Literature update week 06 (2020)

[1] *Rastogi A, Dunbar RL, Thacker HP et al.* **Abrogation of postprandial triglyceridemia with dual PPAR alpha/gamma agonist in type 2 diabetes mellitus: a randomized, placebo-controlled study**. Acta diabetologica 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32030508
ABSTRACT
AIMS: Lowering postprandial lipemia may mitigate cardiovascular risk in patients with diabetic dyslipidemia. This study was aimed to investigate whether saroglitazar suppresses postprandial lipemia in patients with diabetes and dyslipidemia. METHODS: This was a 12-week, prospective, multicenter, randomized, double-blinded, placebo-controlled study of saroglitazar in patients with diabetes and dyslipidemia. Thirty patients were randomized (1:1) to receive saroglitazar 4 mg or placebo orally once daily with metformin for 12 weeks. The primary endpoint was change in plasma triglyceride (TG) area under the curve (AUC) on a standardized 8-h fat tolerance test. RESULTS: Thirty participants were randomized for interventions and eventually data of 19 participants qualified for per protocol analyses. Mean (SD) age in saroglitazar was 53.1 (8.8) years and 54.9 (7.7) years in placebo group. After 12 weeks, saroglitazar significantly lowered postprandial TG-AUC by - 458.3 (144.0) (- 25.7%, 95% CI - 765.1 to - 151.4) versus an increase of + 10.9 (157.9) (+ 0.5%, 95% CI - 325.6 to 347.3) mg/dL h in placebo group ($P < 0.05$). Saroglitazar lowered postprandial TG incremental AUC versus placebo: - 329.4 (89.9) (- 59%) versus + 80.4 (99.4) (+ 10%) mg/dL h ($P < 0.05$). HbA1c (%) decreased by - 0.36 (0.42) in the saroglitazar group as compared to an increase of + 1.26 (0.46) ($P < 0.05$) with placebo. CONCLUSIONS: The saroglitazar treatment significantly improved postprandial TGs in people with diabetic dyslipidemia. TRIAL REGISTRATION: Clinical Trial Registry of India; trial Registration No.: CTRI/2015/06/005845 and Date of registration: June 02, 2015.

[2] *Constantin AT, Covacescu SM, Kozma A et al.* **STATINS TREATMENT AND ORO-DENTAL ASPECTS IN A CASE OF HEREDITARY HYPERCHOLESTEROLEMIA IN A CHILD UNDER 6 YEARS**. Acta endocrinologica (Bucharest, Romania : 2005) 2019; 15:378-383.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32010359
ABSTRACT
Familial hypercholesterolemia (FH) is a genetic disease with autosomal dominant transmission, characterised by high blood cholesterol levels. The evolution of this disease leads to primary atherosclerosis and cardiovascular disease. Patients with HF develop atherosclerosis by the age of 20 and usually do not survive past the age of 30. We present the case and oro-dental aspects of a preschooler that was diagnosed at the age of 4 with FH, compound heterozygote (mutation/genotype1 LDLR: C20IX, exon 4; mutation/genotype2 LDLR: G571E, exon 12) and the experience of our clinic in the management of this patient that received off-label treatment with statins. When diagnosed, his cholesterol level was 932 mg/dL and his LDL-cholesterol level was 792 mg/dL. Treatment with rosuvastatin and ezetimibe was prescribed. Both substances (rosuvastatin and ezetimibe) are not approved for children under the age of 6 in Europe. Taking into considerations the diagnosis and prognosis for unfavorable evolution, treatment with statins was started at the age of 5 years.

[3] *Chen J, Li M, Zhu X et al.* **Atorvastatin reduces cerebral vasospasm and infarction after aneurysmal subarachnoid hemorrhage in elderly Chinese adults**. Aging 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32035420
ABSTRACT

We explored whether acute atorvastatin treatment would improve clinical outcomes and reduce the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage in elderly Chinese adults. Patients (60 to 90 years old) were admitted to intensive care units after surgery to clip or embolize their aneurysms. We assessed 592 patients and assigned 159 to receive atorvastatin (20 mg/day) and 158 to receive placebo once daily for up to 14 days. The primary outcome was the Glasgow outcome scale at 6 months, and secondary outcomes were cerebral vasospasm, 30-days all-cause mortality, cerebral infarction, and delayed ischemic neurological deficit. The incidence of postoperative cerebral vasospasm (39.3% vs 56%, P =0.004) and cerebral infarction (18.7% vs 27.3%, P=0.027) were significantly lower in the atorvastatin group. The study did not detect benefits in the use of atorvastatin for 6 months clinical outcome or 30-day all-cause mortality, but it suggests that atorvastatin together with nimodipine can reduce cerebral vasospasm and cerebral infarction after subarachnoid hemorrhage.

[4] *Aimo A, De Caterina R*. **Aspirin for primary prevention of cardiovascular disease: Advice for a decisional strategy based on risk stratification**. Anatol J Cardiol 2020; 23:70-78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011329
ABSTRACT
The need for aspirin therapy as part of primary prevention of cardiovascular (CV) disease is currently being highly debated, especially after 3 studies in different settings reported that a reduction in ischemic events is largely counterbalanced by an increase in bleeding events. One possible explanation for these results is the progressive reduction in the risk of major adverse cardiovascular events (MACE) as a result of primary prevention, which has accompanied global education programs that have led to patients smoking less, exercising more, and increasingly undertaking lipid-lowering therapies. Based on a meta-regression of the benefits and harmful effects of aspirin therapy in primary prevention as a function of the 10-year risk of MACE, we favor a differentiated and personalized approach that acknowledged differences between patients and emphasized an individualized assessment of benefits and risks. Following general preventive measures (physical exercise, cessation of smoking, treatment of hypertension and hypercholesterolemia, etc.), an individualized approach to prescribing aspirin is still warranted. When patients are less than 70 years of age, clinicians should assess the 10-year CV risk. Aspirin treatment should be considered only when the CV risk is very high and the bleeding risk is low, after taking into account the patient's preferences.

[5] *Fras Z*. **Increased cardiovascular risk associated with hyperlipoproteinemia (a) and the challenges of current and future therapeutic possibilities**. Anatol J Cardiol 2020; 23:60-69.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011323
ABSTRACT
Population, genetic, and clinical studies demonstrated a causative and continuous, from other plasma lipoproteins independent relationship between elevated plasma lipoprotein (a) [Lp(a)] concentration and the development of cardiovascular disease (CVD), mainly those related to athe-rosclerotic CVD, and calcific aortic stenosis. Currently, a strong international consensus is still lacking regarding the single value which would be commonly used to define hyperlipoproteinemia (a). Its prevalence in the general population is estimated to be in the range of 10%-35% in accordance with the most commonly used threshold levels (>30 or >50 mg/dL). Since elevated Lp(a) can be of special importance in patients with some genetic disorders, as well as in individuals with otherwise controlled major risk factors, the

identification and establishment of the proper therapeutic interventions that would lower Lp(a) levels and lead to CVD risk reduction could be very important. The majority of the classical lipid-lowering agents (statins, ezetimibe, and fibrates), as well as nutraceuticals (CoQ10 and garlic), appear to have no significant effect on its plasma levels, whereas for the drugs with the demonstrated Lp(a)-lowering effects (aspirin, niacin, and estrogens), their clinical efficacy in reducing cardiovascular (CV) events has not been unequivocally proven yet. Both Lp(a) apheresis and proprotein convertase subtilisin/kexin type 9 inhibitors can reduce the plasma Lp(a) by approximately 20%-30% on average, in parallel with much larger reduction of low-density lipoprotein cholesterol (up to 70%), what puts us in a difficulty to conclude about the true contribution of lowered Lp(a) to the reduction of CV events. The most recent advancement in the field is the introduction of the novel apolipoprotein (a) [apo(a)] antisense oligonucleotide therapy targeting apo(a), which has already proven itself as being very effective in decreasing plasma Lp(a) (by even >90%), but should be further tested in clinical trials. The aim of this review was to present some of the most important accessible scientific data, as well as dilemmas related to the currently and potentially in the near future more widely available therapeutic options for the management of hyperlipoproteinemia (a).

[6] *Hu T, Shen H, Huang H et al.* **Cholesterol-lowering drug pitavastatin targets lung cancer and angiogenesis via suppressing prenylation-dependent Ras/Raf/MEK and PI3K/Akt/mTOR signaling**. Anticancer Drugs 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011362
ABSTRACT
Therapeutic agents that target both tumor cell and vascular endothelial cell may achieve additional anti-tumor efficacy, particularly in lung cancer due to the critical roles of angiogenesis during lung cancer progression and metastasis. In this work, we showed that pitavastatin, a novel cholesterol-lowering drug, potently inhibited lung cancer cells and angiogenesis. This was achieved by the induction of apoptosis and inhibition of proliferation of lung cancer cells and human lung tumor-associated endothelial cell. Pitavastatin was not only effective to chemo-sensitive but also chemo-resistant lung cancer cells. This was also consistent with the finding that pitavastatin significantly enhanced cisplatin's efficacy in lung cancer xenograft model without causing toxicity in mice. We further showed that pitavastatin inhibited lung tumor angiogenesis in vitro and in vivo through suppressing human lung tumor-associated endothelial cell migration and morphogenesis without affecting adhesion. Mechanistically, we showed that pitavastatin acted on lung cancer cells and human lung tumor-associated endothelial cell through suppressing prenylation-dependent Ras/Raf/MEK and PI3K/Akt/mTOR signaling. Our work is the first to demonstrate the inhibitory effects of pitavastatin on Ras-mediated signaling. Our findings provide pre-clinical evidence to repurpose pitavastatin for the treatment of lung cancer.

[7] *Hoekstra M, Van Eck M*. **Probucol-induced hypocholesterolemia is not associated with exacerbated foam cell formation in ABCG1 knockout mice**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32033777
ABSTRACT

Literature update week 06 (2020)

[8] *Sari G, Meester EJ, van der Zee LC et al.* **A mouse model of humanized liver shows a human-like lipid profile, but does not form atherosclerotic plaque after western type diet**. Biochem Biophys Res Commun 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32014257
ABSTRACT
Mouse models are a crucial and often used tool to provide insight into the underlying mechanisms of human atherosclerosis. However, mice profoundly differ from humans in lipoprotein synthesis and metabolism, key factors in atherosclerotic plaque formation. Mouse models often require genetic and dietary modifications to mimic human pathophysiology, shifting from a high-density lipoprotein to an low-density lipoprotein dominant lipoprotein profile. We examined the suitability of mice with a humanized liver as a model for lipoprotein studies and studies on plaque formation, given the central role of hepatocytes in lipoprotein synthesis and metabolism. Our results show a progressive humanization of the mouse liver and a humanized lipoprotein profile. However, no atherosclerotic plaque formation was observed in the studied time frame, despite presence of functional macrophages and application of a high cholesterol western-type diet. The humanized-liver mouse model therefore might require further modifications to induce atherosclerosis, yet seems a valuable model for in vivo studies on lipoprotein metabolism.

[9] *Yang J, Zeng P, Liu L et al.* **Food with calorie restriction reduces the development of atherosclerosis in apoE-deficient mice**. Biochem Biophys Res Commun 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32007274
ABSTRACT
Calorie restriction (CR) ameliorates various diseases including cardiovascular disease. However, its protection and underlying mechanisms against atherosclerosis remain un-fully elucidated. In this study, we fed apoE deficient (apoE(-/-)) mice in Control group a high-fat diet (HFD, 21% fat plus 0.5% cholesterol) or in CR group a CR diet (CRD, 2% fat plus 0.5% cholesterol, approximately 40% calorie restriction and same levels of cholesterol, vitamins, minerals and amino acids as in HFD). After 16 weeks feeding, compared with HFD, CRD substantially reduced atherosclerosis in mice. CRD increased SMC and collagen content but reduced macrophage content, necrotic core and vascular calcification in lesion areas. Mechanistically, CRD attenuated bodyweight gain, improved lipid profiles but had little effect on macrophage lipid metabolism. CRD also inhibited expression of inflammatory molecules in lesions. Taken together, our study demonstrates CRD effectively reduces atherosclerosis in apoE(-/-) mice, suggesting it as a potent and reproducible therapy for atherosclerosis management.

[10] *Furtado RHM, Giugliano RP*. **What Lessons Have We Learned and What Remains to be Clarified for PCSK9 Inhibitors? A Review of FOURIER and ODYSSEY Outcomes Trials**. Cardiology and therapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32026310
ABSTRACT
For more than half a century, low-density lipoprotein cholesterol (LDL-C) has been recognized as a major risk factor for incident atherosclerotic cardiovascular disease. The discovery of proprotein convertase subtilisin-kexin type 9 (PCSK9) in 2003, which prevents LDL-C receptor recycling, identified a new target for drug intervention. Recently, two large-scale randomized clinical outcomes trials involving fully human anti-PCSK9 monoclonal antibodies tested the hypothesis that targeting this

pathway would reduce cardiovascular events. Both the FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) and ODYSSEY OUTCOMES trials met their primary efficacy endpoints, confirming findings reported earlier that major adverse cardiovascular events can be reduced by a further lowering of LDL-C beyond that achieved with statin therapy. In both trials, there were incremental reductions in LDL-C of > 50% from baseline, with no major safety concerns, over the trials' median follow-up time (2.2 and 2.8 years, respectively). While there were differences in design, lipid management and overall results, key messages from both studies were similar. However, post-publication, additional questions have arisen, especially regarding drug effects over the long-term, including a potential mortality benefit.

[11] *Meng X, Yin J, Yu X, Guo Y*. **MicroRNA-205-5p Promotes Unstable Atherosclerotic Plaque Formation In Vivo**. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32034643
ABSTRACT
PURPOSE: Atherosclerosis is a narrowing of the arteries caused by plaque buildup. MicroRNAs (miRNAs) have been proposed to participate in the pathogenesis of atherosclerosis. Here, we aimed to investigate miR-205-5p's role in promoting atherosclerotic progression. METHODS: Knock-in (KI) mice with human/murine miR-205-5p within the murine host gene for miR-205 (MIR205HG) were crossed with apolipoprotein E knockout (Apoe(-/-)) mice. This miR-205KI Apoe(-/-) murine model was employed to study the impact of miR-205-5p in Apoe(-/-) mice susceptible to atherosclerotic plaque formation. RESULTS: miR-205KI Apoe(-/-)mice developed larger, more unstable plaques relative to their Apoe(-/-) counterparts (0.45 vs. 0.26 mm(2), P < 0.001). miR-205KI Apoe(-/-) mice exhibited lower serum levels of high-density lipoprotein cholesterol (HDL-C) (5.18 vs. 19.31 mg/dL, P < 0.001) and triglycerides (32.79 vs. 156.76 mg/dL, P < 0.001) with system-wide reversal of cholesterol transport. Macrophages derived from miR-205KI Apoe(-/-) mice exhibited ~ 20% lowered cholesterol efflux capability with enhanced pro-inflammatory gene expression through lipid raft formation. Bone marrow transplantation demonstrated that bone marrow (BM) donor cells with miR-205-5pKI simulated plaque formation independent of the recipients' miR-205-5p status. CONCLUSIONS: miR-205-5p encourages unstable atherogenesis in vivo. miR-205-5p also adversely influences lipid metabolism and promotes a pro-inflammatory macrophage phenotype. Our findings advocate miR-205-5p as a potential therapeutic target for combating unstable atherogenesis.

[12] *Douiev L, Sheffer R, Horvath G, Saada A*. **Bezafibrate Improves Mitochondrial Fission and Function in DNM1L-Deficient Patient Cells**. Cells 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32012656
ABSTRACT
Mitochondria are involved in many cellular processes and their main role is cellular energy production. They constantly undergo fission and fusion, and these counteracting processes are under strict balance. The cytosolic dynamin-related protein 1, Drp1, or dynamin-1-like protein (DNM1L) mediates mitochondrial and peroxisomal division. Defects in the DNM1L gene result in a complex neurodevelopmental disorder with heterogeneous symptoms affecting multiple organ systems. Currently there is no curative treatment available for this condition. We have previously described a patient with a de novo heterozygous c.1084G>A (p.G362S) DNM1L mutation and studied the effects of

a small molecule, bezafibrate, on mitochondrial functions in this patient's fibroblasts compared to controls. Bezafibrate normalized growth on glucose-free medium, as well as ATP production and oxygen consumption. It improved mitochondrial morphology in the patient's fibroblasts, although causing a mild increase in ROS production at the same time. A human foreskin fibroblast cell line overexpressing the p.G362S mutation showed aberrant mitochondrial morphology, which normalized in the presence of bezafibrate. Further studies would be needed to show the consistency of the response to bezafibrate, possibly using fibroblasts from patients with different mutations in DNM1L, and this treatment should be confirmed in clinical trials. However, taking into account the favorable effects in our study, we suggest that bezafibrate could be offered as a treatment option for patients with certain DNM1L mutations.

[13] *Xi Y, Zhang Y, Zhu S et al.* **PPAR-Mediated Toxicology and Applied Pharmacology**. Cells 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32028670
ABSTRACT
Peroxisome proliferator-activated receptors (PPARs), members of the nuclear hormone receptor family, attract wide attention as promising therapeutic targets for the treatment of multiple diseases, and their target selective ligands were also intensively developed for pharmacological agents such as the approved drugs fibrates and thiazolidinediones (TZDs). Despite their potent pharmacological activities, PPARs are reported to be involved in agent- and pollutant-induced multiple organ toxicity or protective effects against toxicity. A better understanding of the protective and the detrimental role of PPARs will help to preserve efficacy of the PPAR modulators but diminish adverse effects. The present review summarizes and critiques current findings related to PPAR-mediated types of toxicity and protective effects against toxicity for a systematic understanding of PPARs in toxicology and applied pharmacology.

[14] *Sultan F, Kaur R, Mir AH et al.* **Rosuvastatin and retinoic acid may act as 'pleiotropic agents' against beta-adrenergic agonist-induced acute myocardial injury through modulation of multiple signalling pathways**. Chemico-biological interactions 2020; 318:108970.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32007421
ABSTRACT
Cardiovascular disorders constitute the principal cause of deaths worldwide and will continue as the major disease-burden by the year 2060. A significant proportion of heart failures occur because of use and misuse of drugs and most of the investigational agents fail to achieve any clinical relevance. Here, we investigated rosuvastatin and retinoic acid for their "pharmacological pleiotropy" against high dose beta-adrenergic agonist (isoproterenol)-induced acute myocardial insult. Rats were pretreated with rosuvastatin and/or retinoic acid for seven days and the myocardial injury was induced by administering isoproterenol on the seventh and eighth day. After induction, rats were anaesthetized for electrocardiography, then sacrificed and different samples were collected/stored for various downstream assays. Myocardial injury with isoproterenol resulted in increased cardiac mass, decreased R-wave amplitude, increased QRS and QT durations; elevated levels of cardiac markers like cTnI, CK-MB, ALT and AST; increased lipid peroxidation, protein carbonylation and tissue nitric oxide levels; decreased endogenous antioxidants like SOD, CAT, GR, GST, GPx and total antioxidant activity; increased inflammatory markers like TNF-alpha and IL-6; decreased the mRNA expression of Nrf2 and Bcl-2; increased the mRNA expression of Bax, eNOS and iNOS genes. Pretreatment with rosuvastatin

and/or retinoic acid mitigated many of the above biochemical and pathological alterations. Our results demonstrate that rosuvastatin and retinoic acid exert cardioprotective effects and may act as potential agents in the prevention of beta-adrenergic agonist-induced acute myocardial injury in rats. Cardioprotective potential of rosuvastatin and retinoic acid could be attributed to their influence on the redox pathways, immunomodulation, membrane stability, Nrf2 preservation, iNOS and Bax expression levels. Thus, they may act directly or indirectly at various steps, the breakpoints, in the pathophysiological cascade responsible for cardiac injury. Our study gives insights about the pharmacological pleiotropism of rosuvastatin and retinoic acid.

[15] *Shah NP, Ahmed HM, Wilson Tang WH*. **Familial hypercholesterolemia: Detect, treat, and ask about family**. Cleveland Clinic journal of medicine 2020; 87:109-120.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32015064
ABSTRACT
Familial hypercholesterolemia is an autosomal dominant disorder that affects the metabolism of low-density lipo-protein cholesterol (LDL-C) through mutations in the gene for LDL receptor (LDLR), and less commonly in those for apolipoprotein B (APOB), proprotein convertase subtili-sin-kexin type 9 (PCSK9), and others. Patients with these mutations have elevated plasma levels of LDL-C and, as a result, an increased risk of atherosclerotic cardiovascular disease beginning in childhood, leading to significant risk of illness and death.

[16] *Karimi Z, Mousavizadeh A, Rafiei H et al.* **The Effect of Using Olive Oil and Fish Oil Prophylactic Dressings on Heel Pressure Injury Development in Critically Ill Patients**. Clinical, cosmetic and investigational dermatology 2020; 13:59-65.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32021369
ABSTRACT
Introduction and Aim: Prevention of pressure injuries in patients hospitalized in intensive care units is significantly important. Therefore, in the present study, the effect of using olive oil and fish oil prophylactic dressings on the development of heel pressure injuries was investigated. Methods: The present study was a clinical trial conducted in the intensive care unit of Shahid Beheshti Hospital, in Yasuj. Fifty patients, who were at moderate to high risk of pressure injuries development, were randomly divided into two groups based on the mean score of the Braden scale. In one group, patients' heels were dressed using olive oil prophylactic dressing, and in the other group, patients' heels were dressed using fish oil prophylactic dressing. The dressings were changed 3 times a day. Collected data were then analyzed using SPSS v16. Results: No significant difference was determined in demographic variables among the two groups ($p<0.05$). In terms of the development of heel pressure injuries, none of the patients in the olive oil and fish oil groups had pressure injuries. Conclusion: There were no statistically significant differences in either treatment group related to heel pressure injuries outcomes during the 7 days observed in the study. Additionally, both dressings had the same effects. Further studies are recommended in this regard.

[17] *Makinen P, Ruotsalainen AK, Yla-Herttuala S*. **Nucleic Acid-Based Therapies for Atherosclerosis**. Current atherosclerosis reports 2020; 22:10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32034521
ABSTRACT

PURPOSE OF REVIEW: Atherosclerosis is characterized by accumulation of lipids and chronic inflammation in medium size to large arteries. Recently, RNA-based antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are being developed, along with small molecule-based drugs and monoclonal antibodies, for the treatment of risk factors associated with atherosclerosis.. The purpose of this review is to describe nucleic acid-based therapeutics and introduce novel RNAs that might become future tools for treatment of atherosclerosis. RECENT FINDINGS: RNA-based inhibitors for PCSK9, Lp(a), ApoCIII, and ANGPTL3 have been successfully tested in phase II-III clinical trials. Moreover, multiple microRNA and long non-coding RNAs have been found to reduce atherogenesis in preclinical animal models. Clinical trials especially with ASOs and siRNAs directed to liver, targeting cholesterol and lipoprotein metabolism, have shown promising results. Additional research in larger patient cohorts is needed to fully evaluate the therapeutic potential of these new drugs.

[18] *Khare A, Gaur S*. **Cholesterol-Lowering Effects of Lactobacillus Species**. Current microbiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32020463
ABSTRACT
Probiotics are the living and non-pathogenic microbial supplements which, upon administration in adequate quantities, influence the host organism positively by improving gut health and enhancing intestinal mucosal integrity. They suppress potentially pathogenic microorganisms by competing with them for nutrients as well as space for gut adherence. Lactobacillus species are the most commonly used bacteria in the probiotic preparations and studies show that they have cholesterol-lowering effects on the hosts. Lipids are biological molecules that are insoluble in water and bile salts play a major role in their digestion as they are synthesized and conjugated to taurine or glycine in the liver. Bile salt hydrolase deconjugates taurine or glycine from bile salts. Cholesterol metabolism is influenced by the effect of Lactobacillus species on microbial populations as well as overall metabolic activity of human intestinal microflora. Deconjugation of bile salt, concentration of short-chain fatty acids and molar proportion of propionate constitute the major processes by which cholesterol lowering is brought about by Lactobacillus species. This review summarizes the cholesterol-lowering properties of this species. A significant number of Lactobacillus strains have been known to display substantial bile salt hydrolase activities and identifying those strains for use in therapeutic purposes can be a great advancement. Here, this identification is done using phylogenetic relationship for different identified potential probiotic Lactobacillus strains.

[19] *Maranhao RC, Pala D, Freitas FR*. **Lipoprotein removal mechanisms and aging: implications for the cardiovascular health of the elderly**. Current opinion in endocrinology, diabetes, and obesity 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011347
ABSTRACT
PURPOSE OF REVIEW: The speed of removal from the plasma of apolipoprotein B-containing lipoproteins, for example, chylomicrons, VLDL and LDL is determinant of the plasma concentration of these lipoproteins, is influenced by genetic features and ambient factors, and has implications in atherogenesis. As aging increases the clinical complications of atherosclerosis, it is important to appraise the status of the removal mechanisms in elderly individuals. RECENT FINDINGS: Removal of triglyceride-rich lipoproteins remnants is delayed but the triglyceride breakdown is unchanged in elderly individuals. The discovery of PCSK9, enzyme that degrades LDL receptors, and the recent

observation that PCSK9 is elevated in the elderly raises another hypothesis to account for the increased LDL-cholesterol levels in the elderly. The removal of cholesterol from cells by HDL, the first step of cholesterol reverse transport is also less efficient in the elderly, which may compromise the body cholesterol homeostasis. SUMMARY: Aging determines reduction of the efficiency of lipoprotein plasma removal mechanisms, which is implicated in increased incidence of cardia complications. Moreover, aging is frequently accompanied by physical activity reduction, weight gain, and metabolic disturbances that can further decrease the efficacy of the removal mechanisms. This knowledge is important for promoting cardiovascular health in the elderly and prolonging survival.

[20] *D'Erasmo L, Di Costanzo A, Arca M*. **Autosomal recessive hypercholesterolemia: update for 2020**. Current opinion in lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011344
ABSTRACT
PURPOSE OF REVIEW: This review summarizes the current knowledge regarding autosomal recessive hypercholesterolemia (ARH) and provides new insight into the natural history and therapeutic management of this lipid disorder. RECENT FINDINGS: Novel homozygous and compound heterozygous ARH-causing mutations have been reported in the literature, to date. The long-term follow-up of a cohort of ARH patients demonstrated that, despite intensive treatment with conventional lipid-lowering therapies, their low-density lipoprotein (LDL) cholesterol levels remain far from target and this translates into a poor cardiovascular prognosis. ARH is also associated with increased risk of developing aortic valve stenosis. However, lomitapide, a microsomal triglyceride transfers protein inhibitor, may represent a new opportunity for the effective treatment of ARH. SUMMARY: ARH is an ultrarare disorder of LDL metabolism caused by mutations in the LDLRAP1 gene. It is inherited as a recessive trait and causative mutations, though heterogeneous, are all predicted to be loss-of-function. Recent investigations have demonstrated that ARH can be considered a phenocopy of homozygous familial hypercholesterolemia, where the risk of atherosclerotic cardiovascular diseases and aortic valve stenosis remains elevated despite conventional therapies. The combination of lomitapide with the conventional LDL-C-lowering medications appears to be a promising approach to treat this condition.

[21] *Sherratt SCR, Lero M, Mason RP*. **Are dietary fish oil supplements appropriate for dyslipidemia management? A review of the evidence**. Current opinion in lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32022752
ABSTRACT
PURPOSE OF REVIEW: The purpose of this review is to assess if dietary fish oil supplements are appropriate for patients with elevated triglycerides and cardiovascular risk based on a critical analysis of their composition, quality, and regulatory oversight. RECENT FINDINGS: Approximately 19 million people in the United States take fish oil supplements, many for the purpose of treating or preventing heart disease. Unlike prescription drugs, fish oil supplements are classified as food by the Food and Drug Administration (FDA) and not subject to rigorous clinical testing or manufacturing oversight. Analysis of widely used fish oil supplements show that they may have lower amounts of omega-3 than advertised as well as significant levels of saturated fat and oxidized oils which actually may contribute to dyslipidemia. Clinical outcome trials have failed to show a benefit with fish oil supplements and other low-dose mixed omega-3 fatty acids. SUMMARY: Owing to lack of rigorous regulatory oversight

and widespread evidence of quality concerns, fish oil supplements are not an appropriate substitute for FDA approved prescription omega-3 fatty acids in the treatment of elevated triglycerides or the prevention of cardiovascular events.

[22] *Patoulias D, Stavropoulos K, Imprialos K et al.* **Pharmacological Management of Cardiac Disease in Patients with Type 2 Diabetes: Insights into Clinical Practice**. Current vascular pharmacology 2020; 18:125-138.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013815
ABSTRACT
BACKGROUND: Type 2 Diabetes Mellitus (T2DM) has emerged as a growing pandemic. Cardiovascular disease (CVD) constitutes another major health problem, with coronary heart disease being the leading cause of cardiovascular death. Patients with T2DM require a multilevel therapeutic approach, both for primary and secondary prevention of CVD. OBJECTIVE: To present and summarize the most recent, highest level evidence retrieved from literature, relevant to the pharmaceutical management of CVD in T2DM. METHODS: We conducted a comprehensive search of the literature on MEDLINE from its inception till today, primarily for relevant systematic reviews, meta-analyses and randomized controlled trials. RESULTS: There is a trend towards more intensified therapeutic interventions in T2DM, concerning glycemic, lipid and blood pressure control. New drugs, such as sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors might evolve as key players in the management of diabetes and its complications within the next years. Classic drugs, such as those targeting the renin-angiotensinaldosterone system, statins and aspirin remain first-line treatment options, both for primary and secondary prevention of CVD. Lifestyle interventions should always be integrated into a complete therapeutic strategy in diabetic patients. Novel drugs, such as finerenone and LCZ696 have provided significant results in cardiovascular outcome studies; however, their role in T2DM has to be further elucidated. CONCLUSION: Pharmaceutical approach of CVD in T2DM is multilevel and complex. Drug classes featuring pleiotropic effects may boost our armamentarium in the fight against CVD.

[23] *Blanchard C, Ledoux S, Verhaegen A et al.* **Roux-en-Y gastric bypass, but not sleeve gastrectomy, decreases plasma PCSK9 levels in morbidly obese patients**. Diabetes Metab 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32032671
ABSTRACT
AIM: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a master regulator of low-density lipoprotein cholesterol (LDL-C) metabolism, acting as an endogenous inhibitor of the LDL receptor. While it has been shown that bariatric surgery differentially affects plasma LDL-C levels, little is known of its effects on plasma PCSK9 concentrations. Therefore, the present study aimed to: (i) investigate the effect of sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) on plasma PCSK9 concentrations; and (ii) correlate baseline or postoperative plasma PCSK9 concentration variations with anthropometric and metabolic parameters. METHODS: Fasting plasma PCSK9 levels were measured by ELISA in morbidly obese patients before and 6 months after bariatric surgery. Patients were recruited from three prospective cohorts (in Nantes and Colombes in France, and Antwerp in Belgium). RESULTS: A total of 156 patients (34SG, 122RYGB) were included. Plasma PCSK9, LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) levels were significantly reduced after RYGB (-19.6%, -16.6% and -19.5%, respectively; $P<0.0001$), but not after SG. In all patients, postoperative PCSK9 change was

positively correlated with fasting plasma glucose (FPG; r=0.22, P=0.007), HOMA-IR (r=0.24, P=0.005), total cholesterol (r=0.17, P=0.037) and non-HDL-C (r=0.17, P=0.038) variations, but not LDL-C. In contrast to what was observed for glucose parameters (FPG, HOMA-IR), correlation between PCSK9 and non-HDL-C changes after RYGB was independent of total weight loss. CONCLUSION: RYGB, but not SG, promotes a significant reduction in plasma PCSK9 levels, and such changes in circulating PCSK9 levels after RYGB appear to be more associated with glucose improvement than with lipid homoeostasis parameters.

[24] *Mba CM, Mbacham W, Sobngwi E, Mbanya JC*. **Is PCSK9 Associated with Plasma Lipid Levels in a Sub-Saharan African Population of Patients with Obesity and Type 2 Diabetes?** Diabetes, metabolic syndrome and obesity : targets and therapy 2019; 12:2791-2797.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32021342
ABSTRACT
Purpose: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of circulating LDL cholesterol. There are inconsistent data in some populations concerning the association between PCSK9, LDL and CRP. The emerging importance of the inhibition of PCSK9 for the treatment of hypercholesterolemia warrants investigations in different populations. The aim of this study from a Sub-Saharan African population was to evaluate the association between PCSK9 and hs-CRP levels and plasma lipid levels in patients with type 2 diabetes (T2D) and obese and lean controls. Patients and methods: A cross-sectional analytical study was conducted in a major hospital in Yaounde, Cameroon in a cohort of 162 participants (53% females). There were 54 non-obese T2D patients matched for age and sex to 54 obese nondiabetic and 54 nondiabetic lean subjects. PCSK9 level was assessed by sandwich ELISA method and hsCRP by nephelometry. Results: PCSK9 and hs-CRP levels were significantly higher in obese and T2D subjects when compared to lean controls ($p<0.001$ and $p=0.002$, respectively). The association between PCSK9 and triglyceride levels in the overall population was gender dependent ($p=0.04$) and subgroup analysis showed a significant positive correlation between PCSK9 and triglyceride levels in males but not in females ($r=0.56$, $p=0.02$ and $r=0.2$ and $p=0.1$, respectively). Multilinear regression analysis identified BMI as an independent predictor for PCSK9 levels and this association was maintained after adjustment for confounders; adjusted beta-coefficient; 36.1 (95% CI; 29.2-47.4). We did not find an association between PCSK9 and any plasma lipid levels in obese and T2D subjects, nor between PCSK9 and hs-CRP levels. Conclusion: Obese and type 2 diabetes subjects have higher PCSK9 levels when compared to lean controls, suggesting that these metabolic states potentially impact PCSK9 levels in Cameroonian patients.

[25] *Pingali U, Nutalapati C, Illendulla VS*. **Evaluation of the Effect of Fish Oil Alone and in Combination with a Proprietary Chromium Complex on Endothelial Dysfunction, Systemic Inflammation and Lipid Profile in Type 2 Diabetes Mellitus - A Randomized, Double-Blind, Placebo-Controlled Clinical Study**. Diabetes, metabolic syndrome and obesity : targets and therapy 2020; 13:31-42.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32021349
ABSTRACT
Purpose: This study was conducted to evaluate the effectiveness of fish oil alone and with an adjunct, a proprietary chromium complex (PCC), on cardiovascular parameters - endothelial dysfunction, lipid profile, systemic inflammation and glycosylated hemoglobin - in a 12-week randomized, double-blind,

placebo-controlled clinical study in type 2 diabetes mellitus subjects. Patients and Methods: In this randomized, double-blind, parallel group study, 59 subjects in three groups completed the study: Group A, fish oil 2000 mg; Group B, fish oil 2000 mg + PCC 10 mg (200 microg of Cr(3+)); and Group C, fish oil 2000 mg + PCC 20 mg (400 microg of Cr(3+)) daily for 12 weeks (2000 mg of fish oil contained 600 mg of eicosapentaenoic acid [EPA] and 400 mg of docosahexaenoic acid [DHA], the omega-3 fatty acids). Endothelial function, by estimating reflection index (RI), biomarkers of oxidative stress (nitric oxide [NO], malondialdehyde [MDA], glutathione [GSH]) and inflammatory biomarkers (high-sensitivity C-reactive protein [hsCRP], intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], endothelin-1) were evaluated at baseline, and 4 and 12 weeks. Lipid profile, platelet aggregation and glycosylated hemoglobin [HbA1c) were tested at baseline and 12 weeks. Any reported adverse drug reactions were recorded. Statistical analysis was performed using GraphPad Prism 8. Results: The present study shows that fish oil by itself, at a dose of 2000 mg (600 mg of EPA + 400 mg of DHA) per day, led to significant, but only modest, improvement in cardiovascular parameters (RI from -2.38+/-0.75 to -3.92+/-0.60, MDA from 3.77+/-0.16 to 3.74+/-0.16 nM/mL, NO from 30.60+/-3.18 to 32.12+/-3.40 microM/L, GSH from 568.93+/-5.91 to 583.95+/-6.53 microM/L; p</=0.0001), including triglyceride levels. However, when PCC was added to fish oil, especially at the 20 mg dose, there were highly significant improvements in all the parameters tested (RI from -2.04+/-0.79 to -8.73+/-1.36, MDA from 3.67+/-0.39 to 2.89+/-0.34 nM/mL, NO from 28.98+/-2.93 to 40.01+/-2.53 microM/L, GSH from 553.82+/-8.18 to 677.99+/-10.19 microM/L; p</=0.0001), including the lipid profile. It is noteworthy that the triglycerides were decreased significantly by addition of 20 mg of PCC although the dose of fish oil was only 2 g/day and the baseline triglyceride levels were only about 200 mg/dL. Fish oil alone did not significantly decrease the HbA1c, whereas the addition of 20 mg of PCC did. Conclusion: Addition of PCC, especially at 20 mg dose, significantly improves the efficacy of fish oil in addressing cardiovascular risk factors compared to fish oil given alone.

[26] *Tuttle KR, McGill JB*. **Evidence-based treatment of hyperglycemia with incretin therapies in patients with type 2 diabetes mellitus and advanced chronic kidney disease**. Diabetes Obes Metab 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32009296
ABSTRACT
Type 2 diabetes mellitus (T2DM) is the leading cause of chronic kidney disease (CKD). The prevalence of CKD is growing in parallel with the rising number of patients with T2DM globally. At present, the optimal approach to glycemic control in patients with T2DM and advanced CKD (categories 4 and 5) remains uncertain, since these patients were largely excluded from clinical trials of glucose-lowering therapies. Nonetheless, clinical trial data are available for the use of incretin therapies, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, for patients with T2DM and advanced CKD. This review discusses the role of incretin therapies in the management of these patients. Since the presence of advanced CKD in patients with T2DM is associated with a markedly elevated risk of cardiovascular disease (CVD), treatment strategies must include the reduction of both CKD and CVD risks because death, particularly of cardiovascular causes, is more likely than progression to end-stage kidney disease. The management of hyperglycemia is essential for good diabetes care even in advanced CKD. Current evidence supports an individualized approach to glycemic management in patients with T2DM and advanced CKD, taking account of the needs of each patient, including the presence of comorbidities and concomitant therapies. Although additional studies are

needed to establish optimal strategies for glycemic control in patients with T2DM and advanced CKD, treatment regimens with currently available pharmacotherapy can be individually tailored to meet the needs of this growing patient population.

[27] *Qiu Y, Shen L, Fu L et al.* **The glucose-lowering effects of alpha-glucosidase inhibitor require a bile acid signal in mice**. Diabetologia 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32034442
ABSTRACT
AIMS/HYPOTHESIS: Bile-acid (BA) signalling is crucial in metabolism homeostasis and has recently been found to mediate the therapeutic effects of glucose-lowering treatments, including alpha-glucosidase inhibitor (AGI). However, the underlying mechanisms are yet to be clarified. We hypothesised that BA signalling may be required for the glucose-lowering effects and metabolic benefits of AGI. METHODS: Leptin receptor (Lepr)-knockout (KO) db/db mice and high-fat high-sucrose (HFHS)-fed Fxr (also known as Nr1h4)-KO mice were treated with AGI. Metabolic phenotypes and BA signalling in different compartments, including the liver, gut and endocrine pancreas, were evaluated. BA pool profiles were analysed by mass spectrometry. The islet transcription profile was assayed by RNA sequencing. The gut microbiome were assayed by 16S ribosomal RNA gene sequencing. RESULTS: AGI lowered microbial BA levels in BA pools of different compartments in the body, and increased gut BA reabsorption in both db/db and HFHS-fed mouse models via altering the gut microbiome. The AGI-induced changes in BA signalling (including increased activation of farnesoid X receptor [FXR] in the liver and inhibition of FXR in the ileum) echoed the alterations in BA pool size and composition in different organs. In Fxr-KO mice, the glucose- and lipid-lowering effects of AGI were partially abrogated, possibly due to the Fxr-dependent effects of AGI on decelerating beta cell replication, alleviating insulin hypersecretion and improving hepatic lipid and glucose metabolism. CONCLUSIONS/INTERPRETATION: By regulating microbial BA metabolism, AGI elicited diverse changes in BA pool composition in different host compartments to orchestrate BA signalling in the whole body. The AGI-induced changes in BA signalling may be partly required for its glucose-lowering effects. Our study, hence, sheds light on the promising potential of regulating microbial BA and host FXR signalling for the treatment of type 2 diabetes. DATA AVAILABILITY: Sequencing data are available from the BioProject Database (accession no. PRJNA600345; www.ncbi.nlm.nih.gov/bioproject/600345).

[28] *Kim E, Park KR, Jang IJ et al.* **A Fixed-Dose Combination Of Gemigliptin And Rosuvastatin Exhibits Similar Pharmacokinetics, Pharmacodynamics, And Safety Compared To That Of A Loose Combination In Healthy Subjects**. Drug design, development and therapy 2019; 13:3879-3885.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32009778
ABSTRACT
Purpose: Fixed-dose combination (FDC) of gemigliptin and rosuvastatin may improve medication compliance of patients with comorbid type 2 diabetes and dyslipidemia. Pharmacokinetics (PK), pharmacodynamics (PD), and safety of gemigliptin/rosuvastatin 50/20 mg FDC was compared with a loose combination of individual tablets in healthy subjects. Patients and methods: A randomized, open-label, single-dose, two-period, two-sequence, two-treatment crossover study was conducted. Subjects received FDC or a loose combination of gemigliptin (50 mg) and rosuvastatin (20 mg) during each period, with a 14-day washout. Serial blood samples were collected up to 72 hrs after dosing to measure plasma concentrations of gemigliptin, its active metabolite LC15-0636, and rosuvastatin for

PK assessment, and DPP-4 activity for PD assessment. PK and PD parameters were calculated using a non-compartmental method. Safety profiles were evaluated throughout the study. Results: Thirty-seven subjects completed the study. The concentration-time profiles of gemigliptin, LC15-0636, and rosuvastatin were similar between FDC and loose combination, respectively. For each of the three compounds, the geometric mean ratios (90% confidence interval) of FDC to loose combination for Cmax and AUClast fell within the bioequivalence range of 0.8-1.25. Inhibition of DPP-4 activity-time profiles after administration of FDC and loose combination was overlapping, and Imax and AUEClast were similar. Both FDC and the loose combination were well tolerated. Conclusion: PK, PD, and safety profiles of gemigliptin, its metabolite, and rosuvastatin were similar between FDC and loose combination. The FDC of gemigliptin (50 mg) and rosuvastatin (20 mg) can be used as an alternative to a loose combination, which is expected to improve patient compliance.

[29] *Yang H, Li N, Zhou Y et al.* **Cost-Effectiveness Analysis of Ezetimibe as the Add-on Treatment to Moderate-Dose Rosuvastatin versus High-Dose Rosuvastatin in the Secondary Prevention of Cardiovascular Diseases in China: A Markov Model Analysis**. Drug design, development and therapy 2020; 14:157-165.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32021100
ABSTRACT
Background: For patients with inadequate control of cholesterol using moderate-dose statins in the secondary prevention of cardiovascular diseases (CVD), either doubling the dose of statins or adding ezetimibe should be considered. The cost-effectiveness of them is unknown in the Chinese context. The aim of this study is to compare the cost and effectiveness of the two regimens, and estimate the incremental cost-effectiveness ratio (ICER). Methods: A Markov model of five health statuses were used to estimate long-term costs and quality-adjusted life-years (QALYs) of the two treatment regimens from the healthcare perspective. The effectiveness data used to calculate the transition probability was based on a previously published randomized trial. The utility data was gathered from literature and the costs were gathered from the electronic medical record system of West China Hospital in Chinese Yuan (CNY) in 2017 price. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted. Results: The ICER for ezetimibe plus moderate-dose rosuvastatin was 47,102.99 CNY per QALY for 20 years simulation, which did not reach the threshold of per capita gross domestic product (GDP) of 59,660 CNY per QALY in 2017 in China. Non-CVD-related mortality and CVD-related mortality contributed most to the ICER. Conclusion: Adding ezetimibe to the moderate-dose statin in secondary prevention for CVD is cost-effective, compared with the high-dose statin in the Chinese context whose low-density lipoprotein cholesterol (LDL-c) was not inadequately controlled by moderate-dose statin alone.

[30] *Feghaly JJ, Mooradian AD*. **The Rise and Fall "ing" of the HDL Hypothesis**. Drugs 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32020556
ABSTRACT
Earlier epidemiological studies have shown an inverse correlation between high-density lipoprotein cholesterol (HDLc) and coronary heart disease (CHD). This observation along with the finding that reverse cholesterol transport is mediated by HDL, supported the hypothesis that the HDL molecule has a cardioprotective role. More recently, epidemiological data suggest a U-shaped curve correlating HDLc and CHD. In addition, randomized clinical trials of drugs that significantly increase plasma HDLc levels,

such as nicotinic acid and cholesterol ester transfer protein (CETP) inhibitors failed to show a reduction in major adverse cardiovascular events. These observations challenge the hypothesis that HDL has a cardioprotective role. It is possible that HDL quality and function is optimal only when de novo synthesis of apo A-I occurs. Inhibition of turnover of HDL with currently available agents yields HDL molecules that are ineffective in reverse cholesterol transport. To test this hypothesis, newer therapeutic drugs that increase de novo production of HDL and apo A-I should be tested in clinical trials.

[31] *Garber AJ, Handelsman Y, Grunberger G et al.* **CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY**. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2020; 26:107-139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32022600
ABSTRACT
Abbreviations: A1C = hemoglobin A1C; AACE = American Association of Clinical Endocrinologists; ABCD = adiposity-based chronic disease; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACCORD BP = Action to Control Cardiovascular Risk in Diabetes Blood Pressure; ACE = American College of Endocrinology; ACEI = angiotensin-converting enzyme inhibitor; AGI = alpha-glucosidase inhibitor; apo B = apolipoprotein B; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrant; BMI = body mass index; BP = blood pressure; CCB = calcium channel blocker; CGM = continuous glucose monitoring; CHD = coronary heart disease; CKD = chronic kidney disease; DKA = diabetic ketoacidosis; DPP4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; ER = extended release; FDA = Food and Drug Administration; GLP1 = glucagon-like peptide 1; HDL-C = high-density-lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density-lipoprotein cholesterol; LDL-P = low-density-lipoprotein particle; Look AHEAD = Look Action for Health in Diabetes; NPH = neutral protamine Hagedorn; OSA = obstructive sleep apnea; PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease; RCT = randomized controlled trial; SU = sulfonylurea; SGLT2 = sodium-glucose cotransporter 2; SMBG = self-monitoring of blood glucose; T2D = type 2 diabetes; TZD = thiazolidinedione.

[32] *Jose FPdME, Goulart AC, Sommer Bittencourt M et al.* **Relationship between TSH Levels and the Advanced Lipoprotein Profile in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)**. Endocrine research 2020:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32019383
ABSTRACT
Purpose/aims: The relationship between thyroid-stimulating hormone (TSH) and lipoprotein subfractions by Vertical Auto Profile (VAP) is unclear. We aimed to evaluate lipoprotein profiles according to TSH levels in euthyroid individuals.Material and Methods: Cross-sectional analysis of 3,525 participants from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) with no previous thyroid disease and who were not on lipid-lowering medication. Total-cholesterol and its fractions, lipoprotein subfractions, triglycerides, and triglyceride-rich lipoprotein cholesterol [TRL-C (VLDL1+2-C, VLDL3-C, IDL-C)] were determined by VAP. Associations between TSH quintiles and lipoprotein

subfractions were evaluated by crude and adjusted linear regression models.Results: For the total sample, significant beta-coefficients in full adjusted models for the 5(th) quintile of TSH (compared to 1(st)) were found for the following VAP lipids and lipoproteins: IDL-C (beta: 0.90; 0.11 to 1.69); VLDL-C (beta: 2.80; 1.51 to 4.08), triglycerides (beta: 18.66; 8.07 to 29.25), non-HDL-C (beta: 4.63; 0.50 to 8.75 mg/dl), TRL-C (beta:1.93;0.70 to 3.17), VLDL3-C (beta: 1.04; 0.50 to 1.57), as well as, TC/HDL-C (beta: 0.15; 0.03 to 0.26) and TG/HDL-C ratio (beta: 0.49;0.21 to 0.77). In women, similar results were found for VLDL-C, triglycerides, non-HDL-C, TRL-C, VLDL3-C, TC/HDL-C and TG/HDL-C-ratios. In men, we also found positive associations between the highest quintile of TSH with VLDL-C, triglycerides, VLDL3-C and TG/HDL-C.Conclusions: In the ELSA-Brasil, the highest TSH levels were mostly positively associated with lipoprotein levels, particularly TG, TRL and their remnants. Notwithstanding, our findings suggest that TSH levels within the normal range have little impact on the atherogenic profile.

[33] *Lassenius MI, Toppila I, Bergius S et al.* **Cardiovascular event rates increase after each recurrence and associate with poor statin adherence**. European journal of preventive cardiology 2020:2047487320904334.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013604
ABSTRACT
AIMS: The study evaluated the quality of cardiovascular prevention in real-world clinical practice. The recurrence of up to five cardiovascular events was assessed, as data on recurrence beyond the first event and interindividual variations in event rates past the second event have been sparse. Low-density lipoprotein cholesterol concentrations and lipid-lowering therapy use were investigated. METHODS: This retrospective register-based study included adult patients with an incident cardiovascular event between 2004 and 2016 treated in the hospital district of southwest Finland. Patients were followed for consecutive cardiovascular events or cardiovascular death, low-density lipoprotein cholesterol and statin purchases. The timing of event recurrence was evaluated, and predictive factors were assessed. RESULTS: A wide interindividual variation in cardiovascular event recurrence was observed, each additional event caused an increased risk, the median time of recurrence decreased from 7 to one year for the second and fifth event. Event rates increased correspondingly from 12 to 43/100 patient-years and were most pronounced in the first years following the previous event. The low-density lipoprotein cholesterol goal (<1.8 mmol/l) was reached by 18% in the year after the event and statin underuse was associated with an increased risk of recurrence. Six months after the index event high intensity statins were used by only 22% of the cohort. CONCLUSION: The study provides new perspectives on individual risk assessment showing that event rates are not stable for all patients but increase 1.2-1.9-fold per consecutive event. The underuse of statins and poor adherence support the identification of these patients for intensified multifactorial preventive measures.

[34] *Sever P, Gouni-Berthold I, Keech A et al.* **LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial**. European journal of preventive cardiology 2020:2047487320902750.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32019364
ABSTRACT
AIMS: Some trials have reported diminished efficacy for statins in the elderly, and in women compared with men. We examined the efficacy and safety of evolocumab by patient age and sex in the FOURIER

trial, the first major cardiovascular outcome trial of a PCSK9 inhibitor. METHODS AND RESULTS: FOURIER was a randomised, double blind trial, comparing evolocumab with placebo in 27,564 patients with atherosclerotic cardiovascular disease receiving statin therapy (median follow-up 2.2 years). The primary endpoint was cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation. Cox proportional hazards models were used to assess the efficacy of evolocumab versus placebo stratified by quartiles of patient age and by sex. There were small variations in the cardiovascular event rate across the age range (for the primary endpoint, Kaplan-Meier at 3 years 15.6%, >69 years, vs. 15.1%, </=56 years, P = 0.45); however, the relative efficacy of evolocumab was consistent regardless of patient age (for the primary endpoint (Q1 hazard ratio, 95% confidence interval) 0.83, 0.72-0.96, Q2 0.88, 0.76-1.01, Q3 0.82, 0.71-0.95, Q4 0.86, 0.74-1.00; Pinteraction = 0.91), and the key secondary endpoint (cardiovascular death, myocardial infarction, stroke) (Q1 0.74 (0.61-0.89), Q2 0.83 (0.69-1.00), Q3 0.78 (0.65-0.94), Q4 0.82 (0.69-0.98)); Pinteraction = 0.81). Women had a lower primary endpoint rate than men (Kaplan-Meier at 3 years 12.5 vs. 15.3%, respectively, P < 0.001). Relative risk reductions in the primary endpoint and key secondary endpoint were similar in women (0.81 (0.69-0.95) and 0.74 (0.61-0.90), respectively) compared with men (0.86 (0.80-0.94) and 0.81 (0.73-0.90), respectively), Pinteraction = 0.48 and 0.44, respectively. Adverse events were more common in women and with increasing age but, with the exception of injection site reactions, there were no important significant differences reported by those assigned evolocumab versus placebo. CONCLUSIONS: The efficacy and safety of evolocumab are similar throughout a broad range of ages and in both men and women.

[35] *Tillmann T*. **New risk prediction models in England may lead to targeted PCSK9 inhibitor treatment, for patients with established cardiovascular disease**. European journal of preventive cardiology 2020:2047487320904513.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32019368
ABSTRACT

[36] *Grygoruk S, Sirko A, Dudukina S, Matsuga O*. **SURVIVAL RATE IN PATIENTS WITH MULTIFOCAL ATHEROSCLEROSIS WHO UNDERWENT SURGICAL CAROTID AND CORONARY REVASCULARISATION**. Georgian medical news 2019:18-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011289
ABSTRACT
Aim - short-term outcomes of cerebral and coronary artery revascularisation surgeries performed with different methods and different timing have been well studied, but the long-term outcomes have not. The study aim was to determine the long-term survival rates in patients with combined atherosclerotic cerebral and coronary artery lesions who underwent surgical revascularisation of both territories. We evaluated the survival functions of six groups of patients with combined atherosclerotic cerebral and coronary artery lesions who underwent revascularisation using different methods in different sequences and at different time periods of both territories. Survival in each group was determined from postoperative Day 30 by using the Kaplan-Meier method and compared by using the log-rank test. Survival was also compared among the groups in which alternative methods of carotid and coronary territories revascularisation were used. The 5-year survival rates were similar between patients who underwent endovascular revascularisation of both territories (cerebral and coronary arteries stenting) or combined surgery (coronary arteries stenting + carotid endarterectomy). The 5-10-

year survival rate was higher in patients who underwent combined surgery than in the other patients (p=0.026). The main causes of death in all groups were cardiac or cerebral events. The 10-year survival rates did not significantly differ between patients who underwent cerebral artery stenting prior to coronary artery bypass grafting and those who underwent simultaneous carotid endarterectomy + coronary artery bypass grafting (p=0.532). The results of this study can be useful for selecting the tactics of surgical cerebral and coronary artery revascularisation, identifying the sequence of respective surgeries and time management.

[37] *Trivedi AN, Kelaher M*. **Copayment Incentive Increased Medication Use And Reduced Spending Among Indigenous Australians After 2010**. Health affairs (Project Hope) 2020; 39:289-296.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32011934
ABSTRACT
Australian health policy has prioritized efforts to close the ten-year life expectancy gap between indigenous and nonindigenous Australians, a disparity largely driven by cardiovascular disease and diabetes. Because out-of-pocket spending poses a barrier to accessing medications for chronic conditions, in 2010 the Australian government reduced or eliminated medication copayments for indigenous people with chronic disease or risk factors for chronic disease. In this quasi-experimental study we found that the copayment reductions were associated with a 39 percent relative increase in the use of medications and a 61 percent reduction in out-of-pocket spending. Among indigenous Australians who qualified for the largest copayment reductions, overall use of medications increased by 156 percent-including increases of 26-109 percent in the use of lipid-lowering, hypertension, and diabetes medications. These findings suggest that Australia's novel strategy of targeted copayment reductions improved access to prescription medications among indigenous Australians, a population with a high burden of chronic conditions and marked social disadvantage.

[38] *Zanetti D, Bergman H, Burgess S et al.* **Urinary Albumin, Sodium, and Potassium and Cardiovascular Outcomes in the UK Biobank: Observational and Mendelian Randomization Analyses**. Hypertension 2020:Hypertensionaha11914028.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32008434
ABSTRACT
Urinary biomarkers are associated with cardiovascular disease, but the nature of these associations is not well understood. We performed multivariable-adjusted regression models to assess associations of random spot measurements of the urine sodium-potassium ratio (UNa/UK) and urine albumin adjusted for creatinine with cardiovascular risk factors, cardiovascular disease, and type 2 diabetes mellitus (T2D) in 478 311 participants of the UK Biobank. Further, we assessed the causal relationships of these kidney biomarkers, used as proxies for kidney function, with cardiovascular outcomes using the 2-sample Mendelian randomization approach. In observational analyses, UNa/UK showed significant inverse associations with atrial fibrillation, coronary artery disease, ischemic stroke, lipid-lowering medication, and T2D. In contrast, urine albumin adjusted for creatinine showed significant positive associations with atrial fibrillation, coronary artery disease, heart failure, hemorrhagic stroke, lipid-lowering medication, and T2D. We found a positive association between UNa/UK and albumin with blood pressure (BP), as well as with adiposity-related measures. After correcting for potential horizontal pleiotropy, we found evidence of causal associations of UNa/UK and albumin with BP (beta systolic BP >/=2.63; beta diastolic BP >/=0.85 SD increase in BP per SD change in UNa/UK and urine

albumin adjusted for creatinine; P</=0.04), and of albumin with T2D (odds ratio=1.33 per SD change in albumin, P=0.02). Our comprehensive study of urinary biomarkers performed using state-of-the-art analyses of causality mirror and extend findings from randomized interventional trials which have established UNa/UK as a risk factor for hypertension. In addition, we detect a causal feedback loop between albumin and hypertension, and our finding of a bidirectional causal association between albumin and T2D reflects the well-known nephropathy in T2D.

[39] *Han T, Paramsothy P, Hong J et al.* **High-resolution MRI assessed carotid atherosclerotic plaque characteristics comparing men and women with elevated ApoB levels**. The international journal of cardiovascular imaging 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32020410
ABSTRACT
Previous studies demonstrated that men were more likely to have plaque rupture and are at greater risk for myocardial infarction and stroke than women. We evaluated differences in carotid plaque characteristics by MRI between men and women with mild-moderate atherosclerosis and elevated ApoB levels. One hundred eighty-two subjects (104 men and 78 women) with CAD or carotid stenosis (>/= 15% by ultrasound), ApoB >/= 120 mg/dL and carotid MRI scan were included. Percent wall volume (%WV) was calculated as (wall volume/total vessel volume) x 100%. Three major plaque compositions, fibrous tissue (FT), calcification (CA) and lipid rich necrotic core (LRNC), were identified and quantified using published MRI criteria. Adventitial and plaque neovascularization as fractional plasma volume (Vp) and permeability as transfer constant (K(trans)) were analyzed using kinetic modeling. These characteristics were compared between men and women. Men, compared to women, were younger (54 +/- 8 vs. 58 +/- 8 years, p = 0.01), had higher rate of previous MI (46 vs. 26%, p = 0.005) but lower proportions of metabolic syndrome (37 vs. 59%, p = 0.003). After adjusting for between-gender differences, men were significantly more likely to have LRNC (OR 2.22, 95% CI 1.04-4.89, p = 0.04) and showed significantly larger %LRNC than women (diff = 4.3%, 95% CI 1.6-6.9%, p = 0.002), while %WV, FT, and CA were similar between men and women. There were no statistically significant differences in adventitial and plaque Vp or K(trans). Men were significantly more likely to have LRNC and had larger LRNC than women. However, men and women showed relatively similar levels of adventitial and plaque neovascularization and permeability.Trial registration: NCT00715273 at ClinicalTrials.gov. Registered 15 July 2008, retrospectively registered.

[40] *Lee HC, Lin YH*. **The Pathogenic Role of Very Low Density Lipoprotein on Atrial Remodeling in the Metabolic Syndrome**. International journal of molecular sciences 2020; 21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32019138
ABSTRACT
Atrial fibrillation (AF) is the most common persistent arrhythmia, and can lead to systemic thromboembolism and heart failure. Aging and metabolic syndrome (MetS) are major risks for AF. One of the most important manifestations of MetS is dyslipidemia, but its correlation with AF is ambiguous in clinical observational studies. Although there is a paradoxical relationship between fasting cholesterol and AF incidence, the beneficial benefit from lipid lowering therapy in reduction of AF is significant. Here, we reviewed the health burden from AF and MetS, the association between two disease entities, and the metabolism of triglyceride, which is elevated in MetS. We also reviewed scientific evidence for the mechanistic links between very low density lipoproteins (VLDL), which

primarily carry circulatory triglyceride, to atrial cardiomyopathy and development of AF. The effects of VLDL to atria suggesting pathogenic to atrial cardiomyopathy and AF include excess lipid accumulation, direct cytotoxicity, abbreviated action potentials, disturbed calcium regulation, delayed conduction velocities, modulated gap junctions, and sarcomere protein derangements. The electrical remodeling and structural changes in concert promote development of atrial cardiomyopathy in MetS and ultimately lead to vulnerability to AF. As VLDL plays a major role in lipid metabolism after meals (rather than fasting state), further human studies that focus on the effects/correlation of postprandial lipids to atrial remodeling are required to determine whether VLDL-targeted therapy can reduce MetS-related AF. On the basis of our scientific evidence, we propose a pivotal role of VLDL in MetS-related atrial cardiomyopathy and vulnerability to AF.

[41] *Agar R, Prendergast M, Maher V*. **Evaluation of lipid services in the Republic of Ireland**. Irish journal of medical science 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32030623
ABSTRACT
BACKGROUND: Abnormal cholesterol profiles are a major risk factor for cardiovascular disease and severe triglyceride disorders cause life threatening pancreatitis. Identification and treatment of these disorders are essential. AIM: We evaluated the services available in Ireland to manage these problems. METHODS: We contacted key personnel in 40 hospitals, 32 public and 8 private providing lipid measurements to assess investigation and treatment availability during 2017/2018. RESULTS: In public hospitals, 4 had designated lipid clinics (Dublin 3, Galway 1) (2.9 times < UK), 19 had general clinics and 9 had no service. In private hospitals, 2 had designated clinics, Limerick and Cork, and others had interested physicians. Clinics were run by cardiologists, chemical pathologists, endocrinologists or clinical pharmacologists. One clinic had a lipid nurse versus 75% in the UK. All but one provided full lipid profiles, 15 ordered Lp(a), 9 apoproteins B/A-1 and 9 genetic testing. Lp(a) and apoprotein measurements were provided locally in one hospital and one provided genetic testing. Lipid-lowering drugs were used in all hospitals and 45% had access to PCSK-9 inhibitors. No hospital provided LDL apheresis or plasma exchange. Limitations for service provision included lack of physician interest n = 9, nursing support n = 22, office space n = 13, clinic space n = 22, laboratory support n = 16, nutritional support n = 12 and pharmacy support n = 5. CONCLUSIONS: There are very limited resources available to manage lipid problems in the republic of Ireland relative to the under-resourced UK. Most services rely on interested physicians but ancillary resources are lacking. Where services are available, all drug treatments are utilised.

[42] *Korhonen MJ, Pentti J, Hartikainen J et al.* **Lifestyle Changes in Relation to Initiation of Antihypertensive and Lipid-Lowering Medication: A Cohort Study**. Journal of the American Heart Association 2020; 9:e014168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32019405
ABSTRACT
Background Lifestyle modification is a key component of cardiovascular disease prevention before and concurrently with pharmacologic interventions. We evaluated whether lifestyle factors change in relation to the initiation of antihypertensive or lipid-lowering medication (statins). Methods and Results The study population comprised 41 225 participants of the FPS (Finnish Public Sector) study aged >/=40 years who were free of cardiovascular disease at baseline and responded to >/=2

consecutive surveys administered in 4-year intervals in 2000-2013. Medication use was ascertained through pharmacy-claims data. Using a series of pre-post data sets, we compared changes in body mass index, physical activity, alcohol consumption, and smoking between 8837 initiators and 46 021 noninitiators of antihypertensive medications or statins. In participants who initiated medication use, body mass index increased more (difference in change 0.19; 95% CI, 0.16-0.22) and physical activity declined (-0.09 metabolic equivalent of task hour/day; 95% CI, -0.16 to -0.02) compared with noninitiators. The likelihood of becoming obese (odds ratio: 1.82; 95% CI, 1.63-2.03) and physically inactive (odds ratio: 1.08; 95% CI, 1.01-1.17) was higher in initiators. However, medication initiation was associated with greater decline in average alcohol consumption (-1.85 g/week; 95% CI, -3.67 to -0.14) and higher odds of quitting smoking (odds ratio for current smoking in the second survey: 0.74; 95% CI, 0.64-0.85). Conclusions These findings suggest that initiation of antihypertensive and statin medication is associated with lifestyle changes, some favorable and others unfavorable. Weight management and physical activity should be encouraged in individuals prescribed these medications.

[43] *Quispe R, Michos ED, Martin SS et al.* **High-Sensitivity C-Reactive Protein Discordance With Atherogenic Lipid Measures and Incidence of Atherosclerotic Cardiovascular Disease in Primary Prevention: The ARIC Study**. Journal of the American Heart Association 2020; 9:e013600.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013698

ABSTRACT

Background Inflammation is an independent causal risk factor for atherosclerotic cardiovascular diseases (ASCVDs). However, whether hsCRP (high-sensitivity C-reactive protein) is prognostic across various levels of atherogenic lipid measures such as low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B and total cholesterol/high-density lipoprotein cholesterol in primary prevention is unknown. Methods and Results We studied 9748 ARIC (Atherosclerosis Risk in Communities) study participants who were free of ASCVD at baseline (visit 4, 1996-1998) and had measurements of lipids, apolipoprotein B, and hsCRP. We used multivariable adjusted Cox models to estimate the risk of incident ASCVD events associated with hsCRP levels (less than/greater than or equal to median) in individuals where triple lipid measures combined (low-density lipoprotein cholesterol + non-high-density lipoprotein cholesterol + apolipoprotein B) or quadruple measures combined [triple + total cholesterol/high-density lipoprotein cholesterol] were less than versus greater than or equal to median cut points. Mean age of participants was 62.6+/-5.6 years; 59% women, 22% black. There were 1574 ASCVD events over median (interquartile range) follow-up of 18.4 (12.8-19.5) years, and discordance between hsCRP and lipid measures was prevalent in 50% of the population. hsCRP greater than or equal to median (2.4 mg/L), compared with less than median, was associated with an increased risk of ASCVD in individuals with less than median levels of the triple (adjusted hazard ratio, 1.33; 95% CI, 1.09-1.60) and quadruple (adjusted hazard ratio,1.47; 95% CI, 1.18-1.85) lipid measures. Such increased risk was consistent among individuals with low (<7.5%) or high (>/=7.5%) estimated risk by the pooled cohort equation. There were no interactions by sex, diabetes mellitus, or statin use. Conclusions Our findings suggest that inflammation is independently associated with ASCVD regardless of atherogenic lipid levels and pooled cohort equation risk score in individuals without known ASCVD.

[44] *Masson W, Huerin M, Lobo LM et al.* **Impact of the 2019 European Guidelines on Diabetes in Clinical Practice: Real and Simulated Analyses of Lipid Goals**. Journal of cardiovascular development and disease 2020; 7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32033316
ABSTRACT
BACKGROUND: Recent European guidelines on diabetes, prediabetes, and cardiovascular disease developed for the European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) significantly changed some concepts on risk stratification, lipid goals, and recommendations for the use of lipid-lowering drugs. The objectives of this work were to describe the lipid-lowering treatment prescribed for patients with diabetes and to determine the percentage of patients that achieved the lipid goals recommended by the 2019 ESC/EASD Guidelines on Diabetes in real and simulated scenarios. METHODS: A multicenter, cross-sectional study was performed. Subjects >18 years with type 2 diabetes were included. The recommendations of the 2019 ESC/EASD Guidelines were followed. The real and simulated (ideal setting using adequate doses of statins +/- ezetimibe) scenarios were analyzed. RESULTS: Overall, 528 patients were included. In total, 62.5% of patients received statins (17.1% high intensity). Most patients were stratified as "very high risk" (54.2%) or "high risk" (43.4%). Only 13.3% achieved the double lipid goal (LDL-C and non-HDL-C goals according to the risk categories). In the simulation analysis, the proportion of subjects that did not reach the therapeutic objective decreased in all risk strata, although a considerable proportion of subjects persisted outside the target. CONCLUSION: The difficulty of achieving lipid goals in diabetic patients was considerable when applying the new guidelines. The situation would improve if we optimized treatment, but the prescription of new lipid-lowering drugs could be limited by their high cost.

[45] *Souza DR, Pieri B, Comim VH et al.* **Fish oil reduces subclinical inflammation, insulin resistance, and atherogenic factors in overweight/obese type 2 diabetes mellitus patients: A pre-post pilot study**. Journal of diabetes and its complications 2020:107553.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32014347
ABSTRACT
OBJECTIVE: Insulin resistance-associated obesity and type 2 diabetes mellitus (T2DM) are commonly accompanied with metabolic lipid abnormalities and are characterized by hypertriglyceridemia and low HDL-c levels (atherogenic index plasma, AIP). The primary molecular mechanism that is known to cause insulin resistance is chronic low-grade inflammation. Considering that omega-3 fatty acid reduces subclinical inflammation, we hypothesized that fish oil could affect insulin resistance and AIP. Therefore, the present study evaluated the effects of fish oil supplementation on the inflammatory, insulin resistance, and atherogenic factors in overweight/obese T2DM patients. RESEARCH DESIGNS AND METHODS: In this study, we recruited 32 overweight and/or obese patients diagnosed with T2DM for over one year and who exhibited hypertriglyceridemia. These patients received fish oil supplementation (4.0g/day) for eight weeks. Anthropometric and body composition measurements were obtained. In addition, blood samples were collected before and after omega-3 supplementation for the evaluation of lipid profile, glycemia, insulin, and inflammation. RESULTS: As expected, patients showed reduction in the TNFalpha, IL-1beta, and Il-6 levels after fish oil supplementation and showed improved insulin sensitivity (HOMA-IR) without observed alterations in anthropometric and body composition. These observations were followed by reduction in the levels of triglycerides and non-esterified fatty acids, increase in HDL cholesterol levels, and a significant reduction in

triglycerides/HDL-c ratio, and total cholesterol/HDL-c ratio. CONCLUSION: Fish oil supplementation is effective in reducing the levels of proinflammatory cytokines, improving insulin resistance, and reducing atherogenic factors in overweight/obese and T2DM patients independent of weight loss.

[46] *Sun CJ, McCudden C, Brisson D et al.* **Calculated Non-HDL Cholesterol Includes Cholesterol in Larger Triglyceride-Rich Lipoproteins in Hypertriglyceridemia**. Journal of the Endocrine Society 2020; 4:bvz010.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32010872
ABSTRACT
Context: Calculated non-high-density lipoprotein (HDL) cholesterol (non-HDLC) should selectively include cholesterol from atherogenic lipoproteins to be a reliable risk marker of cardiovascular disease. In hypertriglyceridemia (HTG), there is increased abundance of larger and less atherogenic triglyceride-rich lipoproteins (TRL), namely, larger very-low-density lipoproteins (VLDL), and chylomicrons. Objective: We aim to demonstrate that serum triglyceride (TG) level has a substantial impact on non-HDLC's ability to represent cholesterol from atherogenic lipoproteins, even though TG is not part of the calculation for non-HDLC. Design: Analysis of lipid profile data. Settings: Lipid Clinic patient cohort, and Biochemistry Laboratory patient cohort. Patients or Other Participants: 7,492 patients in the Lipid Clinic cohort with baseline lipid profiles documented prior to starting lipid-lowering medications and 156,311 lipid profiles from The Ottawa Hospital Biochemistry Laboratory cohort. Intervention: None. Main Outcome Measure: Our modeling process includes derivation of TG-interval-specific lipoprotein composition factor (LCF) for TRL, which represents the mass ratio of cholesterol to TG in TRL. A high LCF indicates that the TRLs are mainly the cholesterol-rich atherogenic remnant lipoproteins. A low LCF indicates that the TRLs are mainly the TG-rich larger VLDL and chylomicrons. Results: As serum TG increases, there is progressive decline in the LCF for TRL, which indicates that the calculated non-HDLC level reflects progressive inclusion of cholesterol from larger TRL. This is shown in both cohorts. Conclusions: Calculated non-HDLC is influenced by TG level. As TG increases, non-HDLC gradually includes more cholesterol from larger TRL, which are less atherogenic than LDL and remnant lipoproteins.

[47] *Lee EJ, Kwon SU, Park JH et al.* **Changes in High-Density Lipoprotein Cholesterol and Risks of Cardiovascular Events: A Post Hoc Analysis from the PICASSO Trial**. J Stroke 2020; 22:108-118.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32027796
ABSTRACT
BACKGROUND AND PURPOSE: Whether pharmacologically altered high-density lipoprotein cholesterol (HDL-C) affects the risk of cardiovascular events is unknown. Recently, we have reported the Prevention of Cardiovascular Events in Asian Patients with Ischaemic Stroke at High Risk of Cerebral Haemorrhage (PICASSO) trial that demonstrated the non-inferiority of cilostazol to aspirin and superiority of probucol to non-probucol for cardiovascular prevention in ischemic stroke patients (clinicaltrials.gov: NCT01013532). We aimed to determine whether on-treatment HDL-C changes by cilostazol and probucol influence the treatment effect of each study medication during the PICASSO study. METHODS: Of the 1,534 randomized patients, 1,373 (89.5%) with baseline cholesterol parameters were analyzed. Efficacy endpoint was the composite of stroke, myocardial infarction, and cardiovascular death. Cox proportional hazards regression analysis examined an interaction between the treatment effect and changes in HDL-C levels from randomization to 1 month for each study arm.

RESULTS: One-month post-randomization mean HDL-C level was significantly higher in the cilostazol group than in the aspirin group (1.08 mmol/L vs. 1.00 mmol/L, P<0.001). The mean HDL-C level was significantly lower in the probucol group than in the non-probucol group (0.86 mmol/L vs. 1.22 mmol/L, P<0.001). These trends persisted throughout the study. In both study arms, no significant interaction was observed between HDL-C changes and the assigned treatment regarding the risk of the efficacy endpoint. CONCLUSIONS: Despite significant HDL-C changes, the effects of cilostazol and probucol treatment on the risk of cardiovascular events were insignificant. Pharmacologically altered HDL-C levels may not be reliable prognostic markers for cardiovascular risk.

[48] *Shen Y, Shi L, Nauman E et al.* **Association between Hemoglobin A1c and Stroke Risk in Patients with Type 2 Diabetes**. J Stroke 2020; 22:87-98.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32027794
ABSTRACT
BACKGROUND AND PURPOSE: The association between hemoglobin A1c (HbA1c) and stroke risk along with its subtypes is rarely reported. We aimed to investigate the association between HbA1c and the risk of incident stroke in patients with type 2 diabetes based on real world data from three healthcare systems. METHODS: We performed a retrospective cohort study of 27,113 African Americans and 40,431 whites with type 2 diabetes. Demographic, anthropometric, laboratory, and medication information were abstracted from the National Patient-Centered Clinical Research Network common data model. Incident stroke events including both ischemic and hemorrhagic stroke were defined. RESULTS: During a mean follow-up period of 3.79+/-1.68 years, 7,735 patients developed stroke (6,862 ischemic and 873 hemorrhagic). Multivariable-adjusted hazard ratios across levels of HbA1c at baseline (<6.0%, 6.0% to 6.9% [reference group], 7.0% to 7.9%, 8.0% to 8.9%, 9.0% to 9.9%, and >/=10%) were 1.07, 1.00, 1.13, 1.23, 1.27, and 1.37 (Ptrend <0.001) for total stroke, 1.02, 1.00, 1.13, 1.20, 1.24, and 1.35 (Ptrend <0.001) for ischemic stroke, and 1.40, 1.00, 1.14, 1.47, 1.47, and 1.51 (Ptrend=0.002) for hemorrhagic stroke. When we used an updated mean value of HbA1c, the U-shaped association of HbA1c with stroke risk did not change. This U-shaped association was consistent among patients of different subgroups. The U-shaped association was more pronounced among patients taking antidiabetic, lipid-lowering, and antihypertensive medications compared with those without these medications. CONCLUSIONS: These data suggest that diabetes management may have to be individualized according to the guideline recommendations rather than intensively attempting to lower HbA1c.

[49] *Xenoulis PG, Cammarata PJ, Walzem RL et al.* **Serum triglyceride and cholesterol concentrations and lipoprotein profiles in dogs with naturally occurring pancreatitis and healthy control dogs**. Journal of veterinary internal medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32012351
ABSTRACT
BACKGROUND: Previous studies have reported an association between hyperlipidemia and pancreatitis in dogs, but details of this association remain poorly defined. HYPOTHESIS/OBJECTIVES: To compare serum triglyceride and cholesterol concentrations and lipoprotein profiles between dogs with naturally occurring pancreatitis and healthy dogs. ANIMALS: Seventeen dogs with a clinical diagnosis of pancreatitis (Group 1) and 53 healthy control dogs (Group 2). METHODS: Prospective case-control study. RESULTS: In Group 1, 3/17 dogs (18%) had hypertriglyceridemia whereas in Group 2, 4/53 dogs

(7.5%) had hypertriglyceridemia (odds ratio [OR], 2.63; 95% confidence interval [CI], 0.52-13.14; P = .35). A significant difference was found in serum triglyceride concentrations between Group 1 (median, 67 mg/dL) and Group 2 (median, 54 mg/dL; P = .002). In Group 1, 4/17 dogs (24%) had hypercholesterolemia, whereas 1/53 (1.9%) dogs in Group 2 had hypercholesterolemia (OR, 16; 95% CI, 1.64-155.5; P = .01). No significant difference was found in serum cholesterol concentrations between Group 1 (median, 209 mg/dL) and Group 2 (median, 227 mg/dL; P = .56). Lipoprotein profiles were significantly different between Group 1 and Group 2 dogs (Eigenvalues, 0.6719; R(2) = 1.0; P = .001). CONCLUSIONS AND CLINICAL IMPORTANCE: Most dogs with pancreatitis (>70%) had serum triglyceride and cholesterol concentrations within reference intervals. In the small percentage of dogs that had hypertriglyceridemia, hypercholesterolemia, or both, increases were mild. Important differences were identified in lipoprotein profiles between dogs with pancreatitis and healthy control dogs. Dogs with pancreatitis had higher low-density lipoprotein fractions and lower triglyceride-rich lipoprotein and high-density lipoprotein fractions than healthy dogs.

[50] *Mbikay M, Mayne J, Chretien M*. **The enigma of soluble LDLR: could inflammation be the key?** Lipids in health and disease 2020; 19:17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32014013
ABSTRACT
Soluble low-density lipoprotein receptor (sLDLR) is the circulating ectodomain of transmembrane LDLR. Its blood level strongly correlates with that of triglycerides (TG). This correlation has eluded satisfactory explanation. Hypertriglyceridemia and shedding of the ectodomain of many transmembrane receptors often accompany inflammatory states. The shedding mostly occurs through cleavage by a disintegrin-and-metalloproteinase-17 (ADAM-17), an enzyme activated by inflammation. It reduces the cellular uptake of TG-loaded lipoproteins, causing their accumulation in circulation; hence the correlation between plasma sLDLR and TG. Soluble LDLR could become a new surrogate marker of inflammation.

[51] *Zhu L, Sha L, Li K et al.* **Dietary flaxseed oil rich in omega-3 suppresses severity of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in rats**. Lipids in health and disease 2020; 19:20.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32028957
ABSTRACT
BACKGROUND: Type 2 diabetes mellitus (T2DM) is closely associated with hyperglycemia, abnormal lipid profiles, chronic low-grade inflammation and gut dysbiosis. Dietary intervention plays a crucial role in the control of diabetes. Flaxseed oil (FO), a plant-derived omega-3 (omega-3) polyunsaturated fatty acids (PUFAs), is rich in alpha-linolenic acid (ALA) which has been proved to benefit for chronic metabolic disease. However, the exact effects of dietary FO on T2DM remains largely unclear. METHODS: In the present study, SD rats were randomly allocated into four groups: pair-fed (PF) with corn oil (CO) group (PF/CO); DM with CO group (DM/CO); PF with FO group (PF/FO); DM with FO group (DM/FO). A diabetic rat model was generated by a single intraperitoneal injection of streptozotocin-nicotinamide (STZ-NA). After 5 weeks of intervention, rats were euthanized and associated indications were investigated. RESULTS: Dietary FO significantly reduced fasting blood glucose (FBG), glycated hemoglobin (GHb), blood lipid, plasma lipopolysaccharide (LPS), interleukin (IL)-1beta, tumor necrosis factor (TNF)-alpha, IL-6, IL-17A and malondialdehyde (MDA), compared to control group, respectively.

Moreover, body mass (BM) and superoxide dismutase (SOD) in DM/FO group were dramatically increased respectively, compared with those in DM/CO group. But insulin (INS) and homeostasis model assessment of insulin resistance (HOMA-IR) remained no significant difference between DM/CO group and DM/FO group. Sequencing analysis of gut microbiota showed a reduction in the relative abundance of Firmicutes and Blautia, as well as a reduction in the ratio of Bacteroidetes-Firmicutes in DM/FO group compared to DM/CO group. An elevation in the relative abundance of Bacteroidetes and Alistipes were detected in DM/FO group. Acetic acid, propionic acid and butyric acid belonging to short chain fatty acids (SCFAs) as gut microbiota metabolites, were dramatically increased after FO intervention. Correlation analysis revealed that the relative abundance of Firmicutes and Blautia were positively correlated with IL-1beta, TNF-alpha, IL-6, IL-17A or LPS, respectively. Additionally, Bacteroidetes and Alistipes were negatively correlated with LPS. CONCLUSIONS: Taken together, dietary FO ameliorated T2DM via suppressing inflammation and modulating gut microbiota, which may potentially contribute to dietary control of diabetes.

[52] *Pandak WM, Kakiyama G*. **The acidic pathway of bile acid synthesis: Not just an alternative pathway()**. Liver research 2019; 3:88-98.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32015930
ABSTRACT
Over the last two decades, the prevalence of obesity, and metabolic syndromes (MS) such as non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM), have dramatically increased. Bile acids play a major role in the digestion, absorption of nutrients, and the body's redistribution of absorbed lipids as a function of their chemistry and signaling properties. As a result, a renewed interest has developed in the bile acid metabolic pathways with the challenge of gaining insight into novel treatment approaches for this rapidly growing healthcare problem. Of the two major pathways of bile acid synthesis in the liver, the foremost role of the acidic (alternative) pathway is to generate and control the levels of regulatory oxysterols that help control cellular cholesterol and lipid homeostasis. Cholesterol transport to mitochondrial sterol 27-hydroxylase (CYP27A1) by steroidogenic acute regulatory protein (StarD1), and the subsequent 7alpha-hydroxylation of oxysterols by oxysterol 7alpha-hydroxylase (CYP7B1) are the key regulatory steps of the pathway. Recent observations suggest CYP7B1 to be the ultimate controller of cellular oxysterol levels. This review discusses the acidic pathway and its contribution to lipid, cholesterol, carbohydrate, and energy homeostasis. Additionally, discussed is how the acidic pathway's dysregulation not only leads to a loss in its ability to control cellular cholesterol and lipid homeostasis, but leads to inflammatory conditions.

[53] **Reduction of cardiovascular risk with icosapent ethyl (Vascepa)**. The Medical letter on drugs and therapeutics 2020; 62:17-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32022786
ABSTRACT

[54] *Grunwald SA, Popp O, Haafke S et al.* **Statin-induced myopathic changes in primary human muscle cells and reversal by a prostaglandin F2 alpha analogue**. Scientific reports 2020; 10:2158.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32034223
ABSTRACT

Statin-related muscle side effects are a constant healthcare problem since patient compliance is dependent on side effects. Statins reduce plasma cholesterol levels and can prevent secondary cardiovascular diseases. Although statin-induced muscle damage has been studied, preventive or curative therapies are yet to be reported. We exposed primary human muscle cell populations (n = 22) to a lipophilic (simvastatin) and a hydrophilic (rosuvastatin) statin and analyzed their expressome. Data and pathway analyses included GOrilla, Reactome and DAVID. We measured mevalonate intracellularly and analyzed eicosanoid profiles secreted by human muscle cells. Functional assays included proliferation and differentiation quantification. More than 1800 transcripts and 900 proteins were differentially expressed after exposure to statins. Simvastatin had a stronger effect on the expressome than rosuvastatin, but both statins influenced cholesterol biosynthesis, fatty acid metabolism, eicosanoid synthesis, proliferation, and differentiation of human muscle cells. Cultured human muscle cells secreted omega-3 and omega-6 derived eicosanoids and prostaglandins. The omega-6 derived metabolites were found at higher levels secreted from simvastatin-treated primary human muscle cells. Eicosanoids rescued muscle cell differentiation. Our data suggest a new aspect on the role of skeletal muscle in cholesterol metabolism. For clinical practice, the addition of omega-n fatty acids might be suitable to prevent or treat statin-myopathy.

[55] *McWilliam SJ, Rosala-Hallas A, Jones AP et al.* **A randomised controlled trial of rosuvastatin for the prevention of aminoglycoside-induced kidney toxicity in children with cystic fibrosis**. Scientific reports 2020; 10:1796.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32020028
ABSTRACT
The PROteKT study tested the hypothesis that rosuvastatin can inhibit aminoglycoside-induced nephrotoxicity in children with Cystic Fibrosis (CF). This open label, parallel group, randomised controlled trial recruited children and young people aged 6 to 18 years with CF at 13 paediatric CF treatment centres in the UK. Participants were randomised equally to either receive oral rosuvastatin (10 mg once daily) or no intervention (control) throughout clinically indicated treatment with intravenous tobramycin. The primary outcome was the difference between the groups in mean fold-change in urinary Kidney Injury Molecule-1 (KIM-1). Fifty (rosuvastatin n = 23, control n = 27) participants were recruited between May 2015 and January 2017. Primary outcome data was available for 88% (rosuvastatin n = 20, control n = 24). The estimated mean treatment difference in the geometric mean-fold change of normalised KIM-1 was 1.08 (95% CI 0.87-1.35, p = 0.48). In total there were 12 adverse reactions, all mild, reported by five participants randomised to rosuvastatin, and one serious adverse event in each group. Whilst no protective effect of rosuvastatin was seen, there was a lower than expected level of nephrotoxicity in the cohort. Therefore, we can neither confirm nor refute the hypothesis that rosuvastatin protects against aminoglycoside nephrotoxicity.

[56] *Lee KA, Staveski SL*. **Is adequate sleep enough, or is it time to add lipid-lowering medication to prenatal vitamin recommendations to improve infant outcomes?** Sleep medicine 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32029364
ABSTRACT

Literature update week 06 (2020)

[57] *Baum SJ, Wade RL, Xiang P et al.* **Demographic And Clinical Characteristics Of Patients Prescribed Proprotein Convertase Subtilisin/kexin Type 9 Inhibitor Therapy And Patients Whose Current Lipid-Lowering Therapy Was Modified**. Therapeutics and clinical risk management 2019; 15:1325-1332.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32009789

ABSTRACT

Purpose: Our objective was to describe the demographic and clinical characteristics of real-world patients in the US with elevated low-density lipoprotein cholesterol (LDL-C) whose lipid-lowering therapy (LLT) horizontal line both proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor and non-PCSK9 inhibitor horizontal line was actively modified. Methods: This retrospective cohort study used linked laboratory (Prognos), pharmacy (IMS Formulary Impact Analyzer), and medical claims (IQVIA Dx/LRx or PharMetrics Plus) data. PCSK9 inhibitor-prescribed patients with LDL-C >/=70 mg/dL (multiply by 0.02586 for mmol/L) at the time of prescription were matched by LDL-C test date to patients whose non-PCSK9 inhibitor therapy was modified by intensifying statin therapy, switching statins without intensification, or augmenting with ezetimibe (N=12,345 in each cohort). Baseline demographics, use of LLT, LDL-C values, atherosclerotic cardiovascular disease (ASCVD) diagnoses and cardiovascular comorbidities, and occurrence of major adverse cardiovascular events (MACE) were assessed during the 2-year pre-index period. Results: Mean age was 66.2 years in the PCSK9 inhibitor cohort and 64.1 years in the cohort whose LLT regimen was otherwise modified. Respectively, mean baseline LDL-C values were 150 and 121 mg/dL; 60.3% and 39.0% of patients had ASCVD diagnoses, and 9.6% and 5.1% had experienced a recent MACE. Prevalence of ASCVD diagnoses in the PCSK9 inhibitor and modified non-PCSK9 inhibitor cohorts, respectively, was 15.5% vs 9.1% for acute coronary syndrome, 20.7% vs 8.7% for coronary revascularization, and 22.2% vs 5.1% for possible familial hypercholesterolemia. In addition, 19.8% of patients in the PCSK9 inhibitor cohort were receiving both statins and ezetimibe vs 5.0% in the modified LLT cohort. Conclusion: Physicians are prescribing PCSK9 inhibitor therapy to patients with markedly elevated LDL-C levels who also have comorbid risk factors for adverse cardiovascular events. These results may be of interest to payers and policymakers involved in devising access strategies for PCSK9 inhibitors.

[58] *Blauw LL, Wang Y, Willems van Dijk K, Rensen PCN*. **A Novel Role for CETP as Immunological Gatekeeper: Raising HDL to Cure Sepsis?** Trends in endocrinology and metabolism: TEM 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32033866

ABSTRACT

Raising HDL using cholesteryl ester transfer protein (CETP) inhibitors failed to show a clinically relevant risk reduction of cardiovascular disease in clinical trials, inviting reconsideration of the role of CETP and HDL in human physiology. Based on solid evidence from studies with isolated macrophages, rodents, and humans, we propose that a major function of CETP may be to modulate HDL in order to help resolve bacterial infections. When gram-negative bacteria invade the blood, as occurs in sepsis, Kupffer cells lose their expression of CETP to increase HDL levels. This rise in HDL prevents systemic endotoxemia by binding lipopolysaccharide and induces a systemic proinflammatory response in macrophages to mediate bacterial clearance. This raises the interesting possibility to repurpose CETP inhibitors for the treatment of sepsis.

Literature update week 06 (2020)

[59] *Alonso R, Perez de Isla L, Muniz-Grijalvo O, Mata P*. **Barriers to Early Diagnosis and Treatment of Familial Hypercholesterolemia: Current Perspectives on Improving Patient Care**. Vascular health and risk management 2020; 16:11-25.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32021224
ABSTRACT
Familial hypercholesterolemia (FH) is a frequent disorder associated with premature atherosclerotic cardiovascular disease. Different clinical diagnosis criteria are available, and cost of genetic testing has been reduced in the last years; however, most cases are not diagnosed worldwide. Patients with FH are at high cardiovascular risk and the risk can be reduced with lifelong lifestyle and pharmacological treatment. Statins and ezetimibe are available as generic drugs in most countries reducing the cost of treatment. However, the use of high-intensity statins combined with ezetimibe and PCSK9 inhibitors, if necessary, is low for different reasons that contribute to a high number of patients not reaching LDL-C targets according to guidelines. On the other hand, cardiovascular risk varies greatly in families with FH; therefore, risk stratification strategies including cardiovascular imaging is another element to consider for improving care and management of FH. There are numerous barriers depending on the awareness, knowledge, perception of risk, management and care of patients living with FH that impact in the diagnosis and treatment of the disorder. In this contemporary review, we analyze different barriers in the diagnosis and care of patients to improve patients' care and prevention of atherosclerotic cardiovascular disease and describe recent advances and strategies to improve the gaps in the care of FH, including global collaboration and advocacy.

[60] *Jia X, Koh S, Al Rifai M et al.* **Spotlight on Icosapent Ethyl for Cardiovascular Risk Reduction: Evidence to Date**. Vascular health and risk management 2020; 16:1-10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32021223
ABSTRACT
Icosapent ethyl is a highly purified formulation of eicosapentaenoic acid, a type of omega-3 fatty acid contained in fish oil. While omega-3 fatty acids have long been thought to have cardioprotective benefits, the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) has helped to establish icosapent ethyl as an evidence-based therapy for risk reduction of atherosclerotic cardiovascular disease (ASCVD). REDUCE-IT, however, was by no means an overnight success story. Close examination of the evidence shows that the trial was a culmination of many lessons learned from previous studies. The purpose of this manuscript is to review contemporary evidence of icosapent ethyl in ASCVD risk reduction and the clinical implication of this promising therapy.

[61] *Ceska R*. **Notes on the new “Recommendations for the treatment of dyslipidemia. Influencing of lipids to reduce cardiovascular risk&#8221**. Vnitr Lek 2020; 65:755-760.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013517
ABSTRACT
New guidelines on dyslipidemia (DLP) related problems appear earlier than planned. Primarily in view of the results of science and large clinical studies, but also with regard to the advent of biological therapy (PCSK9-i) in many Euro-pean countries. Also, the “conventional” hypolipidemic therapy is generified and therefore cheaper, more af-fordable. The recommendations are based, as the preceding ones, on the principle of estimating the overall cardiovascular risk. The innovated SCORE tables are used for this, but more emphasis is placed on non-invasive dia-gnostics using imaging

methods, be it carotid ultrasound or, in particular, non-contrast CT coronarography. Perhaps the most significant outcome is the reduction of LDL-cholesterol (LDL-C) target values to 1.4 mmol/l and a 50% reduction of baseline LDL-C in patients belonging to the highest risk groups, and in secondary prevention. Moreover, in the case of “extreme” risk the goal is to reduce LDL-C below 1 mmol/l. Essential to DLP therapy is statin treatment. Especially in patients with acute coronary syndrome and those in the highest risk categories, the maximum tolerated doses of statin should be used, if necessary in combination with ezetimibe. Where this maximum “routine” treatment is insufficient to achieve the target values, PCSK9-i therapy is indicated. However the recommendations do not by any means omit non-pharmacological therapy, quite the opposite, it is always emphasized as the first step of DLP therapy. Worthy of notice is the introduction of the term “atherosclerotic cardiovascular disease” - ASCVD, which replaces the older and less accurate CVD.

[62] *Fabryova U, Nemcova A*. **Hyperlipidemia management in Slovakia: observational study**. Vnitr Lek 2020; 65:761-769.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013518
ABSTRACT
AIM: A multicountry observational study was conducted to gain insight into the current management of elevated low density lipoprotein cholesterol (LDL-C) in high-risk (HR) and very high-risk (VHR) patients with hyperlipidaemia across central and eastern Europe and Israel. Here we present data from the Slovakian subpopulation. METHODS: We enrolled adult patients who were receiving lipid-lowering therapy (LLT) and attending a specialist (cardiologist/diabetologist/internist) for a routine visit at 9 sites (including academic/specialist centers) across Slovakia. Data were collected retrospectively from patients records for the 12 months preceding enrolment. RESULTS: 150 patients, mean (range) age 62.8 (26-84) years were enrolled, including 24 with familial hypercholesterolemia and 109 secon-dary prevention patients. Almost all patients (147; 98.0 %) were receiving statins, as monotherapy (114; 76.0 %) or in combination with other LLT (33; 22.0 %): 11 (7.3 %) were classified as having statin intolerance symptoms. Mean LDL-C levels were 3.0 (1.1-7.1) mmol/l at the first, and 2.6 (0.7-7.7) mmol/l at the last, visit of the observation period. Only 2/16 (12.5 %; 95 % CI 1.6-38.4 %) HR patients and 40/134 (29.9 %; 22.3-38.4 %) VHR patients achieved their recom-mended LDL-C targets of < 2.5 and < 1.8 mmol/l, respectively, during observation. In the FH subset 2/15 (13.3 %; 1.7-40.5 %) HR and 2/9 (22.2 %; 2.8-60.0 %) VHR patients achieved these targets. In patients with definite/probable FH (Dutch Lipid Clinic Network score 6), these targets were attained by 2/15 (13.3 %; 1.7-40.5) HR patients and 0/6 VHR patients. A total of 41 patients (27.3 %) experienced CV events (3) during the 12-month observation period. CONCLUSION: Our findings provide a picture of patients treated for hyperlipidemia across Slovakia. We found that, despite widespread statin use, a substantial proportion of patients, particularly those with FH, are undertreated and fail to achieve the LDL-C targets recommended in European guidelines. They consequently remain at excess risk of cardiovascular events.

[63] *Petrak O, Ceska R*. **Vascular age**. Vnitr Lek 2020; 65:770-774.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013519
ABSTRACT
Age can be evaluated according to many criteria. Of course the objective measure is the calendar age which may differ from the biological age. The biological age more or less correlates with the vascular

age. The concept of vascular age is based on the statement that “An individual is as old as his blood vessels”. The process of vascular aging already starts in childhood. Arterial aging may essentially be viewed from two standpoints. First, it involves stiffening of arteries and loss of their elasticity; second, degenerative changes and formation of atherosclerotic plaques occur, being the cause of ischemia, especially in case of the development of atherothrombosis. Both these processes can be monitored: The change of elasticity (arteriosclerosis) mainly by examination of pulse wave velocity (PWV), atherosclerosis then primarily with non-invasive methods, ultrasound or CT angiography examination. From the clinical point of view it is particularly important whether we can influence vascular age in some way. Evidence is available now that atherosclerosis can be affected by hypolipidemic treatment, arteriosclerosis then in particular by ACE inhibitors. The aforementioned possibility of influencing vascular age brings us to another problem, which is compliance of patients. With regard to that it is good that in a situation where we have two drugs affecting vascular age, we can use their fixed combination. It is available as a combination of atorvastatin and perindopril.

[64] *Tumova E, Vrablik M*. **Importance of fixed-dose combinations in cardiovascular prevention: the possibility of treating two diagnoses with a single pill**. Vnitr Lek 2020; 65:809-814.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32013525
ABSTRACT
In the care of a cardiovascular risk patient there is certainly a more frequent situation in which we try to influence several risk factors at the same time. Treatment of a single self-occurring risk factor is rather an exception. In most cases, we need to intervene with more risk factors, often involving combination therapy, which can achieve the desired goals more quickly and reliably. However, with the number of tablets taken by the patient, the patients willingness to take long-term and correct use decreases, which has a significant impact on the effectiveness of therapy and the development of individual cardiovascular risk. In an effort to control all risk factors for cardiovascular disease, there is a growing need to extend the availability of fixed drug formulations to suit the patients ease of use and suitably formulated with varying dose grades to meet the needs of our attending physicians. With regard to the fact that early intervention of risk factors brings greater benefits than deferred, we are looking for appropriate ways to manage it. The current intervention of arterial hypertension and dyslipidemia with safe and proven drugs seems to be one of the ways to further improve the results of the prevention of cardiovascular diseases. The new fixed combination of atorvastatin with perindopril, which is entering the Czech market right now, appears to be in many ways an ideal “tablet for cardiovascular prevention”.