Literature update week 29 (2020)

[1] *Şimşek B, Çınar T, Tanık VO et al.* **In-hospital statin initiation characteristics and one-year statin adherence rates in patients hospitalised for acute coronary syndrome**. Acta Cardiol 2020:1-7.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32677872
ABSTRACT

INTRODUCTION: In the present study, we aimed to evaluate compliance to lipid lowering guidelines regarding statin prescription on discharge and statin adherence rates during a follow-up period of one year in patients hospitalised with a diagnosis of acute coronary syndrome (ACS). METHODS: In-hospital records of 3506 ACS patients, of which 771 had experienced an ST-elevation myocardial infarction (STEMI) and 2735 had experienced a non-STEMI, were collected. We calculated medication possession ratios (MPRs) for each subject. We designated patients with ≥9 statin refills/year (MPR ≥ 0.75) as the statin-adherent group and patients with <9 statin refills/year (MPR < 0.75) as the statin-non-adherent group. RESULTS: During a 12-month follow-up period, 234 patients in the STEMI group (30.3%) and 391 patients in the non-STEMI group (14.3%) had 12 refills of statin. Thus, only 17.8% of the total study population had complete adherence to statin therapy with an MPR of 1. When patients with ≥9 statin prescriptions were categorised as the statin-adherent group, only 1575 patients (44.9%) were found to be adherent to statin treatment. In multivariate analysis, patients with a non-STEMI diagnosis and high intensity statin treatment had higher rates of non-adherence (OR:1.685, 95%CI:1.412-2.012, $p < .01$ and OR:1.344, 95% CI: 1.147-1.574, $p < .01$, respectively). Patients with prior statin treatment had lower rates of non-adherence(OR:0.437, 95%CI: 0.346-0.553, $p < .01$). CONCLUSION: The present study shows that compliance with guidelines regarding statin initiation during hospitalisation and statin adherence rates during a one-year follow-up period are low for patients treated for ACS. Considering the overwhelming clinical benefits of high-intensity statins in patients with ACS, every effort should be made to increase the rate of optimal use of statins in secondary prevention.

[2] *Miao J, Zang X, Cui X, Zhang J.* **Autophagy, Hyperlipidemia, and Atherosclerosis**. Advances in experimental medicine and biology 2020; 1207:237-264.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32671753
ABSTRACT

Autophagy is an evolutionarily conserved process in eukaryotes that processes the turnover of intracellular substances. Atherosclerosis is a disease caused by multiple factors, it mainly occurs on the walls of large and medium blood vessels and atherosclerotic plaques form in the intima of the blood vessels. Hyperlipidemia is considered to be a very dangerous factor leading to cardiovascular and cerebrovascular diseases, especially atherosclerosis. This chapter mainly introduces the key role of autophagy in hyperlipidemia and atherosclerosis, that is, impaired lipophagy affects the degradation of triacylglycerol, cholesterol, etc., leading to hyperlipidemia in atherosclerosis. In patients, excessive levels of autophagy accelerate the rupture of atherosclerotic plaque. This chapter also describes the advances in the treatment of atherosclerosis and hyperlipidemia by targeted autophagy.

[3] *Boyko T, Marin C, Furnari G et al.* **Safety profile of atorvastatin in the role of burn wound injury conversion**. Am J Surg 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660698

ABSTRACT
BACKGROUND: Atorvastatin could be beneficial in the treatment of burn patients to prevent burn wound progression from partial to full thickness. Our primary aim is to evaluate the safety of atorvastatin in burn patients. METHODS: Single center retrospective chart review of burn patients receiving atorvastatin during admission May 2016-May 2019 with historic controls was performed. Demographics, burn total body surface area, atorvastatin doses, creatinine phosphokinase, aspartate aminotransferase levels and adverse events were analyzed. RESULTS: 48 burn patients received atorvastatin during admission. Nine patients experienced elevated CK or AST levels during admission, but did not correlate with timing of atorvastatin administration and were comparable to levels in control patients. No adverse events associated with atorvastatin were identified. CONCLUSIONS: Atorvastatin administered to patients with burn injuries was not associated with any adverse events or attributable lab abnormalities. We believe that atorvastatin is safe to use in patients with burns and can be safely studied to determine the drug's effect on the prevention of burn wound conversion.

[4] *Chen G, Li J, Wang Z, Liu W*. **Ezetimibe protects against spinal cord injury by regulating autophagy and apoptosis through inactivation of PI3K/AKT/mTOR signaling**. American journal of translational research 2020; 12:2685-2694.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32655800
ABSTRACT
Spinal cord injury (SCI) is a severe traumatic disease of the central nervous system characterized by high incidence and disability rate. We aimed to investigate the therapeutic potential of Ezetimibe (Eze) in SCI and identify the underlying mechanisms. Acute SCI rat model was established by using the modified weight-drop method. Following administration with Eze, the neurological function was evaluated using the Basso, Beattie, and Bresnahan (BBB) locomotor scale score, and the motor neurons were stained with Nissl staining. The pathological changes of spinal cord tissues were tested using Hematoxylin and eosin staining. The presence of apoptotic cells was examined using Terminal dexynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Moreover, the expression of main autophagy markers LC3II/I, Beclin1 and p62 and apoptosis-related proteins was tested using western blot analysis. The changes of PI3K/AKT/mTOR signaling-associated proteins were measured. Experimental results showed that Eze treatment obviously improved functional recovery, the neuronal survival and morphological characteristics of spinal cord. Additionally, Eze administration dramatically upregulated the expression of LC3II/I and Beclin1 whereas downregulated that of p62. Concurrently, significantly reduced apoptosis was observed following Eze intervention, accompanied by increased expression of anti-apoptotic protein Bcl-2 and decreased expression of pro-apoptotic proteins Bax, cleaved caspase-3 and cleaved caspase-9. Further results indicated that Eze treatment remarkably suppressed the expression of phospho-PI3K (p-PI3K), p-AKT and p-mTOR. These findings demonstrated that Eze could protect against SCI by activating autophagy and hindering apoptosis through regulating PI3K/AKT/mTOR signaling, suggesting a potential candidate for SCI therapy.

[5] *Nguyen D, Du N, Sulaica EM, Wanat MA*. **A Review of Bempedoic Acid: A New Drug for an Old Problem**. The Annals of pharmacotherapy 2020:1060028020941083.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674598
ABSTRACT
Objective: To review the pharmacology, pharmacokinetics, safety, and efficacy of bempedoic acid for low-density lipoprotein cholesterol (LDL-C) reduction. Data Sources: A PubMed search was conducted from January 2000 to June 15, 2020, using the keyword bempedoic acid for phase III clinical trials published in the English language. Study Selection and Data Extraction: Articles related to the Food and Drug Administration (FDA) approval of bempedoic acid and other trials relating to the safety and efficacy of this drug were included. Data Synthesis: The findings from this review show that bempedoic acid is a safe and effective option for lowering LDL-C levels in patients requiring LDL-C lowering for primary or secondary prevention of cardiovascular events. Relevance to Patient Care and Clinical Practice: Statin therapy remains the mainstay of treatment for both primary and secondary prevention. However, many patients cannot tolerate statin therapy because of statin-associated muscle symptoms. Bempedoic acid may be a reasonable adjunct for LDL-C reduction, though further evaluation of cardiovascular outcomes with bempedoic acid in this population is needed. Conclusions: The recent FDA approval of bempedoic acid offers an additional option for lowering LDL-C levels in patients with atherosclerotic cardiovascular disease or heterozygous familial hyperlipidemia. Additional data regarding effect on long-term cardiovascular outcomes with bempedoic acid are currently being studied.

[6] *Ansary J, Forbes-Hernández TY, Gil E et al.* **Potential Health Benefit of Garlic Based on Human Intervention Studies: A Brief Overview**. Antioxidants (Basel, Switzerland) 2020; 9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32679751
ABSTRACT
Garlic is a polyphenolic and organosulfur enriched nutraceutical spice consumed since ancient times. Garlic and its secondary metabolites have shown excellent health-promoting and disease-preventing effects on many human common diseases, such as cancer, cardiovascular and metabolic disorders, blood pressure, and diabetes, through its antioxidant, anti-inflammatory, and lipid-lowering properties, as demonstrated in several in vitro, in vivo, and clinical studies. The present review aims to provide a comprehensive overview on the consumption of garlic, garlic preparation, garlic extract, and garlic extract-derived bioactive constituents on oxidative stress, inflammation, cancer, cardiovascular and metabolic disorders, skin, bone, and other common diseases. Among the 83 human interventional trials considered, the consumption of garlic has been reported to modulate multiple biomarkers of different diseases; in addition, its combination with drugs or other food matrices has been shown to be safe and to prolong their therapeutic effects. The rapid metabolism and poor bioavailability that have limited the therapeutic use of garlic in the last years are also discussed.

[7] *Garçon D, Moreau F, Ayer A et al.* **Circulating Rather Than Intestinal PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) Regulates Postprandial Lipemia in Mice**. Arteriosclerosis, thrombosis, and vascular biology 2020:Atvbaha120314194.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32673528
ABSTRACT

OBJECTIVE: Increased postprandial lipemia (PPL) is an independent risk factor for atherosclerotic cardiovascular diseases. PCSK9 (Proprotein convertase subtilisin kexin type 9) is an endogenous inhibitor of the LDLR (low-density lipoprotein receptor) pathway. We previously showed that PCSK9 inhibition in mice reduces PPL. However, the relative contribution of intracellular intestinal PCSK9 or liver-derived circulating PCSK9 to this effect is still unclear. Approach and Results: To address this issue, we generated the first intestine-specific Pcsk9-deficient (i-Pcsk9(-/-)) mouse model. PPL was measured in i-Pcsk9(-/-) as well as in wild-type and streptozotocin-induced diabetic mice following treatment with a PCSK9 monoclonal antibody (alirocumab). Blocking the circulating form of PCSK9 with alirocumab significantly reduced PPL, while overexpressing human PCSK9 in the liver of full Pcsk9(-)(/-) mice had the opposite effect. Alirocumab regulated PPL in a LDLR-dependent manner as this effect was abolished in Ldlr(-/-) mice. In contrast, i-Pcsk9(-/-) mice did not exhibit alterations in plasma lipid parameters nor in PPL. Finally, PPL was highly exacerbated by streptozotocin-induced diabetes mellitus in Pcsk9(+/+) but not in Pcsk9(-/-) mice, an effect that was mimicked by the use of alirocumab in streptozotocin-treated Pcsk9(+/+) mice. CONCLUSIONS: Taken together, our data demonstrate that PPL is significantly altered by full but not intestinal PCSK9 deficiency. Treatment with an PCSK9 monoclonal antibody mimics the effect of PCSK9 deficiency on PPL suggesting that circulating PCSK9 rather than intestinal PCSK9 is a critical regulator of PPL. These data validate the clinical relevance of PCSK9 inhibitors to reduce PPL, especially in patients with type 2 diabetes mellitus.

[8] *Lavin B, Phinikaridou A, Andia ME et al.* **Sustained Focal Vascular Inflammation Accelerates Atherosclerosis in Remote Arteries**. Arteriosclerosis, thrombosis, and vascular biology 2020:Atvbaha120314387.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32673527
ABSTRACT
OBJECTIVE: Evidence from preclinical and clinical studies has demonstrated that myocardial infarction promotes atherosclerosis progression. The impact of focal vascular inflammation on the progression and phenotype of remote atherosclerosis remains unknown. Approach and Results: We used a novel ApoE(-/-) knockout mouse model of sustained arterial inflammation, initiated by mechanical injury in the abdominal aorta. Using serial in vivo molecular MRI and ex vivo histology and flow cytometry, we demonstrate that focal arterial inflammation triggered by aortic injury, accelerates atherosclerosis in the remote brachiocephalic artery. The brachiocephalic artery atheroma had distinct histological features including increased plaque size, plaque permeability, necrotic core to collagen ratio, infiltration of more inflammatory monocyte subsets, and reduced collagen content. We also found that arterial inflammation following focal vascular injury evoked a prolonged systemic inflammatory response manifested as a persistent increase in serum IL-6 (interleukin 6). Finally, we demonstrate that 2 therapeutic interventions-pravastatin and minocycline-had distinct anti-inflammatory effects at the plaque and systemic level. CONCLUSIONS: We show for the first time that focal arterial inflammation in response to vascular injury enhances systemic vascular inflammation, accelerates remote atheroma progression and induces plaques more inflamed, lipid-rich, and collagen-poor in the absence of ischemic myocardial injury. This inflammatory cascade is modulated by

pravastatin and minocycline treatments, which have anti-inflammatory effects at both plaque and systemic levels that mitigate atheroma progression.

[9] *Ye M, Sun J, Chen Y et al.* **Response of serum LDL cholesterol to oatmeal consumption depends on CYP7A1_rs3808607 genotype in Chinese**. Asia Pacific journal of clinical nutrition 2020; 29:423-433.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674250
ABSTRACT

BACKGROUND AND OBJECTIVES: Notable inter-individual differences in cholesterol-lowering effects following oatmeal consumption have been previously reported. Genetic variations may among the reasons for the heterogeneous response to lipid modulations. And to determine whether SNP of cytochrome P450 family 7 subfamily A member 1 gene rs3808607 and isoforms of apolipoprotein E are associated with the inter-individual variations in cholesterol-lowering effects of oatmeal consumption, we did this study. METHODS AND STUDY DESIGN: Data in this study were extracted from a parallel, controlled trial, in which 62 medication-naive hypercholesterolemic patients provided with staple food substitute of either 80 g/d oatmeal (n=31) or 80 g/d refined white rice (n=31) for 45 days. Fasting blood samples were collected at baseline and endpoint of the study for lipid profiling, glycemic testing, and genotyping. RESULTS: Totally, 56 of 62 participants completed the study and were thus included. Genotype- diet interactions were observed between oatmeal consumption and SNP in the cytochrome P450 family 7 subfamily A member 1 gene rs3808607 in regulating LDL cholesterol (p=0.04); rs3808607-TT homozygotes exhibited significantly higher responsiveness to oatmeal (reduction in LDL cholesterol) than G allele carriers (GG/GT) (p=0.02). However, obvious genotype-diet interactions were not observed between oatmeal consumption and apolipoprotein E isoforms in cholesterol and glycemic modulation (p>0.05). CONCLUSIONS: SNP in cytochrome P450 family 7 subfamily A member 1 gene rs3808607 was associated with the extent of LDL cholesterol reduction following oatmeal consumption. Trials with larger sample sizes are required to confirm the findings.

[10] *Ali L, Cupido AJ, Rijkers M et al.* **Common gene variants in ASGR1 gene locus associate with reduced cardiovascular risk in absence of pleiotropic effects**. Atherosclerosis 2020; 306:15-21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32679274
ABSTRACT

BACKGROUND AND AIMS: The rare ASGR1 del12 variant is associated with a beneficial effect on coronary artery disease (CAD) that is disproportionate to the small reductions in plasma LDL cholesterol (LDLc). This unexplained benefit has sparked the debate on potential additional pleiotropic effects of ASGR1 variants. Since ASGR1 has also been implicated in platelet homeostasis, we evaluated platelet function in heterozygous ASGR1 del12 carriers and controls. In addition, we compared the magnitude of various LDLc lowering genetic scores in the UK-biobank using Mendelian randomization. METHODS: Desialylation of platelet surface glycoproteins and platelet aggregation capacity were measured in 12 carriers and 10 controls. We selected 3 common genetic variants in the ASGR1 locus that were significantly associated with plasma LDLc and assessed the association with coronary artery disease (CAD) and compared it with the effects of

HMCGR, LDLR, NCI1L1 and PCSK9 gene scores. RESULTS: Platelet surface GlcNAC residues were significantly lower in carriers but platelet aggregation did not differ. The relative risk reduction of ASGR1 GRS on CAD and myocardial infarction per 10 mg/dl LDLc reduction was 23% (OR 0.77, 95% CI 0.62-0.96). This risk reduction was proportionally similar to the gene risk scores in HMCGR, NPC1L1, PCSK9, and LDLR. CONCLUSIONS: Unlike previous reports, we did not find any evidence for a pleiotropic effect of the rare del12 variant in the ASGR1 locus on CAD, as platelet function did not differ between carriers and controls. Moreover, the observed effect of ASGR1 variants on CAD risk was proportional to the reduction in plasma LDLc levels.

[11] *Grover SP, Mackman N*. **Tissue factor in atherosclerosis and atherothrombosis**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674807
ABSTRACT
Atherosclerosis is a chronic inflammatory disease that is characterized by the formation of lipid rich plaques in the wall of medium to large sized arteries. Atherothrombosis represents the terminal manifestation of this pathology in which atherosclerotic plaque rupture or erosion triggers the formation of occlusive thrombi. Occlusion of arteries and resultant tissue ischemia in the heart and brain causes myocardial infarction and stroke, respectively. Tissue factor (TF) is the receptor for the coagulation protease factor VIIa, and formation of the TF:factor VIIa complex triggers blood coagulation. TF is expressed at high levels in atherosclerotic plaques by both macrophage-derived foam cells and vascular smooth muscle cells, as well as extracellular vesicles derived from these cells. Importantly, TF mediated activation of coagulation is critically important for arterial thrombosis in the setting of atherosclerotic disease. The major endogenous inhibitor of the TF:factor VIIa complex is TF pathway inhibitor 1 (TFPI-1), which is also present in atherosclerotic plaques. In mouse models, increased or decreased expression of TFPI-1 has been found to alter atherosclerosis. This review highlights the contribution of TF-dependent activation of coagulation to atherthrombotic disease.

[12] *Nording H, Baron L, Langer HF*. **Platelets as therapeutic targets to prevent atherosclerosis**. Atherosclerosis 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32653088
ABSTRACT
Cardiovascular disease remains the main cause of death worldwide. For this reason, strategies for the primary prevention of atherosclerosis and atherosclerosis-related pathologies like stroke or myocardial infarction are needed. Platelets are key players of atherosclerosis-related vascular thrombotic pathologies and their role as targets in secondary prevention of atherosclerosis-related complications is uncontested. However, platelets also play an important role in the initiation and progression of atherosclerosis. Currently, though, there is no generally valid recommendation for the use of antiplatelet therapy in primary prevention of cardiovascular disease. Recent clinical studies have shown that the benefit from antiplatelet therapy in primary prevention is counteracted by the entailed bleeding risk. This review addresses the important role platelets play in initiating and sustaining vascular inflammation, which drives atherosclerosis. Specifically, platelet-lipid interactions as well as platelet-endothelium interactions in the context of

atherosclerosis are illustrated. We also depict how platelets help recruit immune cells like monocytes, neutrophils or dendritic cells to the subendothelial space. Finally, we portray the role of complement and platelets in atherosclerosis. Platelets appear to act as mediators of tissue homeostasis and may also modulate the microenvironment of the atherosclerotic plaque. Overall, this review addresses the role of platelets in atherosclerosis with particular focus on potential targets for pharmacological interventions into platelet functions distinct from aggregation. By eliminating the bleeding risk of antiplatelet therapy, platelets are likely to regain a role in primary prevention of cardiovascular disease.

[13] *Fitzgerald X, Herceg A, Douglas K, Siddiqui N*. **Cardiovascular disease risk assessment in an Aboriginal community-controlled health service: comparing algorithms**. Aust J Prim Health 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32654685
ABSTRACT
Aboriginal and Torres Strait Islander people have high rates of cardiovascular disease (CVD). The National Vascular Disease Prevention Alliance (NVDPA) CVD risk assessment algorithm is used for all Australians. The Central Australian Rural Practitioners Association (CARPA) algorithm used in the Northern Territory adds five percentage points to all NVDPA risk scores for Indigenous Australians. Information was extracted from an Aboriginal Community-Controlled Health Service for all Aboriginal and Torres Strait Islander regular clients aged 35-74 years without known CVD (n=1057). CVD risk scores were calculated using both algorithms. Prescription of lipid-lowering medications was assessed. Clients with high-risk scores were reviewed and recalled if required. CVD risk scores were calculated for 362 (34.4%) clients. Clients with high CVD risk comprised 17.7% (NVDPA) or 23.8% (CARPA), with most determined clinically. Clients with low CVD risk comprised 73.7% (NVDPA) or 47.2% (CARPA). More than 30% of those with high risk were not on lipid-lowering medications. Significant health and social issues affected treatment uptake. It is unclear which algorithm is most applicable; however, this service has decided to continue to use the NVDPA algorithm. Use of CVD risk assessment and management of high-risk clients could be increased in primary care.

[14] *Yoval-Sánchez B, Calleja LF, de la Luz Hernández-Esquivel M, Rodríguez-Zavala JS*. **Piperlonguminine a new mitochondrial aldehyde dehydrogenase activator protects the heart from ischemia/reperfusion injury**. Biochimica et biophysica acta. General subjects 2020; 1864:129684.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32679250
ABSTRACT
BACKGROUND: Detoxification of aldehydes by aldehyde dehydrogenases (ALDHs) is crucial to maintain cell function. In cardiovascular diseases, reactive oxygen species generated during ischemia/reperfusion events trigger lipoperoxidation, promoting cell accumulation of highly toxic lipid aldehydes compromising cardiac function. In this context, activation of ALDH2, may contribute to preservation of cell integrity by diminishing aldehydes content more efficiently. METHODS: The theoretic interaction of piperlonguminine (PPLG) with ALDH2 was evaluated by docking analysis. Recombinant human ALDH2 was used to evaluate the effects of PPLG on the kinetics of the enzyme. The effects of PPLG were further investigated in a myocardial infarction model in rats,

evaluating ALDHs activity, antioxidant enzymes, oxidative stress markers and mitochondrial function. RESULTS: PPLG increased the activity of recombinant human ALDH2 and protected the enzyme from inactivation by lipid aldehydes. Additionally, administration of this drug prevented the damage induced by ischemia/reperfusion in rats, restoring heart rate and blood pressure, which correlated with protection of ALDHs activity in the tissue, a lower content of lipid aldehydes, and the preservation of mitochondrial function. CONCLUSION: Activation of ALDH2 by piperlonguminine ameliorates cell damage generated in heart ischemia/reperfusion events, by decreasing lipid aldehydes concentration promoting cardioprotection.

[15] *Cruz TA, Pinho MB, Castilho LR*. **Evaluation of different IRES-mediated tricistronic plasmid designs for expression of an anti-PCSK9 biosimilar monoclonal antibody in CHO cells**. Biotechnology letters 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32676798
ABSTRACT
OBJECTIVES: To compare different approaches for the expression of an anti-PCSK9 biosimilar monoclonal antibody (mAb) in CHO cells using IRES-mediated tricistronic plasmid vectors combining different signal peptides, IRES elements and selection markers. RESULTS: Transient transfection indicated a similar level of secreted mAb 48 h post-transfection for all constructs. However, transfections carried out with circular plasmids showed a higher expression than with linearized plasmids. After two months under selection pressure, only part of the transfected pools recovered. The cultures co-transfected using two antibiotics as selection markers for double selection did not recover. Growth, metabolism and mAb production profiles of the only part of the transfected pools recovered resulting stable pools were compared and the stable pool transfected with circular L1-LC-IRES-H7-HC-IRES-NEO plasmid was chosen for further studies, due to higher cell growth and mAb production. Critical quality attributes of the protein A-purified mAb such as purity, homogeneity, binding affinity to PCSK9, and amino acid sequence were assessed confirming the success of the approach adopted in this study. CONCLUSIONS: The expression platform proposed showed to be efficient to produce a high-quality anti-PCSK9 mAb in stable CHO cell pools and provides benchmarks for fast production of different mAbs for characterization, formulation studies and pre-clinical investigation.

[16] *Fan CH, Hao Y, Liu YH et al.* **Anti-inflammatory effects of rosuvastatin treatment on coronary artery ectasia patients of different age groups**. BMC cardiovascular disorders 2020; 20:330.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32652935
ABSTRACT
BACKGROUND: Coronary artery ectasia (CAE) is an angiographic finding of abnormal coronary dilatation. Inflammation plays a major role in all phases of atherosclerosis. We investigated the relationship between CAE and serum high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels to test our hypothesis that patient age is associated with the efficacy of anti-inflammatory therapy for CAE. METHODS: We conducted a prospective analysis of 217 patients with CAE treated at the Department of Cardiology, Shanghai East Hospital, Ji'an Campus and the Baoshan People's Hospital, from January 1,

2015 to July 30, 2019. Baseline data of patients, including sex; age; and history of hypertension, hyperlipidemia, and diabetes, were collected from patient medical records. Study participants were grouped by age as follows: CAE-A (n = 60, age ≤ 50 years), CAE-B (n = 83, 50 years <age ≤ 70 years), and CAE-C (n = 74, age > 70). Additionally, there was a control (NC) group (n = 73) with normal coronary arteries. RESULTS: All patients received oral rosuvastatin therapy (10 mg, QN quaque nocte) when they were diagnosed with CAE and maintained good follow-up, with a loss rate of 0.0% at the end of the 6-month follow-up. The NC group received regular symptom-relieving treatments and rosuvastatin therapy. Of these four groups, the inflammatory markers, hs-CRP and IL-6, were significantly higher in patients with CAE than in the NCs (p < 0.05). Post-hoc tests showed that hs-CRP and Il-6 levels had significant differences between the CAE-A and CAE-C groups (P = 0.048, P = 0.025). Logistic regression analysis showed that hs-CRP (OR = 1.782, 95% CI: 1.124-2.014, P = 0.021) and IL-6 (OR = 1.584, 95% CI: 1.112-1.986, P = 0.030) were independent predictors of CAE. The inflammatory markers were higher in the CAE-A group than in the CAE-B group and higher in the CAE-B group than in the CAE-C group. Follow-up after 6 months of rosuvastatin therapy showed a significantly greater reduction in hs-CRP and IL-6 levels in the CAE-A group than in the CAE-B group, which again were greater in the CAE-B group than in the CAE-C group. CONCLUSIONS: Anti-inflammatory therapy using rosuvastatin was more effective in younger CAE patients, indicating the need for early statin therapy in CAE.

[17] *Hsu HY, Lin CJ, Lee YS et al.* **Efficacy of more intensive lipid-lowering therapy on cardiovascular diseases: a systematic review and meta-analysis**. BMC cardiovascular disorders 2020; 20:334.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660417
ABSTRACT
BACKGROUND: Cardiovascular disease is the leading cause of morbidity and mortality with incidence rates of 5-10 per 1000 person-years, according to primary prevention studies. To control hyperlipidemia-a major risk factor of cardiovascular disease-initiation of lipid-lowering therapy with therapeutic lifestyle modification or lipid-lowering agent is recommended. Few systematic reviews and meta-analyses are available on lipid-lowering therapy for the primary prevention of cardiovascular diseases. In addition, the operational definitions of intensive lipid-lowering therapies are heterogeneous. The aim of our study was to investigate whether intensive lipid-lowering therapies reduce greater cardiovascular disease risks in primary prevention settings. METHODS: MEDLINE, EMBASE, and Cochrane Library databases were searched from inception to March 2019 for randomized controlled trials. We used random effects model for overall pooled risk ratio (RR) estimation with cardiovascular events of interest and all-cause mortality rate for the intensive lipid-lowering group using the standard lipid-lowering group as the reference. The Cochrane Risk of Bias Tool was used for quality assessment. RESULTS: A total of 18 randomized controlled trials were included. The risk reductions in cardiovascular outcomes and all-cause mortality associated with more intensive vs. standard lipid-lowering therapy across all trials were 24 and 10%, respectively (RR 0.76, 95% confidence interval 0.68-0.85; RR 0.90, 95% confidence interval 0.83-0.97); however, the risk reduction varied by baseline LDL-C level in the trial. A greater risk reduction was noted with higher LDL-C level. Intensive lipid-lowering for coronary heart disease protection was more pronounced in the

non-diabetic populations than in the diabetic populations. CONCLUSIONS: More intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels than less intensive LDL-C lowering. Intensive lipid-lowering was associated with a significant risk reduction of coronary heart disease and must be considered even in the non-diabetic populations.

[18] *Kristensen MS, Green A, Nybo M et al.* **Lipid-lowering therapy and low-density lipoprotein cholesterol goal attainment after acute coronary syndrome: a Danish population-based cohort study**. BMC cardiovascular disorders 2020; 20:336.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660429
ABSTRACT

BACKGROUND: Patients with acute coronary syndrome (ACS) are at high risk of recurrent cardiovascular (CV) event. The European guidelines recommend low-density lipoprotein cholesterol (LDL-C) levels < 1.8 mmol/L and early initiation of intensive lipid-lowering therapy (LLT) to reduce CV risk. In order to reduce the risk of further cardiac events, the study aimed to evaluate LDL-C goal attainment and LLT intensity in an incident ACS population. METHODS: A cohort study of patients with residency at Funen in Denmark at a first-ever ACS event registered within the period 2010-2015. Information on LLT use and LDL-C levels was extracted from national population registers and a Laboratory database at Odense University Hospital. Treatments and lipid patterns were evaluated during index hospitalization, at 6-month and 12-month follow-up. RESULTS: Among 3040 patients with an LDL-C measurement during index hospitalization, 40.7 and 39.0% attained the recommended LDL-C target value (< 1.8 mmol/L) within 6- and 12-month follow-up, respectively. During 6- and 12-month follow-up, a total of 89.2% (20.2%) and 88.4% (29.7%) used LLT (intensive LLT). Of the intensive LLT users, 43.4 and 47.7% reached the LDL-C target value at 6- and 12-month follow-up. The frequency of lipid monitoring was low: 69.5, 77.7 and 53.6% in patients with a first-ever ACS during index hospitalization, 6- and 12-month follow-up, respectively. CONCLUSION: Using national health registers and laboratory data, a considerably gap was observed between treatment guidelines and clinical practice in the management of dyslipidemia leaving very high-risk patients without adequate lipid management strategy. Therefore, improved lipid management strategies aimed at reaching treatment targets are warranted.

[19] *Guo S, Wang M, Yu Y et al.* **The association of erythrocyte sedimentation rate, high-sensitivity C-reactive protein and diabetic kidney disease in patients with type 2 diabetes**. BMC endocrine disorders 2020; 20:103.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660469
ABSTRACT

BACKGROUND: To evaluate the association between high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR), and diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM). METHODS: A cross-sectional study was conducted in 1210 patients with T2DM, among whom 265 had DKD. The severity of DKD was assessed by estimated-glomerular filtration rate (eGFR) and urinary albumin creatinine ratio (ACR). The relationship between ESR, hsCRP and DKD was analyzed by multivariate logistic analysis. The relationship between ESR and eGFR, ESR or ACR was analyzed by multivariate linear regression. RESULTS: ESR (23.0 [12.0 ~ 41.5] mm/h versus 12.0

[7.0 ~ 22.0] mm/h, P < 0.001) and hsCRP (3.60 [2.20 ~ 7.65] versus 2.90 [1.80 ~ 5.60] mg/L mg/L, P < 0.01) values were significantly higher in patients with DKD than those without. Patients with higher ESR or hsCRP had lower eGFR and higher ACR. After adjusted for gender, age, hemoglobin, plasma proteins, HbA(1c), lipid profiles, and the usage of renin-angiotensin system inhibitors, ESR but not hsCRP was independently associated with the rate and severity of DKD in patients with T2DM. CONCLUSION: ESR was independently associated with the rate and severity of DKD in patients with T2DM.

[20] *Hornik ES, Altman-Merino AE, Koefoed AW et al.* **A clinical trial to evaluate the effect of statin use on lowering aldosterone levels**. BMC endocrine disorders 2020; 20:105.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32664962
ABSTRACT

BACKGROUND: Statins are the first-line pharmaceutical agent in the management of hypercholesterolemia and cardiovascular (CV) risk reduction, and the most commonly prescribed class of drugs worldwide. Studies describing CV risk reduction independent of LDL-cholesterol lowering have evoked an interest in the pleiotropic mechanisms of statins' benefits. We recently demonstrated that administration of statins in animal models lowers aldosterone levels and observed an association between statin use and reduced aldosterone levels in two human cohorts, with lipophilic statins displaying a greater effect than hydrophilic statins. Therefore, we designed a randomized, placebo-controlled, double-blinded intervention study to assess whether statin treatment lowers aldosterone in a type-dependent manner in humans, with simvastatin (lipophilic) showing a greater effect than pravastatin (hydrophilic). METHODS/DESIGN: One hundred five healthy participants will be recruited from the general population to enroll in a 12-week, randomized, placebo-controlled, double-blinded, 3-arm clinical trial. Ninety participants are anticipated to complete the protocol. After baseline assessment of aldosterone levels, participants will be randomized to daily simvastatin, pravastatin, or placebo. Aldosterone levels will be assessed after 2 days on study drug and again after 6 weeks and 12 weeks on study drug. Prior to each aldosterone assessment, participants will consume an isocaloric sodium and potassium-controlled run-in diet for 5 days. Assessments will occur on an inpatient research unit to control for diurnal, fasting, and posture conditions. The primary outcome will compare 12-week angiotensin II-stimulated serum aldosterone by study drug. Secondary outcomes will compare baseline and 12-week 24-h urine aldosterone by study drug. DISCUSSION: Results from this rigorous study design should provide strong support that statins lower aldosterone levels in humans. These results may explain some of the beneficial effects of statins that are not attributed to the LDL-lowering effect of this important class of medications. Results would demonstrate that statin lipophilicity is an important attribute in lowering aldosterone levels. The outcomes of this program will have implications for the design of studies involving statin medications, as well as for the differential use of classes of statins. TRIAL REGISTRATION: ClinicalTrials.gov; NCT02871687 ; First Posted August 18, 2016.

[21] *Seeßle J, Gan-Schreier H, Kirchner M et al.* **Plasma Lipidome, PNPLA3 polymorphism and hepatic steatosis in hereditary hemochromatosis**. BMC gastroenterology 2020; 20:230.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32680469
ABSTRACT
BACKGROUND: Hereditary hemochromatosis (HH) is an autosomal recessive genetic disorder with increased intestinal iron absorption and therefore iron Overload. iron overload leads to increased levels of toxic non-transferrin bound iron which results in oxidative stress and lipid peroxidation. The impact of iron on lipid metabolism is so far not fully understood. The aim of this study was to investigate lipid metabolism including lipoproteins (HDL, LDL), neutral (triglycerides, cholesterol) and polar lipids (sphingo- and phospholipids), and PNPLA3 polymorphism (rs738409/I148M) in HH. METHODS: We conducted a cohort study of 54 subjects with HH and 20 healthy subjects. Patients were analyzed for their iron status including iron, ferritin, transferrin and transferrin saturation and serum lipid profile on a routine follow-up examination. RESULTS: HH group showed significantly lower serum phosphatidylcholine (PC) and significantly higher phosphatidylethanolamine (PE) compared to healthy control group. The ratio of PC/PE was clearly lower in HH group indicating a shift from PC to PE. Triglycerides were significantly higher in HH group. No differences were seen for HDL, LDL and cholesterol. Hepatic steatosis was significantly more frequent in HH. PNPLA3 polymorphism (CC vs. CG/GG) did not reveal any significant correlation with iron and lipid parameters including neutral and polar lipids, grade of steatosis and fibrosis. CONCLUSION: Our study strengthens the hypothesis of altered lipid metabolism in HH and susceptibility to nonalcoholic fatty liver disease. Disturbed phospholipid metabolism may represent an important factor in pathogenesis of hepatic steatosis in HH.

[22] *Glerum PJ, Maliepaard M, de Valk V et al.* **Drug switching in the Netherlands: a cohort study of 20 active substances**. BMC Health Serv Res 2020; 20:650.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660480
ABSTRACT
BACKGROUND: For a patient, drug switches are not desirable (either between a brand-name drug and a generic drug, or between two generic drugs of the same active substance). Research into the causes of drug switches, and related adverse drug reactions, is hampered by the absence of quantitative data on drug switches. METHODS: We describe the frequency of drug switches in the Netherlands for a selection of active substances. A retrospective cohort study was conducted using the Drug Information System of the National Health Care Institute in the Netherlands. We studied the Dutch patient population from mid-2009 to 2016. The selection of active substances (n = 20) was made based on a report by Lareb, the Netherlands Pharmacovigilance Centre, on adverse drug reactions related to drug switching, and we used qualitative and quantitative descriptive analyses. A drug switch is defined as the replacement of a patient's prescribed drug with a similar drug from a different manufacturer. RESULTS: We identified 23.8 million drug switches on a total of 206 million (11.6%) similar drug dispenses. The frequency of drug switches demonstrated a yearly peak in the period from January to March. In some months, for atorvastatin, losartan, pantoprazole, and irbesartan, more than 60% of similar drug dispenses were drug switches. Most drug switches (80.3%) were between two generic drugs, and 0.12% of these involved a drug from a European parallel import. The proportion of drug switches between two brand-name drugs decreased from 14.5 to 5.53% during our study period, and of these, 86.5% involved a drug from a European parallel import. CONCLUSIONS: Drug switching is common in the Netherlands, and most of the drug

switches we studied are between generic drugs. The observed annual peak of drug switches is most likely explained by a specific Dutch reimbursement policy. Not only are the data valuable as is, but they also serve as a first step towards elucidating the reasons for the occurrence of these drug switches. In addition, these data can be used to put into perspective the adverse drug reactions associated with drug switching.

[23] *Xu K, Cui X, Wang B et al.* **Healthy adult vegetarians have better renal function than matched omnivores: a cross-sectional study in China**. BMC Nephrol 2020; 21:268.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32652943
ABSTRACT

BACKGROUND: An appropriate diet is an important determinant of kidney health. However, the association between vegetarian diets and renal function is unclear. We aimed to study the association between vegetarian diets and renal function in healthy adults. METHODS: A total of 269 vegetarians and 269 sex- and age-matched nonvegetarian omnivores were enrolled in this cross-sectional study. Basic characteristics and daily dietary intakes were assessed by face-to-face interviews. Blood samples were collected, and renal function was assessed by measuring blood urea nitrogen (BUN), serum creatinine (SCr), uric acid (UA) and the estimated glomerular filtration rate (eGFR). Blood pressure, fasting blood glucose and blood lipid profiles were also assessed. RESULTS: The average age of the vegetarians was 35.4 ± 8.6 years, 82.2% of whom were female. We evaluated the association between vegetarian diets and renal function using multivariate analysis. Compared with omnivores, vegetarians had lower BUN [$\beta = -0.63$, 95% confidence interval (CI): (-0.88, -0.38)], SCr [$\beta = -2.04$, 95% CI:(-4.10, 0.02)], and UA levels [$\beta = -15.15$, 95% CI: (-27.81, -2.50)] and higher eGFRs [$\beta = 4.04$, 95% CI: (0.30, 7.78)] after adjusting for sex, age, body mass index (BMI), physical activity, alcohol consumption, smoking status, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), systolic pressure and fasting blood glucose. Further analysis of food composition and renal function showed that dietary fiber intake was significantly negatively associated with BUN [$\beta = -0.02$, 95% CI: (-0.03, 0.00)], SCr [$\beta = -0.14$, 95% CI: (-0.25, 0.04)], and UA levels [$\beta = -0.72$, 95% CI: (-1.36, 0.07)] and positively associated with the eGFR [$\beta = 0.20$, 95% CI: (0.00, 0.40)]. CONCLUSIONS: Healthy adult vegetarians have better renal function than omnivores, and the higher dietary fiber intake associated with vegetarian diets may contribute to the protective effect on renal function.

[24] *Cai X, Zhang Y, Li M et al.* **Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis**. Bmj 2020; 370:m2297.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32669282
ABSTRACT

OBJECTIVE: To evaluate the associations between prediabetes and the risk of all cause mortality and incident cardiovascular disease in the general population and in patients with a history of atherosclerotic cardiovascular disease. DESIGN: Updated meta-analysis. DATA SOURCES: Electronic databases (PubMed, Embase, and Google Scholar) up to 25 April 2020. REVIEW METHODS: Prospective cohort studies or post hoc analysis of clinical trials were included for analysis if they reported adjusted relative risks, odds ratios, or hazard ratios of all cause mortality or cardiovascular disease for prediabetes compared

with normoglycaemia. Data were extracted independently by two investigators. Random effects models were used to calculate the relative risks and 95% confidence intervals. The primary outcomes were all cause mortality and composite cardiovascular disease. The secondary outcomes were the risk of coronary heart disease and stroke. RESULTS: A total of 129 studies were included, involving 10 069 955 individuals for analysis. In the general population, prediabetes was associated with an increased risk of all cause mortality (relative risk 1.13, 95% confidence interval 1.10 to 1.17), composite cardiovascular disease (1.15, 1.11 to 1.18), coronary heart disease (1.16, 1.11 to 1.21), and stroke (1.14, 1.08 to 1.20) in a median follow-up time of 9.8 years. Compared with normoglycaemia, the absolute risk difference in prediabetes for all cause mortality, composite cardiovascular disease, coronary heart disease, and stroke was 7.36 (95% confidence interval 9.59 to 12.51), 8.75 (6.41 to 10.49), 6.59 (4.53 to 8.65), and 3.68 (2.10 to 5.26) per 10 000 person years, respectively. Impaired glucose tolerance carried a higher risk of all cause mortality, coronary heart disease, and stroke than impaired fasting glucose. In patients with atherosclerotic cardiovascular disease, prediabetes was associated with an increased risk of all cause mortality (relative risk 1.36, 95% confidence interval 1.21 to 1.54), composite cardiovascular disease (1.37, 1.23 to 1.53), and coronary heart disease (1.15, 1.02 to 1.29) in a median follow-up time of 3.2 years, but no difference was seen for the risk of stroke (1.05, 0.81 to 1.36). Compared with normoglycaemia, in patients with atherosclerotic cardiovascular disease, the absolute risk difference in prediabetes for all cause mortality, composite cardiovascular disease, coronary heart disease, and stroke was 66.19 (95% confidence interval 38.60 to 99.25), 189.77 (117.97 to 271.84), 40.62 (5.42 to 78.53), and 8.54 (32.43 to 61.45) per 10 000 person years, respectively. No significant heterogeneity was found for the risk of all outcomes seen for the different definitions of prediabetes in patients with atherosclerotic cardiovascular disease (all P>0.10). CONCLUSIONS: Results indicated that prediabetes was associated with an increased risk of all cause mortality and cardiovascular disease in the general population and in patients with atherosclerotic cardiovascular disease. Screening and appropriate management of prediabetes might contribute to primary and secondary prevention of cardiovascular disease.

[25] *Lu J, Zhao W, Chen T et al.* **Influence of guideline adherence and parameter control on the clinical outcomes in patients with diabetic nephropathy**. BMJ open diabetes research & care 2020; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32675172
ABSTRACT
INTRODUCTION: We assessed the association between guideline adherence and outcomes of clinical parameter control and end-stage kidney disease (ESKD), and further studied the effect of parameter control on ESKD for Chinese patients with diabetic nephropathy (DN). RESEARCH DESIGN AND METHODS: In this retrospective study, 1128 patients with DN (15,374 patient-visit samples) diagnosed by renal biopsy were enrolled. Samples were classified as adherence and nonadherence based on whether prescribed drugs conformed to medication regimen and drug contraindication recommended by guidelines, including American Diabetes Association (ADA) and Chinese guidelines. Guideline adherence rate was calculated on all samples for antihyperglycemic, antihypertensive and lipid-lowering treatments. Clinical parameter control was compared after 3-6 months' therapy between two groups by generalized estimating equation models.

Time-dependent Cox models were applied to evaluate the influence of guideline adherence on ESKD. Latent class mixed model was used to identify distinct trajectories for parameters and their ESKD risks were compared using Cox proportional-hazards models. RESULTS: Guideline adherence rate of antihyperglycemic therapy was the highest, with 72.87% and 68.15% of samples meeting ADA and Chinese guidelines, respectively. Adherence was more likely to have good glycated hemoglobin A1c (HbA1c) control (ADA: OR 1.46, 95% CI 1.12 to 1.88; Chinese guideline: OR 1.42, 95% CI 1.09 to 1.85) and good blood pressure control (ADA: OR 1.35, 95% CI 1.03 to 1.78; Chinese guideline: OR 1.39, 95% CI 1.08 to 1.79) compared with nonadherence. The improvement of patient's adherence showed the potential to reduce ESKD risk. For proteinuria, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure and uric acid, patients in higher-value trajectory group had higher ESKD risk. Proteinuria and LDL-C trajectories were most closely related to ESKD risk, while the risk was not significantly different in HbA1c trajectories. CONCLUSIONS: Guideline adherence and good control of proteinuria and LDL-C in clinical practice are important and in need for improving clinical outcomes in patients with DN.

[26] *Arranto CA, Burkard T, Leuppi-Taegtmeyer AB et al.* **Prevalence of untreated and uncontrolled cardiovascular risk factors in survivors of allogeneic cell transplantation**. Bone Marrow Transplant 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32665676
ABSTRACT
Cardiovascular risk factors (CVRF) are frequent among long-term survivors after allogeneic hematopoietic cell transplantation (HCT) but prospective data on CVRF are sparse. We conducted a cross-sectional single center study including patients who underwent a first HCT mostly for hematologic malignancies at our center between 2000 and 2016, surviving at least 1 year. 260 patients (median age 54 years [range 19-78], 40% female) who were median 6 years (range 1-16) after transplantation were included. Most patients (232, 89%) had peripheral blood stem cell transplantation. cGVHD was present in 41% at the time of study inclusion. Prevalence of hypertension, dyslipidemia, and diabetes was 58%, 63% and 9%, respectively. Untreated hypertension, dyslipidemia and diabetes was found in 15%, 35% and 2%. Among patients with treated hypertension, 38% did not have blood pressure controlled to levels ≤140/90 mmHg. 36% patients under lipid-lowering therapy did not reach their LDL target. Multivariable logistic regression analyses showed that age and diabetes increased the likelihood for hypertension and dyslipidemia, whereas body mass index, cGVHD and male sex predicted hypertension only. In summary, CVRF in long-term survivors are frequent and persisting after cessation of immunosuppression. A large proportion of CVRF are either untreated or uncontrolled.

[27] *Khoury M, Kavey RW, Pierre JS, McCrindle BW*. **Incorporating Risk Stratification into the Practice of Pediatric Preventive Cardiology**. The Canadian journal of cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32679170
ABSTRACT
Atherosclerosis in its earliest stages is associated with the same traditional cardiovascular disease (CVD) risk factors as are associated with manifest CVD events in adulthood. Clustering of risk factors is associated with exponential increases in atherosclerotic burden

from a young age. Some medical conditions and risk behaviors occurring in children can either increase the likelihood of higher levels of risk factors (such as chronic kidney disease) or the presence of risk factor clustering (such as obesity and cardiometabolic syndrome), or are associated with acquired coronary artery pathology (such as Kawasaki disease). This creates a milieu for, or increases the impact of, accelerated atherosclerosis that in turn increases the likelihood of premature CVD. This review highlights the importance of considering the total risk factor and risk condition profile of pediatric patients. An algorithm is provided for stratifying patients into high, moderate and at risk categories, and practical examples are provided as to how the evaluation and management of one risk factor or risk condition might need to be intensified in the context of additional risk factors or risk conditions. For example, for treatment of an adolescent with familial hypercholesterolemia, the target low-density lipoprotein cholesterol level might be lowered by the concomitant presence of low high-density lipoprotein cholesterol or elevated lipoprotein(a) levels. As awareness of cardiovascular risk and atherosclerosis in pediatric patients increases, new at risk conditions that warrant consideration are emerging. The identification and management of high risk individuals is an important part of the overall practice of pediatric preventive cardiology.
Publisher: Abstract available from the publisher.
fre

[28] *Riaño I, Martín L, Varela M et al.* **Efficacy and Safety of the Combination of Pravastatin and Sorafenib for the Treatment of Advanced Hepatocellular Carcinoma (ESTAHEP Clinical Trial)**. Cancers 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674461
ABSTRACT

Pravastatin has demonstrated anti-tumor activity in preclinical and clinical studies. This multicentric randomized double-blind placebo-controlled phase II study (NCT01418729) investigated the efficacy and safety of sorafenib + pravastatin combination on the overall survival (OS) and time to progression (TTP) of patients with advanced hepatocellular carcinoma (aHCC). A total of 31 patients were randomized. Median OS did not differ between both groups (12.4 months for the sorafenib + pravastatin group vs. 11.6 months for the control group). Of note, however, the radiological TTP was higher in patients treated with sorafenib + pravastatin than in the control group (9.9 months vs. 3.2 months; p = 0.008). Considering all the study population, the presence of portal vein thrombosis (PVT) was associated with worse OS, being lower in patients with PVT compared to patients without PVT (6.3 months vs. 14.8 months; p = 0.026). Data also showed a decrease in OS in patients with vascular invasion (VI) compared to patients who did not present it (6.3 months vs. 14.8 months; p = 0.041). The group of patients without dermatological events (DE) showed lower OS (6.9 months vs. 14.5 months; p = 0.049). In conclusion, combination of sorafenib + pravastatin was safe and well-tolerated, prolonging the TTP of patients with aHCC but not improving the OS compared to sorafenib + placebo. The absence of PVT and VI and the development of DE are positive prognostic factors of sorafenib response.

[29] *Pradhan A, Bhandari M, Sethi R*. **Ezetimibe and Improving Cardiovascular Outcomes: Current Evidence and Perspectives**. Cardiology research and practice 2020; 2020:9815016.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32670636
ABSTRACT

Low-density lipoprotein lowering with statins has convincingly and consistently proven to reduce cardiovascular events in both primary and secondary prevention. However, despite high-dose statin therapy, residual cardiovascular risk remains and many patients also do not tolerate statins. Ezetimibe was initially projected as a frontline alternative to statin. It is an intestinal cholesterol absorption inhibitor with modest LDL lowering effects. But, major studies failed to demonstrate any beneficial effect of CV outcomes, and the drug was relegated to oblivion. IMPROVE-IT, a contemporary, large, and well-designed trial, unequivocally demonstrated reduction in CV outcomes with ezetimibe when added to statin therapy. The benefits are seen in both sexes, elderly, CKD, diabetes mellitus, and in patients with prior CABG. It also reduces biomarkers and induces plaque regression like statins. The drug has now established itself as an add-on therapy to statin when monotherapy fails to achieve LDL goals and when it is not tolerated. The combination therapy has excellent safety and efficacy record. It has now been endorsed by major guidelines too in management of dyslipidemia. Yes, ezetimibe can indeed improve cardiovascular outcomes!

[30] *Zhu B, Wang J, Chen K et al.* **A high triglyceride glucose index is more closely associated with hypertension than lipid or glycemic parameters in elderly individuals: a cross-sectional survey from the Reaction Study**. Cardiovascular diabetology 2020; 19:112.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32664945
ABSTRACT

BACKGROUND: Both lipid and glucose abnormalities are associated with hypertension (HTN). However, it is unclear whether the triglyceride-glucose (TyG) index is associated with HTN. Therefore the aim of this study is to investigate the association of the TyG index and HTN and to compare the discriminative power of the TyG index, lipid, glycemic parameters for the risk of HTN in elderly individuals. METHODS: The present study was nested in a longitudinal (REACTION) study from May 2011 to December 2011, which was designed to demonstrate the association of abnormal glucose metabolism with the risk of cancer in the Chinese population. In total, 47,808 participants were recruited in this cross-sectional study. The TyG index was divided into five groups: the < 20% group, the 20-39% group, the 40-59% group, the 60-79% group and the ≥ 80% group, according to quintile division of the subjects. Three multivariate logistic regression models were used to evaluate the association between the TyG vs. lipid parameters, glycemic parameters and HTN. RESULTS: Multivariate logistic regression analysis shows that compared with lipid and glycemic parameters, the TyG index remains significantly associated with HTN in either total subjects or subjects separated into men and women (odds ratio (OR) 1.33, 95% confidence interval (CI) 1.18-1.51, $p < 0.0001$ in total subjects; OR 1.39, 95% CI 1.11-1.74, $p = 0.0042$ in men; OR 1.28, 95% CI 1.11-1.49, $p = 0.0010$ in women). In a stratified analysis, an elevated TyG index is significantly associated with HTN in the subgroup of the oldest age (≥ 65) (OR 1.67, 95% CI 1.30-2.14, $p < 0.0001$), as well as with obesity (Body mass index (BMI) ≥ 28 kg/m(2)) (OR 1.85, 95% CI 1.29-2.66, $p = 0.0009$) or lower estimated glomerular filtration rate (eGFR) (< 90 mL/(min·1.73 m(2))) (OR 1.72, 95% CI 1.33-2.21, $p < 0.0001$). CONCLUSION: The TyG index is significantly associated with HTN and shows

the superior discriminative ability for HTN compared with lipid and glycemic parameters in the Chinese elderly population.

[31] *Amersfoort J, Schaftenaar FH, Douna H et al.* **Diet-induced dyslipidemia induces metabolic and migratory adaptations in regulatory T cells**. Cardiovascular research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32653923
ABSTRACT

AIMS: A hallmark of advanced atherosclerosis is inadequate immunosuppression by regulatory T (Treg) cells inside atherosclerotic lesions. Dyslipidemia has been suggested to alter Treg cell migration by affecting the expression of specific membrane proteins, thereby decreasing Treg cell migration towards atherosclerotic lesions. Besides membrane proteins, cellular metabolism has been shown to be a crucial factor in Treg cell migration. We aimed to determine whether dyslipidemia contributes to altered migration of Treg cells, in part, by affecting cellular metabolism. METHODS AND RESULTS: Dyslipidemia was induced by feeding Ldlr-/- mice a Western-type diet for 16-20 weeks and intrinsic changes in Treg cells affecting their migration and metabolism were examined. Dyslipidemia was associated with altered mTORC2 signaling in Treg cells, decreased expression of membrane proteins involved in migration, including CD62L, CCR7 and S1Pr1, and decreased Treg cell migration towards lymph nodes. Furthermore, we discovered that diet-induced dyslipidemia inhibited mTORC1 signaling, induced PPARδ activation and increased fatty acid (FA) oxidation in Treg cells. Moreover, mass-spectrometry analysis of serum from Ldlr-/- mice with normolipidemia or dyslipidemia showed increases in multiple PPARδ ligands during dyslipidemia. Treatment with a synthetic PPARδ agonist increased the migratory capacity of Treg cells in vitro and in vivo in an FA oxidation dependent manner. Furthermore, diet-induced dyslipidemia actually enhanced Treg cell migration into the inflamed peritoneum and into atherosclerotic lesions in vitro. CONCLUSIONS: Altogether, our findings implicate that dyslipidemia does not contribute to atherosclerosis by impairing Treg cell migration as dyslipidemia associated with an effector-like migratory phenotype in Treg cells. TRANSLATIONAL PERSPECTIVE: Dyslipidemia, in the form of hypercholesterolemia and hypertriglyceridemia, is a driver of atherosclerosis and cardiovascular disease (CVD). Hence, lipid-lowering therapy is a cornerstone in the treatment of CVD. In the past years, the clinical feasibility of immunotherapy to treat CVD has also been established. As regulatory T (Treg) cells are specialized in immunosuppression, these cells represent a promising target for additional immunotherapies. The presented study suggests that dyslipidemia affects the metabolism of Treg cells and their migration towards sites of inflammation such as atherosclerotic lesions, suggesting that lipid-lowering therapy and metabolic immunotherapy might affect Treg cells through previously unidentified mechanisms.

[32] *Ehinger E, Ghosheh Y, Pramod AB et al.* **Classical Monocyte Transcriptomes Reveal Significant Anti-Inflammatory Statin Effect in Women with Chronic HIV**. Cardiovascular research 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32658258
ABSTRACT

AIMS: During virally-suppressed chronic HIV infection, persistent inflammation contributes to the development of cardiovascular disease (CVD), a major comorbidity in people living with HIV (LWH). Classical blood monocytes (CMs) remain activated during antiretroviral therapy and are a major source of pro-inflammatory and pro-thrombotic factors that contribute to atherosclerotic plaque development and instability. METHODS AND RESULTS: Here we identify transcriptomic changes in circulating CMs in peripheral blood mononuclear cell samples from participants of the Women's Interagency HIV Study, selected by HIV and subclinical CVD (sCVD) status. We flow-sorted CM from participants of the Women's Interagency HIV Study and deep-sequenced their mRNA (n = 92). CMs of HIV+ participants showed elevated IL-6, IL-1β, and IL-12β, overlapping with many transcripts identified in sCVD+ participants. In sCVD+ participants LWH, those reporting statin use showed reduced pro-inflammatory gene expression to a level comparable with healthy (HIV-sCVD-) participants. Statin non-users maintained an elevated inflammatory profile and increased cytokine production. CONCLUSION: Statin therapy has been associated with a lower risk of cardiac events, such as myocardial infarction in the general population, but not in those LWH. Our data suggest that women LWH may benefit from statin therapy even in the absence of overt CVD. TRANSLATIONAL PERSPECTIVE: Monocytes from women living with HIV express many more pro-inflammatory genes than uninfected controls. An overlapping list of genes is expressed in samples from women with ultrasound evidence of carotid plaque. The inflammatory burden is enhanced in women with both HIV and carotid plaque, and this is mitigated by statin treatment, almost to the level of healthy participants. Thus, the present monocyte transcriptome data from 92 women support the idea that participants with HIV may specifically benefit from statin treatment, perhaps more so than seronegative subjects.

[33] *Morawietz H, Julius U, Bornstein SR*. **Cardiovascular diseases, lipid-lowering therapies and European registries in the COVID-19 pandemic**. Cardiovascular research 2020; 116:e122-e125.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32678443
ABSTRACT

[34] *Xu H, Jia C, Cheng W et al.* **The Effect of L-carnitine Additive During In Vitro Maturation on the Vitrification of Pig Oocytes**. Cellular reprogramming 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32673085
ABSTRACT
Cryopreservation of oocytes/embryos is an important technique for genetic resources; however, the success of vitrification in pig oocytes remained at a relatively lower level due to the high content of lipid droplets (LDs). Considering the positive effect of L-carnitine on the function of LDs, the present study was designed to investigate the effect of the addition of L-carnitine on the vitrification of porcine cumulus cells of complexes (cumulus/oocyte complexes [COCs]). First, COCs were randomly divided into two groups: one group of COCs were commonly in vitro maturation (IVM) for 42-46 hours (nonvitrification [NV]), while another group of COCs were IVM with 10 mM L-carnitine (NVL [nonvitrification with L-carnitine addition in IVM]). In addition, random parts of COCs with L-carnitine addition were vitrified (VL [vitrification with L-carnitine addition in IVM]), while vitrification was performed on COCs without L-carnitine used as control group (V). Results showed that the maturation

rate of pig oocytes reduced significantly when the vitrification was performed at 16 hours during IVM (VL vs. NVL, 40.09 ± 2.85 vs. 90.76 ± 1.16; V vs. NV, 34.41 ± 2.55 vs. 89.71 ± 1.33, p < 0.01). With the addition of L-carnitine, intracellular LDs were decreased significantly (p < 0.01). However, no difference was observed on the efficiency of vitrification in pig oocytes (VL vs. V, 40.09 ± 2.85 vs. 34.41 ± 2.55, p > 0.05). In addition, not only the reactive oxygen species (ROS) level in pig oocytes with the L-carnitine addition group reduced significantly (p < 0.01), but also the expression of SOD1 gene was improved (p < 0.05). In conclusion, results demonstrated that although no difference could be observed on pig COC vitrification, the LDs and ROS level in pig oocytes could be modified by the addition of L-carnitine, which might be helpful for further development.

[35] *Mahmoodi BK, Tragante V, Kleber ME et al.* **Association of Factor V Leiden with Subsequent Atherothrombotic Events: A GENIUS-CHD Study of Individual Participant Data**. Circulation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32654539
ABSTRACT
Background: Studies examining the role of factor V Leiden among patients at higher risk of atherothrombotic events, such as those with established coronary heart disease (CHD) are lacking. Given that coagulation is involved in the thrombus formation stage upon atherosclerotic plaque rupture, we hypothesized that factor V Leiden may be a stronger risk factor for atherothrombotic events in patients with established CHD. Methods: We performed an individual-level meta-analysis including 25 prospective studies (18 cohorts, 3 case-cohorts, 4 randomized trials) from the GENIUS-CHD consortium involving patients with established CHD at baseline. Participating studies genotyped factor V Leiden status and shared risk estimates for the outcomes of interest using a centrally developed statistical code with harmonized definitions across studies. Cox-regression models were used to obtain age and sex adjusted estimates. The obtained estimates were pooled using fixed-effect meta-analysis. The primary outcome was composite of myocardial infarction and CHD death. Secondary outcomes included any stroke, ischemic stroke, coronary revascularization, cardiovascular mortality and all-cause mortality. Results: The studies included 69,681 individuals of whom 3,190 (4.6%) were either heterozygous or homozygous (n=47) carriers of factor V Leiden. Median follow-up per study ranged from 1.0 to 10.6 years. A total of 20 studies with 61,147 participants and 6,849 events contributed to analyses of the primary outcome. Factor V Leiden was not associated with the combined outcome of myocardial infarction and CHD death (hazard ratio, 1.03; 95% CI, 0.92 - 1.16; $I(2) = 28\%$; P-heterogeneity = 0.12). Subgroup analysis according to baseline characteristics or strata of traditional cardiovascular risk factors did not show relevant differences. Similarly, risk estimates for the secondary outcomes including stroke, coronary revascularization, cardiovascular mortality and all-cause mortality were close to identity. Conclusions: Factor V Leiden was not associated with increased risk of subsequent atherothrombotic events and mortality in high-risk participants with established and treated CHD. Routine assessment of factor V Leiden status is unlikely to improve atherothrombotic events risk stratification in this population.

[36] *Hu X, Chen D, Wu L et al.* **Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection**. Clinica chimica acta; international journal of clinical chemistry 2020; 510:105-110.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32653486
ABSTRACT

BACKGROUND: COVID-19 infection is epidemic worldwide. We describe the serum lipid profile of the patients with COVID-19 infection. METHODS: In this retrospective study, we collected the first clinical laboratory data of 114 patients on admission, and 80 healthy controls. Meanwhile, we monitored the serum lipid profile, COVID-19 nucleic acid and chest CT scan of a severe patient from the early stage of infection to the recovery period for a total of 80 days. RESULTS: Compared with the healthy controls, the patients had sharply decreased concentrations of total cholesterol, HDL-cholesterol and LDL-cholesterol ($P < 0.001$). Among the patients, HDL-cholesterol concentration in severe groups was significantly lower than the common groups [1.01 (0.88-1.20) vs 1.21 (1.02-1.48) mmol/l, $P < 0.001$]. The lipid profile of a severe patient showed that serum cholesterol concentration significantly decreased in the early stage and returned to be normal in the recovery period. Moreover, the change of HDL-cholesterol in this patient was consistent with the results of nucleic acid tests and chest CT scans. In correlation analysis, HDL-cholesterol concentration was negatively correlated with C-reactive protein (CRP, $r = -0.396$, $P < 0.001$) and positively correlated with lymphocytes ($r = 0.336$, $P < 0.001$). The area under curve (AUC) in receiver operating characteristic (ROC) of HDL-cholesterol was 0.732 ($P < 0.001$), and, the adjusted odd ratio (OR) of HDL-cholesterol was 0.023 (95% CI 0.002-0.227). CONCLUSIONS: Decreased serum HDL-cholesterol is associated with the severity of COVID-19 infection.

[37] *Xu XY, Guo L, Wang Q et al.* **Association between lipoprotein-associated phospholipase A(2) and lower extremity arterial disease in type 2 diabetes mellitus**. Clinica chimica acta; international journal of clinical chemistry 2020; 510:228-231.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32679127
ABSTRACT

BACKGROUND: Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) is closely related to the development of cardiovascular diseases, and the association between Lp-PLA(2) and lower extremity arterial disease (LEAD) in type 2 diabetes mellitus (T2DM) is inconsistent among previous studies. Thus, the present study aimed to investigate whether the increase in Lp-PLA(2) is related to the occurrence of LEAD in patients with T2DM. METHODS: A total of 519 patients with T2DM (173 patients with LEAD and 346 patients without LEAD) were enrolled in this study. The demographics, medical history, serum lipids, glycosylated hemoglobin, Lp-PLA(2), and ankle-brachial index (ABI) were recorded and analyzed. RESULTS: The diabetes duration, prevalence of female, prevalence of hypertension, and Lp-PLA(2) concentration in the LEAD group were significantly higher than those in the non-LEAD group (duration of diabetes: 15 [10-20] vs 8 [2-12] years, prevalence of female: 49.13% vs 38.73%, prevalence of hypertension: 58.38% vs 38.11%, Lp-PLA(2): 145 [108-178] vs 125 [107-138] ng/ml, $p < 0.05$). Lp-PLA(2) was negatively correlated with ABI ($r = -0.308$, $p < 0.001$). Results of multivariate logistic regression analysis showed that serum Lp-PLA(2) was an independent factor for the development of LEAD (odds ratio: 1.018 [1.007-1.029], $P = 0.001$). CONCLUSIONS: Increased serum Lp-

PLA(2) concentrations are associated with LEAD in patients with T2DM. They are an independent risk factor for the occurrence of LEAD.

[38] *Bhagavathula AS, Aldhaleei WA, Al Matrooshi NO, Rahmani J*. **Efficacy of Statin/Ezetimibe for Secondary Prevention of Atherosclerotic Cardiovascular Disease in Asian Populations: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Clinical drug investigation 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32671595
ABSTRACT

BACKGROUND: Several clinical trials have investigated the effect of statin/ezetimibe combination therapy on secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in the Asian population. OBJECTIVE: This study aimed to summarize study results regarding the effect of statin/ezetimibe combination therapy on lipid parameters and highly sensitive C-reactive protein (HsCRP) biomarkers in ASCVD patients from Asian countries. METHODS: We searched the PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar databases for relevant papers published from 2008 to June 2020. We included randomized controlled trials (RCTs) that (1) were conducted in ASCVD patients in Asian countries; (2) examined the effects of statin/ezetimibe combination therapies compared with a control group; and (3) reported sufficient data on lipid parameters and HsCRP biomarkers. The results were reported as weighted mean differences (WMDs) with 95% confidence intervals (CI) using random-effects models. Funnel plots and Egger's regression test were used to assess publication bias. RESULTS: Twenty-four RCTs were reviewed and 20 were included in the meta-analysis. A total of 4344 participants were included (n = 2197 in the intervention group and n = 2147 in the control group), and the intervention durations ranged from 6 weeks to 3.6 years. Ezetimibe coadministered with statin therapy, compared with control treatment, significantly reduced low-density lipoprotein cholesterol (LDL-C; n = 20 studies) [WMD - 0.39 mmol/L, 95% CI - 0.73 to - 0.05; p < 0.001], triglycerides (TG; n = 18 studies) [WMD - 0.23 mmol/L, 95% CI - 0.33 to - 0.13; p < 0.001], and total cholesterol (TC; n = 17 studies) [WMD - 0.31 mmol/L, 95% CI - 0.45 to - 0.17; p < 0.001). Although the effect of statin/ezetimibe combinations on high-density lipoprotein cholesterol (HDL-C; n = 17 studies) [WMD 0.02 mmol/L, 95% CI - 0.05 to 0.09; p < 0.001) was very minimal and no effect was observed on HsCRP levels (n = 11 studies). CONCLUSIONS: Our study found that statin/ezetimibe combinations reduced LDL-C, TC, and TG levels but had minimal effects on HDL-C and no effect HsCRP biomarkers in ASCVD patients. The statin/ezetimibe therapy enabled a more effective reduction in LDL-C levels; however, the duration of the treatment was suboptimal.

[39] *Abusharar SP, Moku P, Banks S et al.* **Immune mediated necrotizing myopathy: A rare complication of statin therapy**. Clin Pract 2020; 10:1248.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32670535
ABSTRACT

Immune mediated necrotizing myopathy (IMNM) is part of the inflammatory myopathies group of diseases and presents with muscle weakness, myalgias and elevated serum creatine phosphokinase (CPK). Statin-induced IMNM is a rare complication. We present a patient with IMNM secondary to simvastatin use. The patient presented with proximal myopathy, dysphagia, and elevated creatinine kinase levels, and was subsequently found

to have anti-3- hydroxy-3-methylglutaryl-CoA reductase (HMGCR) autoantibodies with a necrotizing process on muscle biopsy. This patient's case was further complicated by sequelae of multiple disease processes, ultimately leading to deterioration of his health.

[40] *Naing C, Ni H*. **Statins for asthma**. The Cochrane database of systematic reviews 2020; 7:Cd013268.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32668027
ABSTRACT

BACKGROUND: Asthma is a common chronic respiratory disease. People with asthma have inflammation of their airways that causes recurrent episodes of wheezing, breathlessness and chest tightness, with or without a cough. Statins possess multiple therapeutic effects, including lowering lipid levels in the blood. Statins are reported to have a potential role as an adjunct treatment in asthma. However, comprehensive evidence of the benefits and harms of using statins is required to facilitate decision making. OBJECTIVES: To assess the benefits and harms of statins as an adjunct therapy for asthma in adults and children. SEARCH METHODS: We searched for studies in the Cochrane Airways Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid SP and Embase Ovid SP, from their inception dates We handsearched the proceedings of major respiratory conferences. We also searched clinical trials registries for completed, ongoing and unpublished studies, and scanned the reference lists of included studies and relevant reviews to identify additional studies. The search is current to 7 February 2020. SELECTION CRITERIA: We included randomised controlled trials (RCTs) with a parallel-group design that assessed statins for at least 12 weeks' duration. We considered all participants with a clinical diagnosis of asthma to be eligible, regardless of age, sex, disease severity and previous or current treatment. We planned to include studies reported as full text, those published as abstract only, and unpublished data. DATA COLLECTION AND ANALYSIS: Two review authors independently screened and selected the studies, extracted outcome data and intervention characteristics from included studies, and assessed risk of bias according to standard Cochrane methodological procedures. We resolved any disagreement through discussion. MAIN RESULTS: We found only one trial involving a total of 60 people living with asthma. The trial compared the effect of atorvastatin with a placebo (dummy treatment containing lactose) in treating people with chronic asthma. The trial did not report data for the primary outcomes or adverse events. There was uncertainty about the relative effect on forced expiratory volume in one second (FEV(1)) and peak expiratory flow (PEF) in the atorvastatin group compared with the placebo group. The study did not report serious adverse effects for the interventions. The included study had internal discrepancies in its reported data. AUTHORS' CONCLUSIONS: The evidence was of very low certainty, so we are unable to draw conclusions about the effectiveness and safety of statins to treat asthma. High-quality RCTs are needed to assess the effect of statins on people with asthma. Well-designed multicentre trials with larger samples and longer duration of treatment are required, which assess outcomes such as adverse events, hospital utilisation and costs, to provide better quality evidence. Future studies that include subgroups of obese people with asthma are also required.

[41] *Liu Y, Chan DKY, Thalamuthu A et al.* **Plasma lipidomic biomarker analysis reveals distinct lipid changes in vascular dementia**. Comput Struct Biotechnol J 2020; 18:1613-1624.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32670502
ABSTRACT
Vascular dementia (VaD) is a complex neurocognitive disorder secondary to a variety of cerebrovascular lesions. Numerous studies have shown that lipid metabolism is involved in the pathobiology of the disease. We examined the plasma lipid profiles in VaD, with the expectation of identifying reliable lipid biomarkers for VaD. 49 VaD patients and 48 healthy controls were recruited from Bankstown-Lidcombe Hospital in Sydney, Australia. Lipids were extracted by single phase 1-butanol/methanol, and untargeted analysis was performed by liquid chromatography coupled-mass spectrometry (LC-MS/MS). Univariate analysis of variance was used to examine the differences in lipid classes and individual lipids between VaD and control groups. In an independent sample of 161 subjects from the Older Australian Twins Study (OATS), elastic net penalization for the generalized linear model (Glmnet) and Random Forest were applied to the lipid levels to subcategorise the sample into vascular cognitive impairment and controls. Most lipids belonging to the classes of ceramides (Cer), cholesterol esters (ChE) and phospholipids were significantly lower in VaD plasma, while glycerides were elevated compared to controls. Levels of ChE, Cer and the two lipid classes together achieved the best accuracy in discriminating VaD from controls, with more than 80% accuracy. The probable VaD group in the OATS sample predicted by the lipid levels showed greater impairment in most cognitive domains, especially attention and processing speed and executive function from controls but did not differ in white matter hyperintensities and DTI measures. As a conclusion, plasma lipids levels, in particular Cer and ChE, are abnormal in VaD and may help discriminate them from healthy controls. Understanding the basis of these differences may provide insights into the pathobiology of VaD.

[42] *Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA et al.* **Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study**. Crit Care 2020; 24:429.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32664990
ABSTRACT

[43] *Freaney PM, Khan SS, Lloyd-Jones DM, Stone NJ.* **The Role of Sex-Specific Risk Factors in the Risk Assessment of Atherosclerotic Cardiovascular Disease for Primary Prevention in Women**. Current atherosclerosis reports 2020; 22:46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32671475
ABSTRACT
PURPOSE OF REVIEW: Robust evidence is emerging regarding the contribution of sex-specific risk factors to a woman's unique risk of atherosclerotic cardiovascular disease (ASCVD). This review summarizes the available literature regarding the association of sex-specific risk factors and ASCVD in women. RECENT FINDINGS: The American College of Cardiology and American Heart Association Guidelines recommend estimation of 10-year risk of a first ASCVD event using the 2013 Pooled Cohort Equations. This can be further personalized by identifying sex-specific risk factors present in a woman's history. There are

multiple vulnerable periods across a woman's life course that are associated with increased risk of ASCVD. Risk factors across the reproductive life course that have been shown to correlate with higher risk for future ASCVD include early menarche, adverse pregnancy outcomes (such as pre-eclampsia or preterm birth), and early natural or surgical menopause. In addition, certain conditions that are more common among women, including autoimmune diseases, history of chest irradiation, and certain chemotherapies, also need to be considered. Finally, risk assessment can be refined with subclinical disease imaging (coronary calcium score) if there remains uncertainty about clinical management with lipid-lowering therapies for primary prevention after inclusion of these risk enhancers. Risk assessment for ASCVD in women requires a personalized approach that incorporates sex-specific risk factors to guide primary prevention measures, such as lipid-lowering therapies. Coronary calcium score imaging may also help further refine risk assessment, but no clinical trials conducted to date have addressed this question.

[44] *Fruchart JC, Hermans MP, Fruchart-Najib J*. **Selective Peroxisome Proliferator-Activated Receptor Alpha Modulators (SPPARMα): New Opportunities to Reduce Residual Cardiovascular Risk in Chronic Kidney Disease?** Current atherosclerosis reports 2020; 22:43.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32671476
ABSTRACT

PURPOSE OF REVIEW: Chronic kidney disease (CKD) poses a major global challenge, which is exacerbated by aging populations and the pandemic of type 2 diabetes mellitus. Much of the escalating burden of CKD is due to cardiovascular complications. Current treatment guidelines for dyslipidemia in CKD prioritize low-density lipoprotein cholesterol management, but still leave a high residual cardiovascular risk. Targeting elevated triglycerides and low plasma high-density lipoprotein cholesterol, a common feature of CKD, could offer additional benefit. There are, however, safety issues with current fibrates (peroxisome proliferator-activated receptor alpha [PPARα] agonists), notably the propensity for elevation in serum creatinine, indicating the need for new approaches. RECENT FINDINGS: Interactions between the ligand and PPARα receptor influence the specificity and potency of receptor binding, and downstream gene and physiological effects. The peroxisome proliferator-activated receptor alpha modulator (SPPARMα) concept aims to modulate the ligand structure so as to enhance binding at the PPARα receptor, thereby improving the ligand's selectivity, potency, and safety profile. This concept has led to the development of pemafibrate, a novel SPPARMα agent. This review discusses evidence that differentiates pemafibrate from current fibrates, especially the lack of evidence for elevation in serum creatinine or worsening of renal function in high-risk patients, including those with CKD. Differentiation of pemafibrate from current fibrates aims to address unmet clinical needs in CKD. The ongoing PROMINENT study will provide critical information regarding the long-term efficacy and safety of pemafibrate in patients with type 2 diabetes mellitus, including those with CKD, and whether the favorable lipid-modifying profile translates to reduction in residual cardiovascular risk.

[45] *Denegri A, Boriani G*. **High sensitivity C-reactive protein (hsCRP) and its implications in cardiovascular outcomes**. Current pharmaceutical design 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32679014

ABSTRACT
Atherosclerosis and its fearsome complications represent the first cause of morbidity and mortality worldwide. Over the last two decades, several evidences have been accumulated, suggesting a central role for inflammation in atheroma development. High sensitivity C-reactive protein (hsCRP) is a well-established marker of cardiovascular (CV) disease; high levels of hsCRP have been associated with adverse CV outcome after acute coronary syndrome (ACS) and, despite some controversy, an active role for hsCRP in initiation and development of the atherosclerotic plaque has been also proposed. Randomized clinical trials focusing on hsCRP have been crucial in elucidating the anti-inflammatory effects of statin therapy. Thus, hsCRP has been progressively considered a real CV risk factor likewise to low-density lipoprotein cholesterol (LDL-C), rising the concept of residual CV inflammatory risk. Subsequent research has been designed to investigate potential new targets of atherothrombotic protection. Despite clinical usefulness of hsCRP is widely recognized, hsCRP may not represent the ideal target of specific anti-inflammatory therapies. Clinical investigations, therefore, have focused also on other inflammatory mediators, restricting hsCRP to an indicator rather than a therapeutic target. The aim of the present review is to provide an illustrative overview on the current knowledge of atherosclerosis and inflammation, highlighting the most representative clinical studies of lipid lowering- and antiinflammatory therapies focused on hsCRP in CV diseases.

[46] *Roger C, Buch C, Muller T et al.* **Simultaneous Inhibition of Peripheral CB1R and iNOS Mitigates Obesity-Related Dyslipidemia Through Distinct Mechanisms**. <u>Diabetes</u> 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32680936

ABSTRACT
Diabetic dyslipidemia (DD), characterized by increased plasma triglycerides (TGs) and decreased high-density lipoprotein cholesterol (HDL) levels, is a major factor contributing to non-alcoholic steatohepatitis (NASH) and cardiovascular risk in type-2 diabetes. Activation of both the cannabinoid-1 receptor (CB1R) and inducible nitric oxide synthase (iNOS) are associated with NASH progression. Here, we tested whether dual-targeting inhibition of hepatic CB1R and iNOS improves DD in diet-induced obese (DIO) mice. DIO mice were treated for 14 days with (S)-MRI-1867, a peripherally-restricted hybrid inhibitor of CB1R and iNOS. (R)-MRI-1867, the CB1R-inactive stereoisomer which retains iNOS inhibitory activity and JD-5037, a peripherally-restricted CB1R antagonist were used to assess the relative contribution of the two targets to the effects of (S)-MRI-1867. (S)-MRI-1867 reduced hepatic steatosis, the rate of hepatic VLDL secretion, upregulated hepatic LDLR expression and reduced the circulating levels of the proprotein convertase subtilisin/kexin type 9 (PCSK9). The decrease in VLDL secretion could be attributed to CB1R blockade while the reduction of PCSK9 levels and the related increase in LDLR resulted from iNOS inhibition via a mTORC1-dependent mechanism. In conclusion, this approach based on the concomitant inhibition of CB1R and iNOS represents a promising therapeutic strategy for the treatment of dyslipidemia.

[47] *Goldberg RB, Stone NJ, Grundy SM*. **The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines**

on the Management of Blood Cholesterol in Diabetes. Diabetes Care 2020; 43:1673-1678.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32669405

ABSTRACT
The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines recently published its 2018 recommendations on management of LDL cholesterol (LDL-C) in people with diabetes. For primary prevention, moderate-intensity statin therapy is recommended for those aged 40-75 years, with a preference for high-intensity statin treatment for older subjects and for those with higher estimated risk or risk-enhancing factors following a patient-clinician discussion. Statin therapy may be reasonable in adults <40 years or >75 years of age where there is less evidence for benefit. For people with diabetes and established atherosclerotic cardiovascular disease, high-intensity statin therapy is recommended. The majority of these subjects have very high risk, and an LDL-C goal of <70 mg/dL is recommended. If this target is not achieved, ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 inhibitor may be added.

[48] *Peters F, Kreutzburg T, Rieß HC et al.* **Optimal Pharmacological Treatment of Symptomatic Peripheral Arterial Occlusive Disease and Evidence of Female Patient Disadvantage: An Analysis of Health Insurance Claims Data**. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32669223

ABSTRACT
OBJECTIVE: Optimal pharmacological treatment (OPT) for peripheral arterial occlusive disease (PAOD) includes prescription of lipid lowering drugs, antithrombotics, and antihypertensives to symptomatic patients affected by intermittent claudication or chronic limb threatening ischaemia. This study sought to determine sex disparities and time trends in prescription of OPT in this population (clinicaltrials.gov NCT03909022). METHODS: Using data from the second largest insurance fund in Germany, BARMER, data on patients with an index admission for symptomatic PAOD between 1 January 2010 and 30 June 2018 with follow up until the end of 2018 were analysed. Sex disparities in post-discharge prescription status six months after index admission were tested and adjusted for patient and healthcare variables using bivariable tests and logistic regression analysis. Time trends in the prescription prevalence of OPT were analysed and tested. RESULTS: There were 83 867 patients (mean age 71.9 years and 45.8% women) eligible for inclusion in the study. When compared with men, women had lower rates of prior outpatient care for PAOD (39.8% vs. 47.0%), were admitted more often with ischaemic rest pain (13.9% vs. 10.4%) and were older (74 vs. 70 y). After discharge, women had a lower rate of prescriptions for lipid lowering drugs (52.4% vs. 59.9%), while they received antihypertensive drugs more often (86.7% vs. 84.1%). We found evidence for a lower prescription prevalence of OPT in females (37.0% vs. 42.7%). Differences in patient and healthcare variables (e.g. demographics, comorbidities, prior treatment) between women and men explained 56% of this gap. The sex prescription gap did not narrow over time despite an overall upward trend in prescription prevalence for both women and men. CONCLUSION: Although presenting older and with more severe symptoms at the index admission for PAOD, women have a

lower prescription prevalence of OPT compared with men, particularly with respect to lipid lowering drugs.

[49] *Naz F, Arish M*. **Battling COVID-19 Pandemic: Sphingosine-1-Phosphate Analogs as an Adjunctive Therapy?** Frontiers in immunology 2020; 11:1102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32670273
ABSTRACT
With the sudden outbreak of COVID-19 patient worldwide and associated mortality, it is critical to come up with an effective treatment against SARS-CoV-2. Studies suggest that mortality due to COVID 19 is mainly attributed to the hyper inflammatory response leading to cytokine storm and ARDS in infected patients. Sphingosine-1-phosphate receptor 1 (S1PR1) analogs, AAL-R and RP-002, have earlier provided in-vivo protection from the pathophysiological response during H1N1 influenza infection and improved mortality. Recently, it was shown that the treatment with sphingosine-1-phosphate receptor 1 analog, CYM5442, resulted in the significant dampening of the immune response upon H1N1 challenge in mice and improved survival of H1N1 infected mice in combination with an antiviral drug, oseltamivir. Hence, here we suggest to investigate the possible utility of using S1P analogs to treat COVID-19.

[50] Myrie SB, Steiner RD, Mymin D. Sitosterolemia. In: GeneReviews(®). Edited by: Adam MP, Ardinger HH, Pagon RA *et al.* Seattle (WA): University of Washington, Seattle Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.; 1993.
[51] *Yu M, Wang W, Wang H*. **The Late-Gestational Triglyceride to High-Density Lipoprotein Cholesterol Ratio Is Associated with Neonatal Macrosomia in Women without Diabetes Mellitus**. Int J Endocrinol 2020; 2020:7250287.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32655633
ABSTRACT
OBJECTIVE: To investigate the associations between late-gestational dyslipidemia, expressed as the ratio between triglycerides (TGs) and high-density lipoprotein cholesterol (HDL), and the risk of macrosomia among nondiabetic pregnant women. METHODS: In this case-control study, 171 pregnant women who delivered macrosomia newborns were recruited from a total of 1856 nondiabetic pregnant women who delivered a singleton, nonanomalous newborn. A total of 684 normal controls were one-to-four matched by age. Logistic regression analysis was used to analyze the association between the TG/HDL ratio and the neonatal body weight as well as the risk of macrosomia. RESULTS: The maternal serum TG and TG/HDL levels were much higher in the macrosomia group, while the maternal serum HDL-C levels were much lower in the macrosomia group than those in the control group. However, the serum total cholesterol (TC) and LDL-C levels were not significantly different between the two groups. Furthermore, maternal TG/HDL levels were positively associated with neonatal body weight. The confounding factors including maternal age, maternal height, gestational age, maternal body mass index (BMI), FPG, SBP, and neonatal sex were adjusted. A positive association between TG/HDL and neonatal body weight was still found. Moreover, the prevalence of macrosomia increased markedly in a dose-dependent manner as with maternal TG/HDL levels increased. CONCLUSIONS: Maternal serum TG/HDL levels at late gestation are positively associated

with neonatal body weight and the risk of macrosomia in women without DM. Maintaining maternal lipid levels in an appropriate range is important in the context of fetal overgrowth and primary prevention of macrosomia.

[52] *Liu CJ, Huang HS*. **Statins significantly alter urinary stone-related urine biochemistry in calcium kidney stone patients with dyslipidemia**. Int J Urol 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32681579
ABSTRACT
OBJECTIVE: To investigate whether the use of statins would alter 24-h urine biochemistry in male patients with calcium kidney stones. METHODS: We prospectively recruited 78 male patients with calcium kidney stones between May 2017 and December 2017, and 30 male controls with matching sex and age, but without kidney stones. All patients were classified into higher- and lower-risk groups of atherosclerotic cardiovascular disease according to the American College of Cardiology/American Heart Association guidelines. Atorvastatin 20 mg per day was prescribed for 12 weeks to the higher risk patients. For kidney stone group, 24-h urine collections were carried out before and after statin therapy. RESULTS: A total of 78 patients and 30 controls were included. Higher-risk patients had significantly higher urine uric acid and calcium levels than lower-risk patients. After atorvastatin treatment for 12 weeks, urine citrate significantly increased ($P < 0.001$) accompanied with increased urine pH ($P < 0.001$), whereas urine uric acid significantly decreased after treatment. Although urine oxalate significantly increased after treatment ($P = 0.037$), we did not find any significant difference in urine calcium, ion activity product of calcium oxalate and ion activity product of calcium phosphate. CONCLUSION: These findings suggest that atorvastatin administration might increase urinary citrate and decrease urinary uric acid in patients with calcium kidney stones and dyslipidemia.

[53] *Furlanetto ML, Jr., Chagas EFB, Slm P*. **Atherosclerotic Extension of Carotid Arteries: An Insertion in Clinical Practice**. Int J Vasc Med 2020; 2020:3120327.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32655952
ABSTRACT
INTRODUCTION: Atherosclerotic disease is a diffuse disease that is strongly associated with age, risk factors, and variable progression. The anatomical prevalence of atheromas does not always follow, a sequence by sectors, and in many cases are concomitant. OBJECTIVES: This study is aimed at studying atherosclerosis in the arterial territories of the carotid and lower limbs, in order to correlate their extension as a form of primary prevention. METHODS: Participating patients with the main risk factors for atherosclerotic disease were composed of two groups: one with chronic peripheral obstructive arterial disease (PAD) and another without PAD. After performing carotid ultrasound Doppler (USD) of all patients, the occasional prevalence of the disease was evaluated. We performed by statistical tests the correlation between the findings in these patients and the risk factors. Obtaining n from 226 patients, in which 116 patients are from the PAD group and 110 patients are from the group without PAD. RESULTS: Our findings add up to 8.8% for lesions over 50% in patients with PAD, with 6.2% over 70% meeting the few published scientific findings. In this study, the correlation was evaluated between carotid stenosis and PAD, in which we observed a positive association. We observed in the studies that the prevalence of moderate and severe carotid stenosis was similar to patients with coronary

artery disease (CAD). There are a number of nonclassical risk factors that we do not evaluate, but even studying the traditional ones, we find that they are less than 27% dependent. CONCLUSION: Therefore, our study proposes an improvement in the clinical approach of patients with PAD for both the carotid and coronary territory, not using only 2 factors traditional risk factors, for the extension study and to consider the PAD that has 10% dependence alone, as effect and projection of the carotid atherosclerotic plaque.

[54] *Didas N, Thitisopee W, Porntadavity S, Jeenduang N*. **Arylesterase activity but not PCSK9 levels is associated with chronic kidney disease in type 2 diabetes**. International urology and nephrology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32661629
ABSTRACT

PURPOSE: Oxidative stress and dyslipidemia have been found to be associated with the progression of chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM) patients. Paraoxonase 1 (PON-1) activity, and proprotein convertase subtilisin kexin type 9 (PCSK9) levels play an important role regarding anti-oxidants, and lipid metabolism, respectively. The aim of this study was to investigate the association of PON-1 activity, and PCSK9 levels with CKD in T2DM. METHODS: A total of 180 T2DM (87 CKD, and 93 non-CKD) with age-, and gender-matched subjects were recruited in this study. PON-1 activity was measured with two kinds of substrate: paraoxon for paraoxonase (PONase) activity and phenylacetate for arylesterase (AREase) activity. PCSK9 levels were measured by enzyme-linked immunosorbent assay (ELISA). RESULTS: AREase activity was significantly lower in CKD compared with non-CKD (225.53 ± 108.73 vs. 257.45 ± 106.12 kU/L, $p = 0.044$) in T2DM, whereas there was no significant difference in PONase activity and PCSK9 levels between CKD and non-CKD groups. In addition, multivariate logistic regression analysis showed that the lowest tertile of AREase increased the risk for CKD in T2DM (OR 3.251; 95% CI 1.333-7.926, $p = 0.010$), whereas PONase activity and PCSK9 levels were not associated with CKD in T2DM. CONCLUSION: Reduced AREase activity can increase the risk for CKD in T2DM patients. AREase activity, but not PONase activity and PCSK9 levels, may be used as the biomarker for predicting the progression of CKD in T2DM.

[55] *Koch EAT, Nakhoul R, Nakhoul F, Nakhoul N*. **Autophagy in diabetic nephropathy: a review**. International urology and nephrology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32661628
ABSTRACT

Diabetes mellitus (DM) is the leading cause of end stage renal disease. 40% of the patients worldwide will require replacement therapy after 20 years of DM worldwide. Early-stage diabetic nephropathy is characterized by hyperfiltration related to hypeglycemia-induced afferent artery vasodilatation with micro-and macroalbuminuria. Later on, proteinuria with arterial hypertension may appear, culminating in glomerular filtration rate (GFR) decline and end stage renal disease. Forty percent of diabetic patients develop microvascular and macrovascular complications, with increased risk among patients with genetic predisposition, such as Haptoglobin 2-2 phenotype. The most frequent complications in the daily clinical practice are diabetic kidney disease, diabetic retinopathy and vascular disease, such as coronary artery disease and stroke. Various pathways are involved in the

pathogenesis of diabetic kidney disease. Chronic systemic inflammation and the inflammatory response, such as increased circulating cytokines (Interleukins), have been recognized as main players in the development and progression of diabetic kidney disease. DM is also associated with increased oxidative stress, and alterations in carbohydrate, lipid and protein metabolism. Overexpression of the renin-angiotensin-aldosterone system (RAAS) in the kidney, the vitamin D-Vitamin D receptor-klotho axis, and autophagy. Differences in the ATG5 protein levels or ATG5 gene expression involved in the autophagy process have been associated with diabetic complications such as diabetic kidney disease. Under normal blood glucose level, autophagy is an important protective mechanism in renal epithelial cells, including podocytes, proximal tubular, mesangial and endothelial cells. Down regulation of the autophagic mechanism, as in hyperglycemic condition, can contribute to the development and progression of diabetic kidney disease.

[56] *Hughes D, Crowley J, O'Shea P et al.* **Lipid reference values in an Irish population**. Irish journal of medical science 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32681272
ABSTRACT
BACKGROUND AND AIMS: There is limited information on reference values for lipids and lipoproteins in an Irish population. In this observational study, we have described the distributions of lipids in a large Irish cohort. METHODS: Over 110,000 lipid profiles were selected from a database of almost 1.5 million consecutive lipid profiles performed in the Clinical Biochemistry Laboratory in University Hospital Galway between 2004 and 2017 to best represent the Irish population. Age- and sex-related reference intervals for both sexes for total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol, from the age of ten to greater than 90 years, were determined. Two methods for estimating LDL cholesterol were also compared. RESULTS: Sex-related differences in lipid distributions arise before the age of 20 years and are life-long. In both sexes total and LDL cholesterol levels gradually increased towards middle age with a decrease towards old age. Levels tended to be higher in males than in females up to mid-life at which stage they cross over with females having on average higher levels. The median of the triglyceride distributions show similar age- and sex-related changes to total cholesterol, but the distributions show a very marked positive skew that is particularly obvious in middle aged males. HDL cholesterol distributions change little throughout life with males having lower levels than females. Changing from the Friedewald formula to that proposed by Martin would impact the management of some patients with dyslipidaemia. CONCLUSIONS: This study provides lipid reference values for clinical biochemistry laboratories and clinicians working in Ireland. It is informative for public health initiatives wishing to target dyslipidaemia as a modifiable risk for cardiovascular disease and for investigators researching geographical and temporal variances in lipid parameters.

[57] *Leucker TM, Gerstenblith G, Schär M et al.* **Evolocumab, a PCSK9-Monoclonal Antibody, Rapidly Reverses Coronary Artery Endothelial Dysfunction in People Living With HIV and People With Dyslipidemia**. Journal of the American Heart Association 2020; 9:e016263.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674634
ABSTRACT

Background PCSK9 (proprotein convertase subtilisin/kexin type 9) is well recognized for its important role in cholesterol metabolism. Elevated levels are associated with increased cardiovascular risk and inhibition with PCSK9 antibodies (PCSK9i) lowers cardiovascular events in patients with coronary artery disease. PCSK9 levels are also elevated in people living with HIV (PLWH) and those with dyslipidemia. Because increased PCSK9 in PLWH is associated with impaired coronary endothelial function, a barometer of coronary vascular health, we tested the hypothesis that PCSK9i improves impaired coronary endothelial function in dyslipidemia without coronary artery disease and in PLWH with nearly optimal/above goal low-density lipoprotein cholesterol levels. Methods and Results We performed a single-center study in 19 PLWH and 11 with dyslipidemia to evaluate the effects of the PCSK9i evolocumab on coronary endothelial function using cine 3T MRI to noninvasively measure coronary endothelial function, assessed as the changes in coronary cross-sectional area and coronary blood flow from rest to that during isometric handgrip exercise, a known endothelial-dependent vasodilator. Before evolocumab, there was a decrease or no coronary vasodilation and no increase in coronary blood flow (the normal responses) to isometric handgrip exercise in either group. Following 6 weeks of evolocumab, 480 mg q4 weeks, the % cross-sectional area changes from rest to isometric handgrip exercise were +5.6±5.5% and +4.5±3.1% in the PLWH and dyslipidemia groups, respectively, both P<0.01 versus baseline. Improved cross-sectional area was paralleled by a significant coronary blood flow improvement in both groups. Conclusions To our knowledge, these data represent the first evidence that PCSK9 inhibition improves coronary artery health in PLWH and people with dyslipidemia. Registration URL: https://www.clinicaltrials.gov; Unique identifier: NCT03500302.

[58] *Fujii Y, Nouso K, Matsushita H et al.* **Low-Density Lipoprotein (LDL)-Triglyceride and Its Ratio to LDL-Cholesterol as Diagnostic Biomarkers for Nonalcoholic Steatohepatitis**. J Appl Lab Med 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674154
ABSTRACT
BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is the most common type of liver disease, but it is difficult to distinguish its pathogenic phenotype, nonalcoholic steatohepatitis (NASH), from nonalcoholic fatty liver (NAFL) without a liver biopsy. We analyzed serum lipids, including low-density lipoprotein triglyceride (LDL-TG), to elucidate their usefulness for diagnosing NASH. PATIENTS AND METHODS: Serum samples obtained from 35 NASH and 9 NAFL biopsy-confirmed patients and 6 healthy volunteers (HLT) were studied for 13 lipid-related markers and compared between HLT, NAFL, and NASH groups. The relationship between histological findings and the lipid markers was also analyzed. RESULTS: There were significant differences in triglyceride, LDL-TG, the ratio of LDL-TG to the LDL-cholesterol (LDL-TG/LDL-C), small dense LDL-C, and apolipoprotein E between the three groups. Among the 5 lipid components, serum LDL-TG level and the ratio of LDL-TG to the LDL-cholesterol (LDL-TG/LDL-C) were significantly elevated in NASH. The median concentrations of LDL-TG in HLT, NAFL, and NASH were 9, 15, and 20 mg/dL (P < 0.001), and those of LDL-TG/LDL-C were 0.097, 0.102, and 0.173 (P < 0.001), respectively. Although the degree of steatosis was not correlated with the LDL-TG/LDL-C, the ratio was significantly higher in patients with lobular inflammation (P = 0.071), ballooning (P = 0.031), and fibrosis (P < 0.001). The area under the receiver

operating characteristic curve of the ratio for distinguishing NASH from NAFL was 0.857. The rest of studied markers showed no significant utility. CONCLUSION: Serum LDL-TG levels and the LDL-TG/LDL-C ratio might serve as simple and noninvasive diagnostic biomarkers for NASH.

[59] *Kotani K, Sakane N.* **Effects of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor on Oxidized Lipoprotein Levels: A Case Report**. J Appl Lab Med 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32674159
ABSTRACT

[60] *Tanner RM, Colantonio LD, Kilgore ML et al.* **Low-density lipoprotein cholesterol levels among individuals experiencing statin-associated symptoms: Data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study**. Journal of clinical lipidology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32680814
ABSTRACT

BACKGROUND: Guidelines recommend adults who discontinue statin therapy because of statin-associated symptoms be reinitiated. Low-density lipoprotein cholesterol (LDL-C) levels achieved after statin reinitiation are unknown. OBJECTIVE: The objective of this study was to determine LDL-C levels after statin reinitiation. METHODS: We analyzed data from 5498 participants in the REasons for Geographic And Racial Differences in Stroke study who reported ever taking a statin. We categorized participants according to their pattern of statin use including those taking a statin who did not experience statin-associated symptoms and continued treatment, and those who discontinued statins because of statin-associated symptoms and were not reinitiated, reinitiated and remained on treatment, and discontinued treatment after being reinitiated. Mortality and vascular event reduction with statin reinitiation was estimated using data from the Cholesterol-Lowering Treatment Trialists Collaboration. RESULTS: After multivariable adjustment, LDL-C was 14.1 (95% CI: 9.9-18.3) mg/dL higher among participants reinitiated and taking a statin compared with those without statin-associated symptoms who continued statin therapy. Mean LDL-C was 18.1 mg/dL (95% CI: 13.0-23.1) and 27.5 mg/dL (95% CI: 20.7-34.4) lower among participants reinitiated and taking a statin compared with those who discontinued statin therapy and were not reinitiated and those who discontinued statins after being reinitiated, respectively. An LDL-C reduction of 18.1 mg/dL with statin reinitiation was projected to reduce all-cause and coronary heart disease mortality by 5.6% and 8.9%, respectively, and myocardial infarction or coronary heart disease death and major vascular events by 10.7% and 9.8%, respectively, over 5 years. CONCLUSION: Reinitiating individuals who discontinue statin therapy may reduce LDL-C and cardiovascular risk.

[61] *Takamiya Y, Kobayashi K, Kudo T et al.* **Comprehensive Efficacy of the Dipeptidyl Peptidase 4 Inhibitor Alogliptin in Practical Clinical Settings: A Prospective Multi-Center Interventional Observational Study**. Journal of clinical medicine research 2020; 12:423-430.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32655736
ABSTRACT

BACKGROUND: This study aimed to verify the safety and efficacy, including glycemic control, of the selective dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes. METHODS: This study used a multi-center, open-label, prospective observational design. Type 2 diabetes patients who were undergoing dietary therapy and/or exercise therapy alone without sufficient glycemic control (hemoglobin A1c (HbA1c) ≥ 6.5% and < 10%) were administered alogliptin (25 mg/day). The long-term effects (6 and 12 months) on blood glucose, blood pressure, heart rate, body weight and lipids were assessed. RESULTS: A final 50 patients were included with a high prevalence of hypertension (77%) and dyslipidemia (72%), and a mean duration of diabetes of 4.5 years. Pre-treatment HbA1c was 7.5% and was significantly decreased at 6 and 12 months (6M: 6.4%, 12M: 6.2%; $P < 0.02$ vs. 0M, respectively). Body weight, blood pressure and low-density lipoprotein cholesterol were significantly decreased by 6 months and maintained at 12 months. Triglycerides showed a significant decrease at 12 months. No significant differences were observed in HbA1c decrease for different grade of age, duration of diabetes, body mass index and renal function. The degree of decrease in HbA1c was most strongly correlated with pre-treatment HbA1c. Adverse events were noted in three patients, with no serious outcomes. CONCLUSION: The blood glucose-lowering effect and safety of alogliptin were demonstrated regardless of baseline HbA1c, although its effect appeared stronger with higher pre-treatment HbA1c values. Additionally, alogliptin appears useful for managing atherosclerotic risk factors such as body weight and blood pressure.

[62] *Rajpal A, Rahimi L, Ismail-Beigi F*. **Factors Leading to High Morbidity and Mortality of COVID-19 in Patients with Type 2 Diabetes**. Journal of diabetes 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32671936
ABSTRACT
COVID-19 is a recent pandemic caused by SARS-Cov-2, a novel coronavirus. Diabetes (mostly type 2 diabetes mellitus, T2DM) and hyperglycemia are among the major comorbidities in patients with COVID-19 leading to poor outcomes. Reports show that patients with diabetes and COVID-19 are at an increased risk for developing severe complications including acute respiratory distress syndrome (ARDS), multi-organ failure and death. Here we explore potential mechanistic links that could explain the observed higher morbidity and mortality in this patient population. Patients with T2DM have an underlying increased level of inflammation associated with obesity and insulin resistance in addition to other comorbidities including HTN, obesity, CVD, dyslipidemia and being older. We review evidence that T2DM with hyperglycemia are among factors that lead to elevated expression of ACE2 in lungs and other tissues; ACE2 is the cellular "receptor" and port of viral entry. The pre-existing chronic inflammation with augmented inflammatory response to the infection and the increasing viral load leads to extreme systemic immune response ("cytokine storm") that is strongly associated with increased severity of COVID-19. Based on the available evidence, it is recommended by a panel of experts that safe but stringent control of blood glucose, blood pressure and lipids be carried out in patients with T2DM, measures that could potentially serve to decrease the severity of COVID-19 should these patients contract the viral infection. Once the infection occurs, then attention should be directed to proper glycemic control with use of insulin and frequent monitoring of blood glucose levels.

[63] *Chen Y, Zhang H, Hu L et al.* **Pravastatin attenuates atherosclerosis after myocardial infarction by inhibiting inflammatory Ly6C(high) monocytosis in apolipoprotein E knockout mice**. J Int Med Res 2020; 48:300060520932816.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32662710
ABSTRACT

OBJECTIVE: To evaluate the protective effect of pravastatin on atherosclerotic development and inflammatory monocyte subset in atherosclerotic apolipoprotein E (ApoE)(-/-) mice after myocardial infarction (MI). METHODS: Male ApoE(-/-) mice (8 weeks old) were fed a high-fat diet for 14 weeks throughout the experiment. A MI model was produced using 18-week-old ApoE(-/-) mice. They were randomly divided into three groups: sham group, MI group, and MI+Pra group (40 mg/kg/day pravastatin). After 4 weeks (at the end of the study period), the mice were sacrificed and cardiac function was evaluated by echocardiography. Aortic lesion areas were evaluated using oil red O staining. Plaque macrophage in aortic sinus was analyzed by immunofluorescence staining. Flow cytometry was used to explore the proportions of monocyte subsets in the blood, spleen, and bone marrow. . RESULTS: Pravastatin improved cardiac function and reduced lesion areas. It also attenuated the supply of monocytes in spleen, especially the inflammatory Ly6C(high) monocyte subset. Pravastatin also subsequently reduced macrophage accumulation in atherosclerotic lesions. CONCLUSIONS: MI accelerated chronic atherosclerosis progress. Pravastatin suppressed atherosclerotic development and inhibited inflammatory monocytosis after MI in ApoE(-/-) mice.

[64] *Hayrapetian A, Berenji GR, Nguyen KL, Li Y.* **(18)F-Sodium fluoride uptake is associated with severity of atherosclerotic stenosis in stable ischemic heart disease**. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32676905
ABSTRACT

BACKGROUND: Increased uptake of (18)F-Sodium fluoride ((18)F-NaF) PET has potential to identify atherosclerotic plaques that are vulnerable to rupture. Whether (18)F-NaF PET can evaluate the significance of atherosclerotic plaque in patients with stable coronary artery disease is less clear. We evaluated (18)F-NaF PET uptake in coronary arteries in patients without acute coronary artery syndrome to determine the association of (18)F-NaF signal uptake with severity of coronary stenosis. METHODS AND RESULTS: We retrospectively identified 114 patients who received both regadenoson stress (82)Rb myocardial perfusion PET and (18)F-NaF PET study with an average interval of 5 months. Out of this cohort, forty-one patients underwent invasive coronary angiography. In a patient-based analysis, patients with ischemic regadenoson stress (82)Rb PET had significantly higher coronary (18)F-NaF uptake than patients with normal myocardial perfusion (P < .01). Among the 41 patients who underwent coronary angiography, per-vessel (18)F-NaF uptake in both obstructive and nonobstructive coronary arteries was significantly higher than in normal coronary arteries (P < .05) regardless of the severity of coronary calcification. There was poor correlation between calcification and (18)F-NaF uptake in coronary arteries (r = 0.41) CONCLUSION: Coronary arterial (18)F-NaF uptake is associated with coronary stenosis severity in patients with stable coronary artery disease. (18)F-NaF PET studies may be useful for characterizing coronary atherosclerotic plaques.

[65] *Merritt RJ, Bhardwaj V, Jami MM*. **Fish oil and COVID-19 thromboses**. Journal of vascular surgery. Venous and lymphatic disorders 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32682081
ABSTRACT

[66] *Varin EM, Hanson A, Beaudry JL et al.* **Hematopoietic vs. enterocyte-derived dipeptidyl peptidase-4 differentially regulates triglyceride excursion in mice**. JCI insight 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32663193
ABSTRACT
Post-prandial triglycerides (TGs) are elevated in people with type 2 diabetes (T2D) and glucoregulatory agents such as Glucagon-like-peptide-1 (GLP-1) receptor agonists and Dipeptidyl Peptidase-4 (DPP-4) inhibitors simultaneously reduce post-prandial TG excursion. Although the glucose-lowering mechanisms of DPP-4 have been extensively studied, how the reduction of DPP-4 activity improves lipid tolerance remains unclear. Here we demonstrate that gut-selective and systemic inhibition of DPP-4 activity reduces post-prandial TG excursion in young mice. Genetic inactivation of Dpp4 simultaneously within endothelial cells (ECs) and hematopoietic cells using Tie2-Cre reduces intestinal lipoprotein secretion under regular chow (RC) diet conditions. Bone marrow transplantation revealed a key role for hematopoietic cells in modulation of lipid responses arising from genetic reduction of DPP-4 activity. Unexpectedly, deletion of Dpp4 in enterocytes increases TG excursion in high fat diet (HFD)-fed mice. Moreover, chemical reduction of DPP-4 activity and increased levels of GLP-1 are uncoupled from triglyceride excursion in older or HFD-fed mice, yet lipid tolerance remains improved in older Dpp4-/- and Dpp4EC-/- mice. Taken together, this study defines new roles for specific DPP-4 compartments, age, and diet as modifiers of DPP-4 activity linked to control of gut lipid metabolism.

[67] *Liu Y, Zhang Z, Xia B et al.* **Relationship between the non-HDLc-to-HDLc ratio and carotid plaques in a high stroke risk population: a cross-sectional study in China**. Lipids in health and disease 2020; 19:168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660519
ABSTRACT
BACKGROUND: Evidence on the association between the non-high-density lipoprotein cholesterol (non-HDLc)-to-high-density lipoprotein cholesterol (HDLc) ratio (non-HDLc/HDLc) and carotid plaques is still limited. This study aims to assess the relationship between the non-HDLc/HDLc and carotid plaques in a population with a high risk of stroke. METHODS: A cross-sectional study based on the community was conducted in Yangzhou, China. Residents (no younger than 40 years old) underwent questionnaire interviews, physical examinations, and laboratory testing during 2013-2014. The subjects with a high risk of stroke were further selected (at least three of eight risk factors including hypertension, atrial fibrillation, type 2 diabetes mellitus, dyslipidaemia, smoking, lack of exercise, overweight, and family history of stroke) or a transient ischaemic attack (TIA) or stroke history. Carotid ultrasonography was then performed on the high stroke risk participants. Carotid plaque was defined as a focal carotid intima-media thickness (cIMT) ≥1.5 cm or a discrete structure protruding into the arterial lumen at least 50% of the

surrounding cIMT. Logistic regression was employed to evaluate the relationship between the non-HDLc/HDLc and carotid plaques. RESULTS: Overall, 839 subjects with a high risk of stroke were ultimately included in the analysis, and carotid plaques were identified in 341 (40.6%) of them. Participants in the highest non-HDLc/HDLc tertile group presented a higher proportion of carotid plaques than did those in the other two groups. After adjustment for other confounders, each unit increase in the non-HDLc/HDLc was significantly associated with carotid plaques (OR 1.55, 95%CI 1.28-1.88). In the subgroup analysis, the non-HDLc/HDLc was positively and significantly associated with the presence of carotid plaques in most subgroups. Additionally, the non-HDLc/HDLc interacted significantly with three stratification variables, including sex (OR 1.31 for males vs. OR 2.37 for females, P interaction = 0.016), exercise (OR 1.18 for subjects without lack of exercise vs. OR 1.99 for subjects with lack of exercise, P interaction = 0.004) and heart diseases (OR 1.40 for subjects without heart diseases vs. OR 3.12 for subjects with heart diseases, P interaction = 0.033). CONCLUSION: The non-HDLc/HDLc was positively associated with the presence of carotid plaques in a Chinese high stroke risk population. A prospective study or randomized clinical trial of lipid-lowering therapy in the Chinese population is needed to evaluate their causal relationship.

[68] *Hwang HW, Yu JH, Jin YJ et al.* **Correlation between the small dense LDL level and nonalcoholic fatty liver disease: Possibility of a new biomarker**. Medicine (Baltimore) 2020; 99:e21162.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32664153
ABSTRACT

Small dense low-density lipoprotein (sdLDL) is a distinct low-density lipoprotein (LDL) cholesterol subclass that has been reported to be associated with metabolic disease. On the other hand, the relationship between the sdLDL level and the nonalcoholic fatty liver disease (NAFLD) severity is unclear. In this study, the sdLDL level was measured in patients with NAFLD to assess its potential as a biomarker for evaluating NAFLD. One hundred and twenty-six patients diagnosed with NAFLD at a single referral hospital from January 2018 to August 2019 were enrolled. The lipoprotein profile was analyzed from a blood test of NAFLD patients, and transient elastography (TE, Fibroscan) was performed to evaluate the degree of NAFLD. Among the 126 patients, 83 patients that could confirm the lipoprotein profile and TE results were finally enrolled in the study. The controlled attenuation parameter (CAP) value obtained from TE did not show any correlation with the total cholesterol, LDL. But, the sdLDL level showed a significant positive correlation with the CAP value (r=0.237, P=.031), and the sdLDL/LDL ratio also showed a significant positive correlation with the CAP value (r=0.235, P=.032). The liver stiffness (LS) measured by TE and the sdLDL level were positively correlated in patients with NAFLD (rho=0.217, P=.049). The sdLDL/LDL ratio also showed a significant positive correlation with the LS value (rho=0.228, P=.038). In addition, the fatty liver index also showed a significant positive correlation with the sdLDL/LDL ratio (r=0.448, P=.000). In this study, the sdLDL level measured by a blood test of NAFLD patients showed a positive correlation with the CAP value and LS, which indicate the degree of hepatic steatosis and fibrosis. These results suggest the possibility of the sdLDL level as a new biomarker of NAFLD, but further studies will be needed to support these results.

[69] *Gómez C, Stücheli S, Kratschmar DV et al.* **Development and Validation of a Highly Sensitive LC-MS/MS Method for the Analysis of Bile Acids in Serum, Plasma, and Liver Tissue Samples**. Metabolites 2020; 10.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660078
ABSTRACT

Bile acids control lipid homeostasis by regulating uptake from food and excretion. Additionally, bile acids are bioactive molecules acting through receptors and modulating various physiological processes. Impaired bile acid homeostasis is associated with several diseases and drug-induced liver injury. Individual bile acids may serve as disease and drug toxicity biomarkers, with a great demand for improved bile acid quantification methods. We developed, optimized, and validated an LC-MS/MS method for quantification of 36 bile acids in serum, plasma, and liver tissue samples. The simultaneous quantification of important free and taurine- and glycine-conjugated bile acids of human and rodent species has been achieved using a simple workflow. The method was applied to a mouse model of statin-induced myotoxicity to assess a possible role of bile acids. Treatment of mice for three weeks with 5, 10, and 25 mg/kg/d simvastatin, causing adverse skeletal muscle effects, did not alter plasma and liver tissue bile acid profiles, indicating that bile acids are not involved in statin-induced myotoxicity. In conclusion, the established LC-MS/MS method enables uncomplicated sample preparation and quantification of key bile acids in serum, plasma, and liver tissue of human and rodent species to facilitate future studies of disease mechanisms and drug-induced liver injury.

[70] *Hide D, Gil M, Andrade F et al.* **Simvastatin-loaded polymeric micelles are more effective and less toxic than conventional statins in a pre-clinical model of advanced chronic liver disease**. Nanomedicine : nanotechnology, biology, and medicine 2020; 29:102267.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32681987
ABSTRACT

Chronic liver disease (CLD) has no effective treatments apart from reducing its complications. Simvastatin has been tested as vasoprotective drug in experimental models of CLD showing promising results, but also limiting adverse effects. Two types of Pluronic® carriers loading simvastatin (PM108-simv and PM127-simv) as a drug delivery system were developed to avoid these toxicities while increasing the therapeutic window of simvastatin. PM127-simv showed the highest rates of cell internalization in rat liver sinusoidal endothelial cells (LSECs) and significantly lower toxicity than free simvastatin, improving cell phenotype. The in vivo biodistribution was mainly hepatic with 50% of the injected PM found in the liver. Remarkably, after one week of administration in a model of CLD, PM127-simv demonstrated superior effect than free simvastatin in reducing portal hypertension. Moreover, no signs of toxicity of PM127-simv were detected. Our results indicate that simvastatin targeted delivery to LSEC is a promising therapeutic approach for CLD.

[71] *Yuan T, Si S, Li Y et al.* **Roles for circulating polyunsaturated fatty acids in ischemic stroke and modifiable factors: a Mendelian randomization study**. Nutrition journal 2020; 19:70.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32652993
ABSTRACT

BACKGROUND: Available data about the effects of circulating polyunsaturated fatty acids (PUFAs) on ischemic stroke (IS) and its main risk factors remains limited and conflicting. Therefore, we conducted Mendelian randomization (MR) to assess whether genetically predicted PUFA affected IS, lipids and blood pressure (BP). METHODS: Genetic instruments associated with IS were derived from ISGC Consortium (n = 29,633), with lipids were derived from GLGC(n = 188,577), with BP were derived from Neale Lab(n = 337,000). The inverse-variance weighted method was the main analysis to estimate the effect of exposure on outcome. Sensitivity analyses included principal components analysis, MR-Egger, weighted median, and weighted mode. RESULTS: Per SD increases in serum α-linolenic acid (ALA) were associated with lower IS risk, with odd ratio (OR) of 0.867(0.782,0.961), arachidonic acid (AA) were associated with higher IS risk (OR: 1.053(1.014,1.094)). Likewise, Per SD increases in ALA were associated with the lower-level low-density lipoprotein cholesterol(LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) (β:-0.122(- 0.144, - 0.101), - 0.159(- 0.182, - 0.135), - 0.148(- 0.171, - 0.126), respectively), AA were associated with the higher-level of LDL-C, HDL-C and TC (β:0.045(0.034,0.056), 0.059(0.050,0.067), 0.055(0.046,0.063), respectively). Linoleic acid (LA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) had little or no association with IS, lipids or BP at Bonferroni-corrected significance. Different analytic methods supported these findings. The intercept test of MR-Egger implied no pleiotropy. CONCLUSIONS: High-level plasma ALA was protective for IS but AA was the opposite. LA, EPA, DHA, and DPA had no effects on IS.

[72] *Tricò D, Nesti L, Frascerra S et al.* **A Protein/Lipid Preload Attenuates Glucose-Induced Endothelial Dysfunction in Individuals with Abnormal Glucose Tolerance**. Nutrients 2020; 12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32664350
ABSTRACT

Postprandial hyperglycemia interferes with vascular reactivity and is a strong predictor of cardiovascular disease. Macronutrient preloads reduce postprandial hyperglycemia in subjects with impaired glucose tolerance (IGT) or type 2 diabetes (T2D), but the effect on endothelial function is unknown. Therefore, we examined whether a protein/lipid preload can attenuate postprandial endothelial dysfunction by lowering plasma glucose responses in subjects with IGT/T2D. Endothelial function was assessed by the reactive hyperemia index (RHI) at fasting, 60 min and 120 min during two 75 g oral glucose tolerance tests (OGTTs) preceded by either water or a macronutrient preload (i.e., egg and parmesan cheese) in 22 volunteers with IGT/T2D. Plasma glucose, insulin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, free fatty acids, and amino acids were measured through each test. RHI negatively correlated with fasting plasma glucose. During the control OGTT, RHI decreased by 9% and its deterioration was associated with the rise in plasma glucose. The macronutrient preload attenuated the decline in RHI and markedly reduced postprandial glycemia. The beneficial effect of the macronutrient preload on RHI was proportional to the improvement in glucose tolerance and was associated with the increase in plasma GLP-1 and arginine levels. In conclusion, a protein/lipid macronutrient preload attenuates glucose-induced endothelial dysfunction in individuals with IGT/T2D by lowering plasma glucose excursions and by increasing GLP-1 and arginine levels, which are known regulators of the nitric oxide vasodilator system.

[73] *Hannachi N, Fournier PE, Martel H et al.* **Statins potentiate the antibacterial effect of platelets on Staphylococcus aureus**. Platelets 2020:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32664773
ABSTRACT

Platelets have largely demonstrated their implication in anti-infectious immunity. This effect is ensured by the secreted molecules stored mostly in platelet alpha granules. Previous studies have reported that Staphylococcus aureus showed sensitivity to this antibacterial effect of platelets. Statins, for their part, have shown a modulating effect on platelet activation. Furthermore, several studies have reported a protective effect of statins in staphylococcal endocarditis. The aim of this study was to investigate the influence of statins on the antibacterial effect of washed platelets. Blood samples were collected from healthy donors (n = 35). PRP was prepared according to the ISTH recommendation. Bacteria were incubated for four hours with untreated-washed platelets, or rather treated by statins and/or GPIIbIIIa antagonists. In order to evaluate the antibacterial effect, the platelet-bacteria mix was spread on the blood agar to count the number of colonies after 18 hours of incubation. Measurement of CD 41 and CD62P expression by flow cytometry was performed to evaluate the effect of statin on bacterial-induced platelet activation. Statins have shown a potentiation of the antibacterial effect of washed platelets (p < .01 for Atorvastatin and Rosuvastatin and p < .001 for Fluvastatin vs untreated washed platelets condition). This effect of statins was dose-dependent and was more significant at 20 µM. The addition of Fluvastatin to platelet-bacterial mix significantly increased the expression of platelet CD41 and CD62P (p < .05 and p < .01 vs resting washed platelets, respectively). Tirofiban, GPIIbIIIa antagonist, reversed the antibacterial effect of washed platelets and suppressed the potentiating effect of statins. Our study demonstrated that statins potentiate the anti-staphylococcal effect of washed platelets. This result may explain the beneficial effect of statins on Staphylococcus aureus infective endocarditis. Further studies are therefore required to explain this effect at the molecular level and to assess its impact in vivo.

[74] *Cicero AFG, Fogacci F, Hernandez AV, Banach M*. **Efficacy and safety of bempedoic acid for the treatment of hypercholesterolemia: A systematic review and meta-analysis**. PLoS medicine 2020; 17:e1003121.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32673317
ABSTRACT

BACKGROUND: Bempedoic acid is a first-in-class lipid-lowering drug recommended by guidelines for the treatment of hypercholesterolemia. Our objective was to estimate its average effect on plasma lipids in humans and its safety profile. METHODS AND FINDINGS: We carried out a systematic review and meta-analysis of phase II and III randomized controlled trials on bempedoic acid (PROSPERO: CRD42019129687). PubMed (Medline), Scopus, Google Scholar, and Web of Science databases were searched, with no language restriction, from inception to 5 August 2019. We included 10 RCTs (n = 3,788) comprising 26 arms (active arm [n = 2,460]; control arm [n = 1,328]). Effect sizes for changes in lipids and high-sensitivity C-reactive protein (hsCRP) serum concentration were expressed as mean differences (MDs) and 95% confidence intervals (CIs). For safety analyses, odds ratios (ORs) and 95% CIs were calculated using the Mantel-Haenszel method. Bempedoic acid significantly reduced total cholesterol (MD -

14.94%; 95% CI -17.31%, -12.57%; p < 0.001), non-high-density lipoprotein cholesterol (MD -18.17%; 95% CI -21.14%, -15.19%; p < 0.001), low-density lipoprotein cholesterol (MD -22.94%; 95% CI -26.63%, -19.25%; p < 0.001), low-density lipoprotein particle number (MD -20.67%; 95% CI -23.84%, -17.48%; p < 0.001), apolipoprotein B (MD -15.18%; 95% CI -17.41%, -12.95%; p < 0.001), high-density lipoprotein cholesterol (MD -5.83%; 95% CI -6.14%, -5.52%; p < 0.001), high-density lipoprotein particle number (MD -3.21%; 95% CI -6.40%, -0.02%; p = 0.049), and hsCRP (MD -27.03%; 95% CI -31.42%, -22.64%; p < 0.001). Bempedoic acid did not significantly modify triglyceride level (MD -1.51%; 95% CI -3.75%, 0.74%; p = 0.189), very-low-density lipoprotein particle number (MD 3.79%; 95% CI -9.81%, 17.39%; p = 0.585), and apolipoprotein A-1 (MD -1.83%; 95% CI -5.23%, 1.56%; p = 0.290). Treatment with bempedoic acid was positively associated with an increased risk of discontinuation of treatment (OR 1.37; 95% CI 1.06, 1.76; p = 0.015), elevated serum uric acid (OR 3.55; 95% CI 1.03, 12.27; p = 0.045), elevated liver enzymes (OR 4.28; 95% CI 1.34, 13.71; p = 0.014), and elevated creatine kinase (OR 3.79; 95% CI 1.06, 13.51; p = 0.04), though it was strongly associated with a decreased risk of new onset or worsening diabetes (OR 0.59; 95% CI 0.39, 0.90; p = 0.01). The main limitation of this meta-analysis is related to the relatively small number of individuals involved in the studies, which were often short or middle term in length. CONCLUSIONS: Our results show that bempedoic acid has favorable effects on lipid profile and hsCRP levels and an acceptable safety profile. Further well-designed studies are needed to explore its longer-term safety.

[75] *Lucchi T, Cesari M, Vergani C*. **[Dislipidemia and lipid lowering drugs: from guidelines to clinical practice. An updated review of the literature.]**. Recenti progressi in medicina 2020; 111:426-443.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32658882
ABSTRACT
The atherosclerotic cardiovascular disease (ASCVD) represents the leading cause of death and disability not only in countries with a high degree of socio-economic development but also in low- middle-income countries. The study of atherosclerosis and the strategies to control ASCVD are evolving. All strategies emphasize the need to lower LDL cholesterol through an appropriate lifestyle and the use of lipid-lowering drugs. A therapy with statin with or without other lipid lowering drugs is recommended in secondary prevention. In primary prevention, the use of the lipid-lowering drug should instead take into account the cost-benefit ratio. Available evidence coming from clinical trials is useful to inform clinical choices but must be associated with a shared decision-making process between doctor and patient.

[76] *Lamiquiz-Moneo I, Civeira F, Mateo-Gallego R et al.* **Diagnostic yield of sequencing familial hypercholesterolemia genes in individuals with primary hypercholesterolemia**. Revista espanola de cardiologia (English ed.) 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32660911
ABSTRACT
INTRODUCTION AND OBJECTIVES: Our objective was to approximate the prevalence of mutations in candidate genes for familial hypercholesterolemia (FH) in a middle-aged Spanish population and to establish the predictive value of criteria for clinical suspicion in

the detection of causative mutations. METHODS: Unrelated individuals aged ≥ 18 years from the Aragon Workers' Health Study (AWHS) with high low-density lipoprotein cholesterol (LDL-C) and clinical suspicion of FH (participants with LDL-C concentrations above the 95th percentile, participants with premature cardiovascular disease and/or participants with high LDL-C [130 mg/dL] under statin therapy), assuming that any participant with FH exhibits at leats 1 trait, were selected and the LDLR, APOB, PCSK9, APOE, STAP1 and LDLRAP1 genes were sequenced by next generation sequencing technology. RESULTS: Of 5400 individuals from the AWHS, 4514 had complete data on lipid levels and lipid-lowering drugs, 255 participants (5.65%) met the criteria for suspicion of FH, 24 of them (9.41%) were diagnosed with hyperlipoproteinemia(a), and 16 (6.27% of those sequenced) were found to carry causative mutations in candidate genes: 12 participants carried 11 different pathogenic LDLR alleles and 4 participants carried 1 pathogenic mutation in PCSK9. LDL-C concentrations> 220 mg/dL and LDL-C> 130 mg/dL despite statin therapy showed the strongest association with the presence of mutations (P=.011). CONCLUSIONS: Our results show that the prevalence of FH in Spain is 1:282 and suggest that the combination of high untreated LDL-C and high levels of LDL-C despite statin therapy are the best predictors of a positive FH genetic test.

[77] *Yang X, Xiong T, Ning D et al.* **Long-term atorvastatin or the combination of atorvastatin and nicotinamide ameliorate insulin resistance and left ventricular diastolic dysfunction in a murine model of obesity**. Toxicology and applied pharmacology 2020; 402:115132.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32659285
ABSTRACT
Current studies aimed at investigating the association between atorvastatin therapy and insulin resistance (IR) appear to be controversial. IR is considered to be an important contributor to inducing cardiac dysfunction through multiple signals. The paradoxical cardiotoxicity of atorvastatin reported under different conditions suggests that the association between atorvastatin treatment, insulin resistance and cardiac function should be clarified further. In this study, C57BL/6 J male mice were fed a high-fat diet (HD) or standard chow diet (SD) for 12 weeks and subsequently randomly divided into four groups: the SD-Control (SD-C) and HD-Control (HD-C) groups treated with saline for 10 months and the HD-A and HD-A + N groups treated with atorvastatin (20 mg/kg/day) alone or atorvastatin combined with nicotinamide (NAM, 1 g/kg/day) for 10 months. Although no significant changes in systolic function and structure were observed between the four groups of mice at an age of 46 or 58 weeks, respectively, long-term treatment with atorvastatin alone or atorvastatin and NAM combination significantly retarded the HD-induced IR and diastolic dysfunction and attenuated both cardiac and hepatic fibrosis in obese mice possibly by regulating the cleavage of osteopontin and then controlling profibrotic activity. Changes in cardiac function and structure were similar between the HD-A and HD-A + N groups; however, mice in the HD-A + N group exhibited better glucose control and marked reduction in body weight and hepatic lipid accumulation. Thus, these results suggest that long-term treatment with atorvastatin or the combination of atorvastatin and nicotinamide may be alternative therapies due to their beneficial effects on IR and diastolic function.

[78] *Ballantyne CM*. **PRECISION MEDICINE FOR CARDIOVASCULAR DISEASE PREVENTION: WHERE DO WE STAND IN 2019 WITH A FOCUS ON INFLAMMATION AND LIPIDS?** <u>Transactions of the American Clinical and Climatological Association</u> 2020; 131:42-47.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32675841
ABSTRACT

In this manuscript, I will discuss where we stand in 2019, with a focus on inflammation and lipids, in regard to precision medicine for cardiovascular disease prevention. This manuscript will reflect my career journey working in the cardiovascular disease field.

[79] *Fazio S, Shapiro MD*. **PREVENTIVE CARDIOLOGY AS NEW SUBSPECIALTY OF CARDIOVASCULAR MEDICINE**. <u>Transactions of the American Clinical and Climatological Association</u> 2020; 131:33-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32675840
ABSTRACT

Although management of ischemic cardiovascular disease has improved by leaps and bounds and significantly reduced the risk of mortality from a heart attack relative to decades past, the life trajectory of the average person (with stress, poor diet, excess body weight, inactivity, smoking, exposure to pollutants, poor management of metabolic comorbidities, etc.) still leads straight to development of this disease. Therefore, we have an unprecedented opportunity to focus on prevention of atherosclerosis before cardiovascular events occur, an endeavor that needs expert intervention with cardiovascular risk assessment, risk factor management, lifestyle counseling, dietary interventions, use of natural supplements, and pharmacotherapy. It is time for the budding specialty of preventive cardiology to come to the fore, from the historic background of fragmented clinical services such as lipid, hypertension, diabetes, endocrine, and cardiology clinics. Many patients need this specialized service, which cannot be provided anywhere else but in a dedicated practice well integrated with all other hospital services. Here we discuss the origin of preventive cardiology, the organization and core competencies required for excellence in this medical art, and the structure for education and fellowship training for professional recognition and board certification.

[80] *Guo Z, Zhao Z, Yang C, Song C*. **Transfer of microRNA-221 from mesenchymal stem cell-derived extracellular vesicles inhibits atherosclerotic plaque formation**. <u>Translational research : the journal of laboratory and clinical medicine</u> 2020.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32659442
ABSTRACT

Mesenchymal stem cells (MSCs) have emerged as a cell-based therapy in many diseases including atherosclerosis (AS) due to their capability of immunomodulation and tissue regeneration. However, the pathway for MSCs' antiatherosclerotic activity remains to be elucidated. Here, we test the hypothesis that microRNA-221 (miR-221) from MSC-derived extracellular vesicles (EVs) alleviates AS. Male ApoE(-/-) mice were fed a high-fat diet for 12 weeks to induce AS, and were then treated with human bone marrow mesenchymal stem cell-derived EVs by tail vein injection. The expression pattern of miR-221 and N-acetyltransferase-1 (NAT1) in AS mice was characterized by quantitative RNA analysis and their interaction was identified by dual-luciferase reporter gene assay. In other studies,

human arterial smooth muscle cells treated with oxidized low-density lipoprotein-were co-cultured with MSC-released EVs to evaluate the EV-mediated transfer of miR-221. NAT1 was highly expressed in atherosclerotic lesions. Adenovirus-mediated NAT1 knockdown resulted in a reduced lipid deposition in AS mice. Human bone marrow mesenchymal stem cell -derived EVs carrying miR-221 were internalized by human arterial smooth muscle cells and transferred their miR-221 contents to downregulate the target gene NAT1. Injection of miR-221-containing EVs inhibited lipid deposition in AS mice, in part by downregulating NAT1. The present study provides evidence that miR-221 shuttled by MSC-derived EVs can inhibit atherosclerotic plaque formation in AS model mice, suggesting that miR-221 may serve as a target for improving MSC-based therapeutic strategy against AS.

[81] *Vozniuk IA, Shamalov NA, Ezhov MV et al.* **[Optimization of lipid-lowering therapy in patients after ischemic stroke. Resolution of the Council of Experts]**. Zh Nevrol Psikhiatr Im S S Korsakova 2020; 120:152-161.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=32678563
ABSTRACT
Hyperlipidemia is the main risk factor for diseases caused by atherosclerosis including ischemic stroke. This publication provides practical recommendations and an algorithm for prescribing lipid-lowering therapy to post-ischemic stroke patients. The algorithm presents the steps for sequential administration of statins, ezetimibe, and PCSK9 inhibitors to achieve target levels of low-density lipoprotein cholesterol.