosclerosis, and consider how combining the complementary modalities of PET and MRI has already furthered our understanding of atherogenesis, advanced drug development, and how it may hold potential for clinical application.

[13] *Landmesser U, Haghikia A, Leiter LA et al.* **Effect of inclisiran, the siRNA against PCSK9, on platelets, immune cells and immunological biomarkers - a pre-specified analysis from ORION-1**. Cardiovascular research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32243492
ABSTRACT
INTRODUCTION: siRNA-based targeting of PCSK9 represents a novel therapeutic approach that may provide a convenient, infrequent and safe dosing schedule to robustly lower LDL-C. Given the long

duration of action, however, establishing safety in particular with respect to immunogenicity is of paramount importance. In earlier clinical studies of other RNA-targeted treatment approaches (antisense oligonucleotide therapy) immunological and haematological adverse-effects, in particular thrombocytopenia and pro-inflammatory effects, have been reported. Here, we present the pre-specified safety analysis from ORION-1 evaluating platelets, immune cells, immunological markers, antidrug antibodies and clinical immunogenicity adverse events under PCSK9 siRNA treatment with inclisiran. METHODS AND RESULTS: The pre-specified safety analysis from ORION-1 was performed in 6 different inclisiran dosing regimens in patients at high risk of cardiovascular disease with elevated LDL-C levels. Patients received either a single-dose (SD: 200mg, n = 60; 300mg, n = 62 or 500mg, n = 66) or double-dose starting regimen (DD: 100mg, n = 62; 200mg, n = 63; or 300mg, n = 61 on days 1 and 90) of inclisiran or placebo (single-dose: n = 65; double-dose: n = 62). The effects of inclisiran on haematological parameters including platelet counts, lymphocytes and monocytes as well as on the immune markers interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) were examined after 180 days. Immunogenicity was further evaluated by analysis of anti-drug-antibodies (ADA) towards inclisiran in 6068 study samples and by careful analysis of immunogenicity adverse events as part of the pharmacovigilance strategy.At day 180 no significant alterations of platelet counts were observed in any of the dosing groups (change from baseline, single dose: 200mg: 0.8%; 300mg: -0.5%; 500mg: -1.8%; double dose: 100mg: 1.3%; 200mg: -0.5%; 300mg: 1.0%; no significant difference for any group as compared to placebo). No significant effects on other immune cells, including leukocytes, monocytes or neutrophils were detected. Notably, no significant increase of inflammatory biomarkers (IL-6 or TNF-alpha) with either the single or double dose regimen became evident. There was no evidence for immunogenicity based on ADA level analysis and careful review of clinical immunogenicity adverse events in none of the treatment regimens. CONCLUSIONS: In this pre-specified safety analysis of ORION-1 for the siRNA therapeutic inclisiran, no adverse effects on measures of inflammation or immune activation nor adverse effects on platelets or clinical immunogenicity adverse events were observed over at least 6-months treatment. These safety findings in the largest analysis of an RNAi study in humans to date provide strong reassurance about the safety of inclisiran and the potential of cardiovascular RNA-targeted therapies.

[14] *Marston NA, Gurmu Y, Melloni GEM et al.* **The Effect of PCSK9 Inhibition on the Risk of Venous Thromboembolism**. Circulation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32223429
ABSTRACT
Background: The relationship between cholesterol levels and risk of venous thromboembolism (VTE) is uncertain. We set out to determine the effect of PCSK9 inhibition on the risk of VTE, explore potential mechanisms, and examine the efficacy in clinically and genetically defined risk subgroups. Methods: We performed a post-hoc analysis of the FOURIER trial testing whether evolocumab reduces the risk of VTE events (deep venous thrombosis or pulmonary embolism). Data from FOURIER and ODYSSEY OUTCOMES were then combined in a meta-analysis to assess class effect of PCSK9 inhibition on the risk of VTE. We also analyzed baseline lipids in FOURIER to investigate potential mechanisms explaining the reduction in VTE with evolocumab. Finally, an exploratory genetic analysis was performed in FOURIER to determine whether a VTE polygenic risk score could identify high-risk patients who would derive the greatest VTE reduction from evolocumab. Results: In FOURIER, the HR for VTE with evolocumab was 0.71 (95%CI 0.50-1.00, p=0.05), with no effect in the 1st year (HR 0.96, [0.57-1.62]) but a 46%

reduction (HR 0.54 [0.33-0.88], p=0.014) beyond 1 year. A meta-analysis of FOURIER and ODYSSEY OUTCOMES demonstrated a 31% relative risk reduction in VTE with PCSK9 inhibition (HR 0.69 [0.53-0.90], p=0.007). There was no relation between baseline LDL-C levels and magnitude of VTE risk reduction. In contrast, in patients with higher baseline Lp(a) levels, evolocumab reduced Lp(a) by 33 nmol/L and risk of VTE by 48% (HR 0.52 [0.30-0.89], p=0.017), whereas in patients with lower baseline Lp(a) levels evolocumab reduced Lp(a) by only 7 nmol/L and had no effect on VTE risk Pinteraction for HR 0.087, Pheterogeneity for ARR 0.037). Modeled as a continuous variable, there was a significant interaction between baseline Lp(a) concentration and magnitude of VTE risk reduction (P=0.04). A polygenic risk score identified patients who were at >2-fold increased risk for VTE and who derived greater relative (Pinteraction=0.04) and absolute VTE reduction (Pheterogeneity=0.009) compared to those without high genetic risk. Conclusions: PCSK9 inhibition significantly reduces the risk of VTE. Lp(a) reduction may be an important mediator of this effect, a finding of particular interest given ongoing development of potent Lp(a) inhibitors.

[15] *Schwartz GG, Steg PG, Szarek M et al.* **Peripheral Artery Disease and Venous Thromboembolic Events After Acute Coronary Syndrome: Role of Lipoprotein(a) and Modification by Alirocumab: Prespecified Analysis of a Randomized Clinical Trial**. Circulation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32223446

ABSTRACT

Background: Patients with acute coronary syndrome (ACS) are at risk for peripheral artery disease (PAD) events and venous thromboembolism (VTE). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce lipoprotein(a) and low-density lipoprotein cholesterol (LDL-C) levels. Our objective was to ascertain whether PCSK9 inhibition reduces the risk of PAD events or VTE after ACS, and if such effects are related to levels of lipoprotein(a) or LDL-C. Methods: This was a prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial, which was conducted in 18 924 patients with recent ACS on intensive or maximum-tolerated statin treatment who were randomized to the PCSK9 inhibitor alirocumab or placebo. In a prespecified analysis, PAD events (critical limb ischemia, limb revascularization, or amputation for ischemia) and VTE (deep vein thrombosis or pulmonary embolism) were assessed. LDL-C was corrected for cholesterol content in lipoprotein(a). Results: At baseline, median lipoprotein(a) and LDL-Ccorrected were 21 and 75 mg/dL, respectively; with alirocumab, median relative reductions were 23.5% and 70.6%, respectively. PAD events and VTE occurred in 246 and 92 patients, respectively. In the placebo group, risk of PAD events was related to baseline quartile of lipoprotein(a) (Ptrend=0.0021), but not baseline quartile of LDL Ccorrected (Ptrend=0.06); VTE tended to associate with baseline quartile of lipoprotein(a) (Ptrend=0.06), but not LDL-Ccorrected (Ptrend=0.85). Alirocumab reduced risk of PAD events (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54-0.89; P=0.004), with non-significantly fewer VTE events (HR, 0.67; 95% CI, 0.44-1.01; P=0.06). Reduction in PAD events with alirocumab was associated with baseline quartile of lipoprotein(a) (Ptrend=0.03), but not LDL-Ccorrected (Ptrend=0.50). With alirocumab, the change from baseline to Month 4 in lipoprotein(a), but not LDL-Ccorrected, was associated with the risk of VTE and the composite of VTE and PAD events. Conclusions: In statin-treated patients with recent ACS, risk of PAD events is related to lipoprotein(a) level and is reduced by alirocumab, particularly among those with high lipoprotein(a). Further study is required to confirm whether risk of VTE is related to lipoprotein(a) level and its reduction with alirocumab. Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT01663402.

[16] *Reiter-Brennan C, Osei AD, Iftekhar Uddin SM et al.* **ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease**. Cleveland Clinic journal of medicine 2020; 87:231-239.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32238379

ABSTRACT

The 2018 and 2019 guidelines from the American College of Cardiology and American Heart Association reflect the complexity of individualized cholesterol management. The documents address more detailed risk assessment, newer nonstatin cholesterol-lowering drugs, special attention to patient subgroups, and consideration of the value of therapy, all with the aim of creating personalized treatment plans for each patient. Overall, the guidelines recommend shared decision-making to meet the individual needs of each patient.

[17] *Liu XR, Xu Q, Xiao J et al.* **Role of oral microbiota in atherosclerosis**. Clinica chimica acta; international journal of clinical chemistry 2020; 506:191-195.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32220421

ABSTRACT

Oral infections are common among individuals of all ages and can activate local and systemic inflammation. The inflammatory response plays an important role in atherosclerosis. An increasing number of studies have reported an association between oral pathogen infection and atherosclerotic coronary heart disease. For instance, epidemiological studies support the positive correlation between oral infections and atherosclerosis. The presence of oral pathogens in human atherosclerotic plaques has been detected by multiple methods, and oral infections promote atherosclerosis in animal experiments. Various mechanisms are involved in oral infections, thereby promoting atherosclerosis. First, oral infections can trigger the local and systemic inflammatory response, causing vascular endothelial damage. Oral-derived pathogens that enter atherosclerotic plaque can activate macrophages and cause an intra-plaque inflammatory response. Second, oral infections can promote intra-plaque macrophage cholesterol accumulation and foam cell formation. Third, oral infections can regulate plasma lipid levels, thereby increasing atherogenic lipid low-density lipoprotein and triglyceride levels. Although atherosclerosis caused by oral infections is currently studied, the precise mechanism remains to be further explored. The rise of gut microbiota research also makes the relationship between oral microbiota and disease, especially the relationship with coronary heart disease, worthy of attention and in-depth research.

[18] *Kim AS*. **Medical Management for Secondary Stroke Prevention**. Continuum (Minneapolis, Minn.) 2020; 26:435-456.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32224760

ABSTRACT

PURPOSE OF REVIEW: This article reviews the evidence base and recommendations for medical management for secondary stroke prevention. RECENT FINDINGS: Recent developments for secondary stroke prevention include evidence to support the use of short-term dual antiplatelet therapy after minor stroke and transient ischemic attack, direct oral anticoagulants for nonvalvular atrial fibrillation, reversal agents for direct oral anticoagulant-associated hemorrhage, and aspirin rather than presumptive anticoagulation with a direct oral anticoagulant for embolic stroke of undetermined source. SUMMARY: Most strokes are preventable. The mainstays of medical management for

secondary stroke prevention include antihypertensive therapy; antithrombotic therapy, with antiplatelet agents for most stroke subtypes or anticoagulants such as warfarin or a direct oral anticoagulant for cardioembolic stroke specifically; cholesterol-lowering therapy, principally with statins, but with potential roles for ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors in selected patients; and glycemic control to prevent microvascular complications from diabetes mellitus or pioglitazone in selected patients with insulin resistance but not diabetes mellitus.

[19] *Cao JY, Waldman B, O'Connell R et al.* **Uric acid predicts long-term cardiovascular risk in type 2 diabetes but does not mediate the benefits of fenofibrate: The FIELD study**. Diabetes Obes Metab 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32243036
ABSTRACT
AIM: To explore the relationship between baseline uric acid (UA) levels and long-term cardiovascular events in adults with type 2 diabetes (T2D) and to determine whether the cardioprotective effects of fenofibrate are partly mediated through its UA-lowering effects. METHODS: Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial were utilized, comprising 9795 adults with T2D randomly allocated to treatment with fenofibrate or matching placebo. Plasma UA was measured before and after a 6-week, active fenofibrate run-in phase in all participants. Cox proportional hazards models were used to explore the relationships between baseline UA, pre-to-post run-in reductions in UA and long-term cardiovascular outcomes. RESULTS: Mean baseline plasma UA was 0.33 mmol/L (SD 0.08). Baseline UA was a significant predictor of long-term cardiovascular events, with every 0.1 mmol/L higher UA conferring a 21% increase in event rate (HR 1.21, 95% CI 1.13-1.29, P < .001). This remained significant after adjustment for treatment allocation, cardiovascular risk factors and renal function. The extent of UA reduction during fenofibrate run-in was also a significant predictor of long-term cardiovascular events, with every 0.1 mmol/L greater reduction conferring a 14% lower long-term risk (HR 0.86, 95% CI 0.76-0.97, P = .015). This effect was not modified by treatment allocation (Pinteraction = .77). CONCLUSIONS: UA is a strong independent predictor of long-term cardiovascular risk in adults with T2D. Although greater reduction in UA on fenofibrate is predictive of lower cardiovascular risk, this does not appear to mediate the cardioprotective effects of fenofibrate.

[20] *Bandgar SA, Jadhav NR, Manjappa AS*. **A remarkable in vitro cytotoxic, cell cycle arresting and proapoptotic characteristics of low-dose mixed micellar simvastatin combined with alendronate sodium**. Drug delivery and translational research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32221848
ABSTRACT
The objective of the present study was to screen the effect of increased simvastatin (SVS) solubility, through mixed micelles as a model approach, on in vitro anticancer efficacy in combination with hydrophilic alendronate sodium (ADS) as a strategy to improve therapeutic efficacy and to repositioning the existing drugs. The SVS-loaded mixed micelles (SVS-MMs) composed of TPGS and Poloxamer-407 were prepared using the film dispersion method and characterized for SVS loading and mean particle size. The optimized SVS-MMs were physically mixed with plain ADS (SVS + ADS MMs) and screened for in vitro cytotoxicity using MTT assay and cell cycle arresting and apoptotic activities using FACS technique. The optimized SVS-MMs showed maximum SVS loading (97.3 +/- 2.3%) with minimum particle size (206 +/- 8 nm). The SVS + ADS MM treatment significantly (P < 0.001) inhibited

the cell growth with low IC50 values against all cells (A549: 0.037 +/- 0.028 mug/mL, MDAMB-231: 0.172 +/- 0.031 mug/mL, PC-3: 0.022 +/- 0.015 mug/mL). Further, the SVS + ADS MM treatment significantly inhibited the cell multiplication in the S phase and resulted in high % of late apoptotic and necrotic cells at low concentration (0.05 and 0.15 mug/mL) as compared other test samples. The above results revealed the significance of encapsulating SVS in the core of MMs (improved solubility), and high efficacy and quick effect of SVS + ADS MM treatment against all cell lines screened. Graphical abstract.

[21] *Maini J, Rehan HS, Yadav M, Gupta LK*. **Exploring the role of adipsin in statin-induced glucose intolerance: a prospective open label study**. Drug metabolism and personalized therapy 2020; 35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32229661
ABSTRACT
Background Evidence from the literature, highlights the increased risk of developing glucose intolerance and type 2 diabetes mellitus (T2DM) with statin therapy. In addition, few animal studies demonstrate that adipsin secreted from adipocytes plays a crucial role in insulin secretion and the development of T2DM. Methods To further explore the role of serum adipsin, in this prospective open label study, 55 newly diagnosed dyslipidemic patients were enrolled. Before starting statin therapy, liver function test (LFT), kidney function test (KFT), lipid profile, glycemic parameters [glycated hemoglobin A (HbA1c), fasting blood sugar (FBS), and postprandial blood sugar (PPBS)], serum insulin, and serum adipsin were estimated. Then these patients were prescribed statin (i.e. atorvastatin, rosuvastatin, or pitavastatin) and after 12 weeks of therapy, all the above investigations were repeated. Results After 12 weeks of statin therapy, the LFT and KFT values remained unchanged and lipid parameters showed significant improvement. But the glycemic parameters deranged significantly ($p < 0.001$), i.e. FBS, PPBS, and HbA1c increased by 12.49% (102.99 +/- 20.76 mg/dL), 24.72% (147.71 +/- 47.29 mg/dL), and 21.43% (6.38 +/- 1.34%), respectively. On the other hand, the baseline adipsin (2.73 +/- 1.99 ng/mL) and insulin (16.13 +/- 12.50 mIU/L) levels reduced significantly ($p < 0.0001$) to 1.43 +/-1.13 ng/mL and 6.91 +/- 5.93 mIU/L, respectively. The reduction in serum adipsin also showed a positive correlation with reduction in serum insulin ($r = 0.85$; $p < 0.0001$). None of the patients experienced any significant adverse effect or reaction leading to discontinuation of therapy. Conclusions There might be an association between reduction in adipsin and development of glucose intolerance by statin therapy.

[22] *Rogacev KS, Laufs U*. **[Lipid management 2020 - medical therapy and lipid apheresis in context]**. Deutsche medizinische Wochenschrift (1946) 2020; 145:464-469.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32236927
ABSTRACT
The recently updated 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidaemias set new, ambitious goals for lipid lowering based on recently generated evidence from large outcome trials. Noninvasive imaging as well as measurement of lipoprotein(a) as a non-traditional risk factor is advocated for the refinement of risk stratification. A highly potent statin - defined as a drug that lowers LDL-cholesterol by 50 % from baseline - is recommended as the standard choice of treatment, whenever medical lipid lowering is indicated. Combining different therapeutic strategies such as a statin with ezetimibe and/or a Proproteinkonvertase Subtilisin Kexin Type 9 inhibitor allows to achieve the new treatment targets. If

needed, lipid apheresis can complement the medical armamentarium. Moreover, lipid apheresis remains the only approved treatment modality for lowering lipoprotein(a), however medical treatments are under current investigation.

[23] *Demetz E, Tymoszuk P, Hilbe R et al.* **The haemochromatosis gene Hfe and Kupffer cells control LDL cholesterol homeostasis and impact on atherosclerosis development**. European heart journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32227235
ABSTRACT
AIMS: Imbalances of iron metabolism have been linked to the development of atherosclerosis. However, subjects with hereditary haemochromatosis have a lower prevalence of cardiovascular disease. The aim of our study was to understand the underlying mechanisms by combining data from genome-wide association study analyses in humans, CRISPR/Cas9 genome editing, and loss-of-function studies in mice. METHODS AND RESULTS: Our analysis of the Global Lipids Genetics Consortium (GLGC) dataset revealed that single nucleotide polymorphisms (SNPs) in the haemochromatosis gene HFE associate with reduced low-density lipoprotein cholesterol (LDL-C) in human plasma. The LDL-C lowering effect could be phenocopied in dyslipidaemic ApoE-/- mice lacking Hfe, which translated into reduced atherosclerosis burden. Mechanistically, we identified HFE as a negative regulator of LDL receptor expression in hepatocytes. Moreover, we uncovered liver-resident Kupffer cells (KCs) as central players in cholesterol homeostasis as they were found to acquire and transfer LDL-derived cholesterol to hepatocytes in an Abca1-dependent fashion, which is controlled by iron availability. CONCLUSION: Our results disentangle novel regulatory interactions between iron metabolism, KC biology and cholesterol homeostasis which are promising targets for treating dyslipidaemia but also provide a mechanistic explanation for reduced cardiovascular morbidity in subjects with haemochromatosis.

[24] *Mortensen MB, Nordestgaard BG*. **2019 vs. 2016 ESC/EAS statin guidelines for primary prevention of atherosclerotic cardiovascular disease**. European heart journal 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32227172
ABSTRACT
AIMS : The 2019 vs. 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) dyslipidaemia guidelines contains new recommendations for primary prevention with statins; however, the potential impact of these changes is unclear. We compared the 2019 and 2016 guidelines regarding statin eligibility and potential impact on prevention of atherosclerotic cardiovascular disease (ASCVD) in the general population. METHODS AND RESULTS : We examined 45 750 individuals aged 40-75 from the Copenhagen General Population Study, all free of ASCVD and statin use at baseline. During the 9.2-year follow-up, 3337 experienced ASCVD (myocardial infarction, stroke, and cardiovascular death). For Class I/A recommendations, 32.3% (95% confidence interval: 31.8-32.7) and 15.4% (15.1-15.7) of individuals were statin eligible according to the 2019 and 2016 guidelines. The increased statin eligibility by the 2019 guidelines was explained by lower low-density lipoprotein cholesterol (LDL-C) thresholds alone (explaining 33.2%), older age range alone (49.4%), older age range in combination with lower LDL-C thresholds (14.7%), and updated SCORE risk algorithm (2.8%). If fully implemented, the estimated percentage of ASCVD events that can be prevented by using high-intensity statins for 10 years were 25% and 11% with the 2019 and 2016 guidelines. Mainly because of older age range in the

2019 guidelines, the corresponding estimated numbers needed to treat (NNT) to prevent one ASCVD event were 19 and 20. CONCLUSION : Due to lower LDL-C threshold and older age range, the 2019 vs. 2016 ESC/EAS guidelines doubles the number of individuals eligible for primary prevention with statins. This considerably improves the potential for ASCVD prevention in the general population, with similar NNT to prevent one event.

[25] *Banefelt J, Lindh M, Svensson MK et al.* **Statin Dose Titration Patterns and Subsequent Major Cardiovascular Events in very High-Risk Patients - Estimates from Swedish Population-based Registry Data**. European heart journal. Quality of care & clinical outcomes 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32239140
ABSTRACT
AIMS: Clinical studies have demonstrated the efficacy of intensive statin therapy in lowering low-density lipoprotein cholesterol and cardiovascular (CV) events. Our objective was to examine statin titration patterns and the association between titration patterns and subsequent CV events in very high-risk patients. METHODS AND RESULTS: Using Swedish national population-based registry data, we identified 192,435 patients with very high risk of atherosclerotic cardiovascular disease initiated on moderate-intensity statin therapy between 2006 and 2013. Outcomes of interest were titration to high-intensity therapy and the major adverse cardiovascular events (MACE) composite (myocardial infarction, ischemic stroke, CV death) outcome. Cumulative incidence of MACE was assessed by titration status one-year post treatment initiation in patients adherent to treatment during the first year, using a 12-week cut-off from initiation to define early, delayed and no up-titration to high-intensity statins. Cox regression analysis was used to estimate adjusted hazard ratios (HRs). In 144,498 eligible patients, early titration was associated with significantly lower risk of MACE in the subsequent two years compared to no up-titration (HR: 0.76, $p < 0.01$). Delayed up-titration was associated with a smaller reduction (HR: 0.88, $p = 0.08$). The majority of patients did not up-titrate. CONCLUSION: Early up-titration to high-intensity statins was independently associated with lower risk of subsequent CV events compared to no up-titration. Delayed up-titration was not associated with the same benefit. Despite the higher risk associated with no up-titration, few patients at very high CV risk who started treatment on moderate-intensity up-titrated to high-intensity, indicating a potential need for more aggressive lipid management of these patients in clinical practice.

[26] *Attar A*. **PCSK9 inhibitors: Going forward and beyond**. European journal of preventive cardiology 2020:2047487320916964.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32237895
ABSTRACT

[27] *Tomlinson B, Chan P, Zhang Y et al.* **Pharmacokinetics of current and emerging treatments for hypercholesterolemia**. Expert opinion on drug metabolism & toxicology 2020:1-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32223657
ABSTRACT
Introduction: Reduction of low-density-lipoprotein cholesterol (LDL-C) and other apolipoprotein B (apoB)-containing lipoproteins reduces cardiovascular (CV) events and greater reductions have greater benefits. Current lipid treatments cannot always achieve desirable LDL-C targets and additional or alternative treatments are often needed.Areas covered: In this article, we review the pharmacokinetics

of the available and emerging treatments for hypercholesterolemia and focus on recently approved drugs and those at a late stage of development.Expert opinion: Statin pharmacokinetics are well known and appropriate drugs and doses can usually be chosen for individual patients to achieve LDL-C targets and avoid adverse effects and drug-drug interactions. Ezetimibe, icosapent ethyl and the monoclonal antibodies evolocumab and alirocumab have established efficacy and safety. Newer oral agents including pemafibrate and bempedoic acid have generally favorable pharmacokinetics supporting use in a wide range of patients. RNA-based therapies with antisense oligonucleotides are highly specific for their targets and those inhibiting apoB, apoCIII, angiopoietin-like protein 3 and lipoprotein(a) have shown promising results. The small-interfering RNA inclisiran has the notable advantage that a single subcutaneous administration may be effective for up to 6 months. The CV outcome trial results and long term safety data are eagerly awaited for these new agents.

[28] *Nikolic D, Banach M, Chianetta R et al.* **An overview of statin-induced myopathy and perspectives for the future**. Expert opinion on drug safety 2020:1-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32233708
ABSTRACT
Introduction: Statins remain the most commonly prescribed lipid-lowering drug class for the treatment of atherosclerotic cardiovascular disease. Their well-recognized side effects are known as statin-associated muscle symptom (SAMS). Some advances in this field have been made in recent years, but the understanding of the mechanisms has lagged. Investigating the specific role of the anti-HMGCR autoantibody, pharmacokinetic genetic variants, characterization of the known phenotypes of statin toxicity, in relation to clinical markers of disease, is of high importance.Areas covered: We summarized currently available findings (on PubMed) related to SAMS and discussed the therapeutic approaches, risk factors, drug interactions, potential novel systems, algorithms and biomarkers for SAMS detection. CoQ10 supplementation has been suggested as a complementary approach to manage SAMS, while vitamin D levels may be useful for both the diagnosis and management.Expert Opinion/Commentary: Further studies might help to understand the easiest way to diagnose SAMS, suitable prevention and an effective non-statin therapy. This review sheds new light on the future directions in both research and clinical practice, which will help with rapid risk assessment, identification of the SAMS risk factors in order to decrease the incidence of statins' adverse effects, and the most effective therapy.

[29] *Bazarbashi N, Miller M*. **Icosapent ethyl: drug profile and evidence of reduced residual cardiovascular risk in patients with statin-managed LDL-C cholesterol**. Expert review of cardiovascular therapy 2020:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32228246
ABSTRACT
INTRODUCTION: Icosapent ethyl (IPE) is a highly purified (>96%) form of eicosapentanoic acid, a marine-derived omega-3 fatty acid known to reduce serum triglyceride (TG) levels. In the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), the addition of 4 g IPE daily resulted in a 25% reduction in cardiovascular events beyond statins and other standard of care therapies. IPE is now the only therapy currently approved by the Food and Drug Administration to treat patients with elevated TGs (150-499 mg/dL) with cardiovascular disease (CVD) or Type 2 diabetes mellitus and two or more CVD risk factors.Areas covered: IPE is a highly purified form of eicosapentanoic acid for patients with elevated TGs as monotherapy or combined with statins and/or

other lipid lowering therapies.The REDUCE-IT Study demonstrated a 25% reduction in the primary outcome measure and 30% reduction in total CVD events in high-risk patients with elevated TGs (135-499 mg/dL) assigned to IPE (4 g daily).Side effects included a statistically significant increased risk of atrial fibrillation and bleeding, although the risk of stroke was reduced and there were no cases of fatal bleeding.The FDA recently approved IPE for treatment of patients with TG levels of 150-499 mg/dL and preexisting CVD or Type 2 diabetes mellitus with two or more risk factors.Expert opinion:IPE has proven to be superior to other forms of omega 3 fatty acid in reducing CVD risk in patients with elevated TG. This could be attributed to multiple factors including the use of highly purified eicosapentaenoic acid ethyl esters without docosahexaenoic acid (DHA), thus preventing the increase in low-density lipoprotein cholesterol associated with DHA especially at high TG levels, reduction in atherogenic TG-rich particles, antioxidant and anti-inflammatory properties, improvement in endothelial function, and stabilization of atherosclerotic plaque.

[30] *Stahel P, Xiao C, Nahmias A, Lewis GF*. **Role of the Gut in Diabetic Dyslipidemia**. Frontiers in endocrinology 2020; 11:116.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32231641
ABSTRACT
Type 2 diabetes (T2D) is associated with increased risk of cardiovascular disease (CVD). In insulin resistant states such as the metabolic syndrome, overproduction and impaired clearance of liver-derived very-low-density lipoproteins and gut-derived chylomicrons (CMs) contribute to hypertriglyceridemia and elevated atherogenic remnant lipoproteins. Although ingested fat is the major stimulus of CM secretion, intestinal lipid handling and ultimately CM secretory rate is determined by numerous additional regulatory inputs including nutrients, hormones and neural signals that fine tune CM secretion during fasted and fed states. Insulin resistance and T2D represent perturbed metabolic states in which intestinal sensitivity to key regulatory hormones such as insulin, leptin and glucagon-like peptide-1 (GLP-1) may be altered, contributing to increased CM secretion. In this review, we describe the evidence from human and animal models demonstrating increased CM secretion in insulin resistance and T2D and discuss the molecular mechanisms underlying these effects. Several novel compounds are in various stages of preclinical and clinical investigation to modulate intestinal CM synthesis and secretion. Their efficacy, safety and therapeutic utility are discussed. Similarly, the effects of currently approved lipid modulating therapies such as statins, ezetimibe, fibrates, and PCSK9 inhibitors on intestinal CM production are discussed. The intricacies of intestinal CM production are an active area of research that may yield novel therapies to prevent atherosclerotic CVD in insulin resistance and T2D.

[31] *Mandatori S, Pacella I, Marzolla V et al.* **Altered Tregs Differentiation and Impaired Autophagy Correlate to Atherosclerotic Disease**. Frontiers in immunology 2020; 11:350.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32231663
ABSTRACT
Atherosclerosis is a progressive vascular disease representing the primary cause of morbidity and mortality in developed countries. Formerly, atherosclerosis was considered as a mere passive accumulation of lipids in blood vessels. However, it is now clear that atherosclerosis is a complex and multifactorial disease, in which the involvement of immune cells and inflammation play a key role. A variety of studies have shown that autophagy-a cellular catalytic mechanism able to remove injured

cytoplasmic components in response to cellular stress-may be proatherogenic. So far, in this context, its role has been investigated in smooth muscle cells, macrophages, and endothelial cells, while the function of this catabolic protective process in lymphocyte functionality has been overlooked. The few studies carried out so far, however, suggested that autophagy modulation in lymphocyte subsets may be functionally related to plaque formation and development. Therefore, in this research, we aimed at better clarifying the role of lymphocyte subsets, mainly regulatory T cells (Tregs), in human atherosclerotic plaques and in animal models of atherosclerosis investigating the contribution of autophagy on immune cell homeostasis. Here, we investigate basal autophagy in a mouse model of atherosclerosis, apolipoprotein E (ApoE)-knockout (KO) mice, and we analyze the role of autophagy in driving Tregs polarization. We observed defective maturation of Tregs from ApoE-KO mice in response to tumor growth factor-beta (TGFbeta). TGFbeta is a well-known autophagy inducer, and Tregs maturation defects in ApoE-KO mice seem to be related to autophagy impairment. In this work, we propose that autophagy underlies Tregs maturation, advocating that the study of this process in atherosclerosis may open new therapeutic strategies.

[32] *Cawley NX, Lyons AT, Abebe D et al.* **Evaluation of the Potential Role of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) in Niemann-Pick Disease, Type C1**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32244519
ABSTRACT
Niemann-Pick disease, type C1, is a cholesterol storage disease where unesterified cholesterol accumulates intracellularly. In the cerebellum this causes neurodegeneration of the Purkinje neurons that die in an anterior-to-posterior and time-dependent manner. This results in cerebellar ataxia as one of the major outcomes of the disease. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a significant role in the regulation of serum cholesterol levels by modulating LDL receptor levels on peripheral tissues. In the central nervous system, PCSK9 may have a similar effect on the closely related VLDL and ApoE2 receptors to regulate brain cholesterol. In addition, regulation of VLDLR and ApoER2 by PCSK9 may contribute to neuronal apoptotic pathways through Reelin, the primary ligand of VLDLR and ApoER2. Defects in reelin signaling results in cerebellar dysfunction leading to ataxia as seen in the Reeler mouse. Our recent findings that Pcsk9 is expressed ~8-fold higher in the anterior lobules of the cerebellum compared to the posterior lobule X, which is resistant to neurodegeneration, prompted us to ask whether PCSK9 could play a role in NPC1 disease progression. We addressed this question genetically, by characterizing NPC1 disease in the presence or absence of PCSK9. Analysis of double mutant Pcsk9(-/-)/Npc1(-/-) mice by disease severity scoring, motor assessments, lifespan, and cerebellar Purkinje cell staining, showed no obvious difference in NPC1 disease progression with that of Npc1(-/-) mice. This suggests that PCSK9 does not play an apparent role in NPC1 disease progression.

[33] *Emruzi Z, Babaheidarian P, Arshad M et al.* **Immune Modulatory Effects of Hypercholesterolemia: Can Atorvastatin Convert the Detrimental Effect of Hypercholesterolemia on the Immune System?** Iranian journal of allergy, asthma, and immunology 2019; 18:554-566.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32245299
ABSTRACT

Many observations showed that hypercholesterolemia can disrupt immune response. Statin drugs that were used for the treatment of hypercholesterolemia patients can interfere in the regulation of the immune response and cytokine secretion. The primary aim of the current study was to investigate the immune response among treatment-naive patients with hypercholesterolemia and healthy subjects. The secondary goal of the study was to determine whether atorvastatin can reverse the detrimental effect of hypercholesterolemia on the immune system. Peripheral blood mononuclear cells (PBMCs) were isolated from 50 patients afflicted with hypercholesterolemia who were treatment-naive along with 50 sex/age-matched hypercholesterolemia patients receiving atorvastatin, and 50 sex/age-matched healthy subjects. Quantitative PCR and ELISA methods were used for gene and protein expression analysis of T helper 1 (Th1) and Th2 related cytokines. Additionally, the expression of the cluster of differentiation (CD) markers on T, B, and natural killer (NK) cells was measured by flow cytometry method. The results showed that hypercholesterolemia and atorvastatin down-regulated the expression of Th1-related cytokines and elevated the levels of Th2-related cytokines. The expression of cell surface markers, CD25 and CD69, was significantly decreased in the treatment-naive, and atorvastatin groups. It seems that atorvastatin is not able to repair the deleterious effects of hypercholesterolemia on the immune system. Moreover, elevated levels of cholesterol along with the administration of atorvastatin tilt the Th1/Th2 balance in favor of Th2 and reduce T cell activation.

[34] *Boccara F, Kumar PN, Caramelli B et al.* **Evolocumab Use in HIV-Infected Patients With Dyslipidemia: Primary Results of the Randomized, Double-blind BEIJERINCK Study**. Journal of the American College of Cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32234462

ABSTRACT

BACKGROUND: People living with HIV (PLHIV) are at increased risk of atherosclerotic cardiovascular disease (ASCVD) and prone to statin-related adverse events from drug-drug interactions with certain antiretroviral regimens. OBJECTIVES: This study sought to evaluate the efficacy and safety of evolocumab in dyslipidemic PLHIV. METHODS: BEIJERINCK is a randomized, double-blind, multinational trial comparing monthly subcutaneous evolocumab 420 mg with placebo in PLHIV with hypercholesterolemia/mixed dyslipidemia taking maximally-tolerated statin therapy. The primary endpoint was the percent change (baseline to week 24) in low-density lipoprotein cholesterol (LDL-C); secondary endpoints included achievement of LDL-C <70 mg/dL and percent change in other plasma lipid and lipoprotein levels. Treatment-emergent adverse events (TEAEs) were also examined. RESULTS: A total of 464 patients were analyzed (mean age of 56.4 years, 82.5% male, mean duration with HIV of 17.4 years). ASCVD was documented in 35.6% of patients, and statin intolerance/contraindications to statin use were present in 20.7% of patients. Evolocumab reduced LDL-C by 56.9% (95% CI: 61.6%, 52.3%) from baseline to week 24 versus placebo. An LDL-C level of <70 mg/dL was achieved in 73.3% of patients in the evolocumab group versus 7.9% in the placebo group. Evolocumab also significantly reduced other atherogenic lipid levels, including non-HDL-C, ApoB, and Lp(a) (all p<0.0001). Evolocumab was well tolerated, and TEAE patient incidence was similar among evolocumab and placebo groups. CONCLUSIONS: Evolocumab was safe and significantly reduced lipid levels in dyslipidemic PLHIV on maximally-tolerated statin therapy. Evolocumab is an effective therapy for lowering atherogenic lipoproteins in PLHIV with high cardiovascular risk.

Literature update week 14 (2020)

[35] *Johnson M, Brook JR, Brook RD et al.* **Traffic-Related Air Pollution and Carotid Plaque Burden in a Canadian City With Low-Level Ambient Pollution**. Journal of the American Heart Association 2020; 9:e013400.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32237976
ABSTRACT
Background The association between fine particulate matter and cardiovascular disease has been convincingly demonstrated. The role of traffic-related air pollutants is less clear. To better understand the role of traffic-related air pollutants in cardiovascular disease development, we examined associations between NO2, carotid atherosclerotic plaque, and cardiometabolic disorders associated with cardiovascular disease. Methods and Results Cross-sectional analyses were conducted among 2227 patients (62.9+/-13.8 years; 49.5% women) from the Stroke Prevention and Atherosclerosis Research Centre (SPARC) in London, Ontario, Canada. Total carotid plaque area measured by ultrasound, cardiometabolic disorders, and residential locations were provided by SPARC medical records. Long-term outdoor residential NO2 concentrations were generated by a land use regression model. Associations between NO2, total carotid plaque area, and cardiometabolic disorders were examined using multiple regression models adjusted for age, sex, smoking, and socioeconomic status. Mean NO2 was 5.4+/-1.6 ppb in London, Ontario. NO2 was associated with a significant increase in plaque (3.4 mm(2) total carotid plaque area per 1 ppb NO2), exhibiting a linear dose-response. NO2 was also positively associated with triglycerides, total cholesterol, and the ratio of low- to high-density lipoprotein cholesterol (P<0.05). Diabetes mellitus mediated the relationship between NO2 and total carotid plaque area (P<0.05). Conclusions Our results demonstrate that even low levels of traffic-related air pollutants are linked to atherosclerotic plaque burden, an association that may be partially attributable to pollution-induced diabetes mellitus. Our findings suggest that reducing ambient concentrations in cities with NO2 below current standards would result in additional health benefits. Given the billions of people exposed to traffic emissions, our study supports the global public health significance of reducing air pollution.

[36] *Courlet P, Livio F, Alves Saldanha S et al.* **Real-life management of drug-drug interactions between antiretrovirals and statins**. The Journal of antimicrobial chemotherapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32240298
ABSTRACT
BACKGROUND: PIs cause drug-drug interactions (DDIs) with most statins due to inhibition of drug-metabolizing enzymes and/or the hepatic uptake transporter OATP1B1, which may alter the pharmacodynamic (PD) effect of statins. OBJECTIVES: To assess the management of DDIs between antiretrovirals (ARVs) and statins in people living with HIV (PLWH) considering statin plasma concentrations, compliance with dosing recommendations and achievement of lipid targets. METHODS: PLWH of the Swiss HIV Cohort Study were eligible if they received a statin concomitantly with ARVs. HDL, total cholesterol (TC) and statin plasma concentration were measured during follow-up visits. Individual non-HDL and TC target values were set using the Framingham score and the 2018 European AIDS Clinical Society recommendations. RESULTS: Data were analysed for rosuvastatin (n = 99), atorvastatin (n = 92), pravastatin (n = 46) and pitavastatin (n = 21). Rosuvastatin and atorvastatin underdosing frequently led to suboptimal PD response. Insufficient lipid control was observed with PIs despite high atorvastatin concentrations, likely explained by inhibition of OATP1B1 resulting in less statin uptake in the liver. Target lipid values were more often achieved with unboosted integrase

inhibitors due to both their favourable DDI profiles and neutral effect on lipids. Insufficient lipid control was common with pravastatin and pitavastatin regardless of co-administered ARVs and despite using maximal recommended statin doses. The latter suggests lower efficacy compared with rosuvastatin or atorvastatin. CONCLUSIONS: Suboptimal management of DDIs with statin underdosing was observed in 29% of prescriptions. Integrase inhibitor-based regimens and/or treatment with rosuvastatin or atorvastatin should be favoured in patients with refractory dyslipidaemia.

[37] *Hua L, Lei M, Xue S et al.* **Effect of fish oil supplementation combined with high-intensity interval training in newly diagnosed non-obese type 2 diabetes: a randomized controlled trial**. Journal of clinical biochemistry and nutrition 2020; 66:146-151.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32231411
ABSTRACT
The additive effect of high-intensity interval training to fish oil supplementation on newly diagnosed type 2 diabetes is unknown. 173 newly diagnosed type 2 diabetes patients were randomly assigned into the control group (received corn oil), fish oil group (eicosapentaenoic acid, EPA:docosahexaenoic acid, DHA = 3:2, total 2.0 g/day), and the fish oil + high-intensity interval training group. Three instructed high-intensity interval training sessions (Monday, Wednesday, and Friday; 10 x 60-s cycling bouts) were performed for 3 months. Glycaemic control was assayed by serum haemoglobin A1c, fast glucose, fast insulin, and adiponectin. Homeostatic model assessment of insulin resistance was utilized to determine the homeostasis of pancreatic function. Fat mass, triglycerides, total cholesterol, low-density lipoproteins, and high-density lipoproteins were measured to indicate cardiovascular risk. Within and between groups analysis were performed with linear mixed-effects modeling (95% CIs and p values). When compared with fish oil, fish oil + high-intensity interval training intervention has significant additive beneficial effects on haemoglobin A1c ($p<0.01$), fast glucose ($p<0.001$), homeostatic model assessment of insulin resistance ($p<0.05$), adiponectin ($p<0.05$), fat mass ($p<0.01$), and total cholesterol ($p<0.01$), but not on fast insulin level to newly diagnosed non-obese type 2 diabetes. High-intensity interval training has an additive effect on fish oil supplementation on glycaemic control, insulin resistance, cardiovascular risk, and fat mass, which indicates the potential necessity of combining high-intensity interval training with fish oil.

[38] *Brown EE, Byrne KH, Davis DM et al.* **Incorporation of genetic testing significantly increases the number of individuals diagnosed with familial hypercholesterolemia**. Journal of clinical lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32220565
ABSTRACT
BACKGROUND: It is estimated that less than 10% of cases of familial hypercholesterolemia (FH) in the United States have been diagnosed. Low rates of diagnosis may in part be attributable to affected patients not meeting the clinical diagnostic criteria of the Dutch Lipid Clinic Network (DLCN), Simon Broome, or US MEDPED diagnostic criteria. OBJECTIVE: The objective of this study was to assess the utility of incorporating genetic testing into a patient's evaluation for FH. METHODS: We retrospectively reviewed patients seen in the Advanced Lipids Disorders Clinic at Johns Hopkins Hospital between January 2015 and May 2018. Between June 2018 and December 2018, patients were consented to a prospective registry. DLCN, Simon Broome, and MEDPED criteria were applied to each patient, before and after genetic testing. Genetic testing included sequencing and deletion duplication analysis of four

genes (LDLR, PCSK9, APOB, and LDLRAP1). RESULTS: The retrospective review and prospective study identified 135 adult probands who were seen in our clinic for evaluation of heterozygous FH. Twenty-nine individuals (21%) were heterozygous for a pathogenic or likely pathogenic monogenic variant. Before genetic testing, using the DLCN criteria, 35 (26%) individuals met criteria for a definite diagnosis of FH. Thirty patients (22%) met criteria using Simon Broome, and 29 (21%) patients met criteria using US MEDPED before genetic analysis. Depending on the criteria, incorporating genetic testing identified 11-14 additional patients with FH. CONCLUSIONS: Incorporating genetic testing diagnosed almost 50% more patients with definite FH in comparison to classification solely on clinical grounds.

[39] *Kim KJ, Yoon J, Won KH et al.* **Assessment of the Efficacy of Lowering LDL Cholesterol with Rosuvastatin 10 mg in Four Korean Statin Benefit Groups as per ACC/AHA Guidelines (NewStaR4G)**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32230818
ABSTRACT
The American College of Cardiology and American Heart Association (ACC/AHA) guidelines identified four statin benefit groups on the basis of atherosclerotic cardiovascular disease risk reduction and proposed statin therapy by evidence-based intensity. Although these guidelines used randomized controlled trials with hard outcomes as exclusive evidence for its recommendations, a limited number of studies conducted in Asian countries makes its application of treatment strategy, intensity, and statin doses uncertain in these population. This prospective, multicenter study aimed to evaluate the efficacy of rosuvastatin 10 mg in the four statin benefit groups requiring high- or moderate-intensity statin therapy according to the ACC/AHA guidelines in the Korean population. The primary endpoint was percentage reduction in low-density lipoprotein (LDL) cholesterol. Secondary endpoints were percentage reduction in other lipids and achievement of >/=50% reduction in LDL cholesterol. Rosuvastatin 10 mg lowered LDL cholesterol by 61.4 mg/dL, a 44.9% decrease from baseline after eight weeks. Reduction of LDL cholesterol >/=50% was achieved in 46.3% of patients. Rosuvastatin 10 mg was generally well tolerated. In the Korean population, rosuvastatin 10 mg was favorable and tolerant in lowering LDL cholesterol in the four statin benefit groups requiring high- or moderate-intensity statin therapy according to the ACC/AHA guidelines.

[40] *Krahel JA, Baran A, Kaminski TW et al.* **Methotrexate Decreases the Level of PCSK9-A Novel Indicator of the Risk of Proatherogenic Lipid Profile in Psoriasis. The Preliminary Data**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32225075
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) exerts an important role in inflammatory processes, lipids homeostasis, and cardiometabolic disorders that are closely associated with psoriasis. The aim of the study was to analyze the clinical and diagnostic value of serum PCSK9 concentrations and their connections with disease severity, inflammation, metabolic syndrome, and impact of systemic therapies in psoriatic patients. The study enrolled thirty-five patients with active plaque-type psoriasis and eighteen healthy volunteers served as controls. Blood samples were obtained before and after 12 weeks of treatment with methotrexate or acitretin. Serum PCSK9 concentrations were measured by the ELISA (Enzyme-Linked Immunosorbent Assay) commercial kits. Morphological and biochemical parameters were assayed using routine laboratory techniques.

Psoriatic patients showed significantly elevated levels of PCSK9 compared to controls ($p < 0.01$), mostly in patients with a mild and moderate course of psoriasis. PCSK9 concentrations correlated positively with BMI and triglyceride levels ($p < 0.05$). Interestingly, PCSK9 had a strong negative correlation with low-density lipoprotein levels and total cholesterol ($p < 0.05$). Three months of monotherapy with methotrexate significantly reduced PCSK9 level ($p < 0.05$), on the contrary, the acitretin group showed a further increase of PCSK9 levels ($p < 0.05$). PCSK9 seems to be a novel marker of psoriasis and a putative explanation of lipid disturbances, which are common in patients with psoriasis and are vital for the further developing of metabolic syndrome. Methotrexate should be considered as a treatment of choice in patients with an elevated PCSK9 concentration.

[41] *Patti AM, Rizvi AA, Giglio RV et al.* **Impact of Glucose-Lowering Medications on Cardiovascular and Metabolic Risk in Type 2 Diabetes**. Journal of clinical medicine 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32225082
ABSTRACT
Type 2 Diabetes Mellitus (T2DM) is associated with a high risk of atherosclerotic cardiovascular (CV) disease. Among the well-known pathophysiologic factors, crucial roles are played by endothelial dysfunction (caused by oxidative stress and inflammation hyperglycemia-linked), increased activity of nuclear factor kB, altered macrophage polarization, and reduced synthesis of resident endothelial progenitor cells. As consequence, a potentially rapid progression of the atherosclerotic disease with a higher propensity to unstable plaque is arguable, finally leading to significantly increased cardiovascular mortality. Main managements are focused on both prevention and early diagnosis, by targeted treatment of hyperglycemia and vascular complications. Innovative therapeutic approaches for T2DM seek to customize the antidiabetic treatment to each patient in order to optimize glucose-lowering effects, minimize hypoglycemia and adverse effects, and prevent cardiovascular events. The newer drugs (e.g., Glucagon Like Peptide-1 Receptor Agonists, GLP-1 RAs; Sodium GLucose coTransporter-2 inhibitors, SGLT2is; DiPeptidyl Peptidase-4 inhibitors, and DPP4is) impact body weight, lipid parameters, and blood pressure, as well as endothelial (dys)functions, inflammatory markers, biomarkers of both oxidative stress, and subclinical atherosclerosis. The present review summarizes the results of the main trials focused on the cardiovascular safety of these drugs from the CV standpoint.

[42] *Watts GF, Chan DC, Pang J et al.* **PCSK9 Inhibition with alirocumab increases the catabolism of lipoprotein(a) particles in statin-treated patients with elevated lipoprotein(a)**. Metabolism 2020; 107:154221.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32240727
ABSTRACT
BACKGROUND: Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL) particle containing apolipoprotein(a) (apo(a)) covalently linked to apolipoprotein B-100 (apoB). Statin-treated patients with elevated Lp(a) have an increased risk of atherosclerotic cardiovascular disease (ASCVD). Recent trials show that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition decreases Lp(a) and cardiovascular events, particularly in high risk patients with elevated Lp(a). We investigated the kinetic mechanism whereby alirocumab, a PCSK9 inhibitor, lowers Lp(a) in statin-treated patients with high Lp(a) and ASCVD. METHODS: The effects of 12-week alirocumab treatment (150 mg every 2 weeks) on apo(a) kinetics were studied in 21 patients with elevated Lp(a) concentration (>0.5 g/L). Apo(a)

fractional catabolic rate (FCR) and production rate (PR) were determined using intravenous D3-leucine administration, mass spectrometry and compartmental modelling. All patients were on long-term statin treatment. RESULTS: Alirocumab significantly decreased plasma concentrations of total cholesterol (-39%), LDL-cholesterol (-67%), apoB (-56%), apo(a) (-25%) and Lp(a) (-22%) (P< 0.001 for all). Alirocumab also significantly lowered plasma apo(a) pool size (-26%, P <0.001) and increased the FCR of apo(a) (+28%, P< 0.001), but did not alter apo(a) PR, which remained significantly higher relative to a reference group of patients on statins with normal Lp(a) (P< 0.001). CONCLUSIONS: In statin-treated patients, alirocumab lowers elevated plasma Lp(a) concentrations by accelerating the catabolism of Lp(a) particles. This may be consequent on marked upregulation of hepatic receptors (principally for LDL) and/or reduced competition between Lp(a) and LDL particles for these receptors; the mechanism could contribute to the benefit of PCSK9 inhibition with alirocumab on cardiovascular outcomes.

[43] *Chen JH, Wu T, Xia WY et al.* **An early neuroprotective effect of atorvastatin against subarachnoid hemorrhage**. Neural regeneration research 2020; 15:1947-1954.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32246644
ABSTRACT
Atorvastatin has been shown to reduce early brain edema and neuronal death after subarachnoid hemorrhage, but its mechanism is not clear. In this study, rat models of subarachnoid hemorrhage were established by autologous blood injection in the cisterna magna. Rat models were intragastrically administered 20 mg/kg atorvastatin 24 hours before subarachnoid hemorrhage, 12 and 36 hours after subarachnoid hemorrhage. Compared with the controls, atorvastatin treatment demonstrated that at 72 hours after subarachnoid hemorrhage, neurological function had clearly improved; brain edema was remarkably relieved; cell apoptosis was markedly reduced in the cerebral cortex of rats; the number of autophagy-related protein Beclin-1-positive cells and the expression levels of Beclin-1 and LC3 were increased compared with subarachnoid hemorrhage only. The ultrastructural damage of neurons in the temporal lobe was also noticeably alleviated. The similarities between the effects of atorvastatin and rapamycin were seen in all the measured outcomes of subarachnoid hemorrhage. However, these were contrary to the results of 3-methyladenine injection, which inhibits the signaling pathway of autophagy. These findings indicate that atorvastatin plays an early neuroprotective role in subarachnoid hemorrhage by activating autophagy. The experimental protocol was approved by the Animal Ethics Committee of Anhui Medical University, China (904 Hospital of Joint Logistic Support Force of PLA; approval No. YXLL-2017-09) on February 22, 2017.

[44] *Wojcik C*. **Emerging lipid lowering agents targeting LDL cholesterol**. Postgraduate medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32243228
ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is the main cause of morbidity and mortality in the US. ASCVD is caused by elevated levels of ApoB lipoproteins, which over many years penetrate the arterial subendothelial space leading to plaque growth and eventually rupture causing clinical symptoms. ApoB lipoprotein levels are approximated in clinical practice by LDL-C measurement. LDL-C lowering agents (statins, ezetimibe and PCSK9 inhibitors) reduce cardiovascular risk in primary and secondary prevention proportionally to LDL-C reduction (23% per 1 mmol/L of LDL). However, for a variety of reasons, many patients do not achieve their recommended LDL-C levels using currently available

therapies. This has prompted the development of new LDL-C lowering drugs in the hope to reduce cardiovascular risk, such as bempedoic acid, inclisiran, gemcabene and evinacumab. Drugs targeting other lipids (triglycerides, HDL-C, lipoprotein (a)), intravascular inflammation or acting by other mechanisms also have a role in atherosclerosis prevention, however, they will not be covered in this review.

[45] *Bork CS, Mortensen LT, Hjelmgaard K, Schmidt EB*. **Marine n-3 fatty acids and CVD: new insights from recent follow-up studies and clinical supplementation trials**. The Proceedings of the Nutrition Society 2020:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32234084
ABSTRACT
Marine n-3 PUFA exert beneficial effects that might inhibit atherosclerosis and reduce vascular disease. Previous studies have, however, reported conflicting results and here we have summarised the early history and the most recent findings from follow-up studies and randomised clinical trials investigating marine n-3 PUFA in relation to the risk of atherosclerotic CVD. Most follow-up studies have suggested that the intake of marine n-3 PUFA may be associated with a lower risk of CVD. Recent studies have also shown that it is important to focus on substitution issues and dietary patterns. Further, the use of gold standard biomarkers of fatty acid exposure such as adipose tissue should be encouraged. Findings from clinical supplemental trials have shown conflicting results and findings from previous meta-analyses and guidelines have generally not supported the use of fish oil supplements for the prevention of CVD. However, a recent meta-analysis including three recent large clinical trials with fish oil supplements reported a moderate beneficial effect on cardiovascular endpoints. Interestingly, results from a large clinical trial (REDUCE-IT) have suggested that supplementation with a high dose of purified EPA ethyl ester for 49 years significantly and markedly reduced the risk of cardiovascular events in patients with CVD and mild hypertriglyceridaemia; findings that need to be confirmed. While it seems appropriate to recommend consumption of fish, particular fatty fish for prevention of CVD, an effect of fish oil supplements is probably at best marginal perhaps apart from patients with hypertriglyceridaemia.

[46] *Hernandez-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K et al.* **Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012**. Salud Publica Mex 2020; 62:137-146.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32237556
ABSTRACT
OBJECTIVE: To describe in a national sample 1) the prevalence, awareness, treatment and control of dyslipidemias 2) the prevalence of dyslipidemias through previous national surveys. MATERIALS AND METHODS: We analyzed data of the National Health and Nutrition Survey 2012, a representative cross-sectional study. Serum samples of 9 566 adults >/=20 years old with fasting >/=8 hours were analyzed for lipid fractions. Age-adjusted prevalences were calculated, by sociodemographic variables. Prevalence of awareness, treatment and control was estimated. A description of the dyslipidemia prevalence reported in previous surveys is reported. RESULTS: Hypoalphalipoproteinemia and elevated LDL-C are the most prevalent dyslipidemias in Mexican adults. One in four adults had hypercholesterolemia at the moment of the interview without previous diagnosis. Awareness, treatment and control of dyslipidemia were 12.6, 3.7 and 3.1%, respec- tively. CONCLUSIONS:

Dyslipidemias are the most prevalent risk factor for cardiovascular diseases in Mexico. Public policies to increase awareness, access to therapy and sustained control are urgently needed.

[47] *De Carlos Artajo J, Castro Unanua N, Muruzabal Huarte E et al.* **[Lipid lowering treatment of severe hypertriglyceridemia with acute pancreatitis caused by everolimus in a patient with a neuroendocrine tumor]**. An Sist Sanit Navar 2020; 43:103-106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32242549

ABSTRACT

Everolimus is an mTOR inhibitor, approved as a treatment for cancer and as an immunosuppressant agent in solid organ transplantation; it frequently produces toxic metabolic effects, particularly of the most severe kind. Its use can cause hyperglycemia, hypercholesterolemia and hypertriglyceridemia; thus, metabolic values should be monitored regularly to prevent these adverse events. We present the case of a woman with an intestinal neuroendocrine tumor who developed two episodes of acute pancreatitis, secondary to severe hypertriglyceridemia caused by everolimus. After treatment with fibrates and omega-3, triglyceride levels returned to baseline, without developing new metabolic or digestive complications. Targeted levels of triglyceride for cancer patients treated with everolimus, should be below 500 or 300 mg/dL, depending on whether life expectancy is less or longer than one year, respectively.