Literature update week 15 (2019)

[1] *Wei Q, Wang J, Shi W et al.* **Improved in vivo detection of atherosclerotic plaques with a tissue factor-targeting magnetic nanoprobe**. Acta biomaterialia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30954623
ABSTRACT
Rupture of atherosclerotic plaques causes acute cardiovascular and cerebrovascular pathology. Tissue factor (TF) is a key factor that affects the development of atherosclerotic plaques and the formation of thrombus and thus constitutes a potential target for the detection of atherosclerotic plaques. In this study, the conjugation of the fusion protein 'enhanced green fluorescent protein with the first epidermal growth factor domain' (EGFP-EGF1) and superparamagnetic iron oxide nanoparticles (EGFP-EGF1-SPIONs) was explored for molecular imaging of TF-positive atherosclerotic plaques. EGFP-EGF1-SPIONs showed improved accuracy, superior contrast effects, and better cytocompatibility compared with common contrast agents in the detection of atherosclerotic plaques of apolipoprotein E knockout (ApoE(-/-)) mice using magnetic resonance imaging. In conclusion, EGFP-EGF1-SPION is a promising TF-targeting nanoprobe to precisely and specifically detect atherosclerotic plaques, which may improve molecular imaging diagnosis of cardiovascular and cerebrovascular events for the comprehensive evaluation of atherosclerosis. STATEMENT OF SIGNIFICANCE: Traditional methods can only display the status of atherosclerosis, but not forecast the progress of lesions efficiently. It remains challenging to evaluate the plaques specifically and sensitively. In this study, we constructed a tissue factor-targeted magnetic nanoprobe to specifically detect plaques by magnetic resonance imaging in vivo, which will improve the diagnostic technology for atherosclerotic plaques and offer molecular level guidance to treat atherosclerosis. Furthermore, this strategy has critical clinical significance on prevention, diagnosis and therapeutic evaluation of cardio-cerebral vascular events.

[2] *Karimi B, Yunesian M, Nabizadeh R, Mehdipour P*. **Serum Level of Total Lipids and Telomere Length in the Male Population: A Cross-Sectional Study**. American journal of men's health 2019; 13:1557988319842973.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30961458
ABSTRACT
Telomeres contain TTAGGG (T; Thymine, A; Adenine and G; Guanine) repetitive sequences and are placed at the end of human chromosomes. Telomere dysfunction is implicated in some age-related and chronic diseases, but its association with total serum lipids and obesity is unknown. Our objective was to determine influenced of total serum lipids on leukocyte telomere lengths (TLs). Participants were selected by cluster sampling from 22 districts of Tehran. The questionnaires were completed by 500 subjects and after the initial assessment in terms of lifestyle, nutrition, home, and job, 300 healthy people, aged 25-40 years were finally selected. TLs and serum level of total lipids were measured by quantitative real-time PCR and the Phillips method, respectively. The average telomere length (T/S) and total lipids were 1.05 +/- 0.3 mg/dl and 643.3 +/- 70.8 mg/dl, respectively. We found that a one unit difference in the following parameters were associated with kilo base pair differences in TL: Age -0.0002 (95% CI [-0.0022, -0.0018]), BMI -0.0019 (95% CI [-0.0003, -0.0034]), TC 0.0001 (95% CI [-0.0006, -0.0007]), TG -0.0010 (95% CI [-0.0015, -0.0004]), PL 0.0001 (95% CI [-0.0005, -0.0007]), and TSL -0.0003 (95% CI [-0.0008, 0.0001]). Spearman correlation analysis revealed an inverse

relationship between TC (R = -0.53; 95% CI [-0.61, -0.44]), TG (R = -0.50; 95% CI [-0.58, -0.41]), PL (R = -0.46; 95% CI [-0.54-0.36]), and TSL (R = -0.63; 95% CI [-0.69, -0.56]) with T/S. Our research suggests that the inverse relationship was found between TL and weight, BMI, age, and TSL which were associated with obesity. High serum lipids concentration may be associated with systemic inflammation and atherosclerosis and may lead to oxidative stress, resulting in telomere shortening.

[3] *Sheu JJ, Hsiao HY, Chung SY et al.* **Endothelial progenitor cells, rosuvastatin and valsartan have a comparable effect on repair of balloon-denudated carotid artery injury**. American journal of translational research 2019; 11:1282-1298.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30972162
ABSTRACT
Endothelial cell (EC) dysfunction plays a crucial role for arterial obstructive disease. This study tested the therapeutic role of autologous endothelial progenitor cells (EPCs)/rosuvastatin-(Rosu)/valsartan-(Val) on repair of injured carotid ECs. Male Sprague-Dawley rats (n = 60) were categorized into five groups [sham-control (SC), left common carotid artery injury induced by balloon denudation (LCA(BD)), LCA(BD) + Rosu (10 mg/kg/day), LCA(BD) + Val (20 mg/kg/day), and LCA(BD) + EPC (1.2 x 10(6))]. By day 5, the LCA was harvested from each rat (n = 6/each time interval in group) after the procedure. Carotid-ring angiogenesis was significantly lower in LCA(BD) than the other groups (all $P < 0.001$). Compared with LCA(BD), the number of EC was significantly higher in LCA(BD) treated with adipose-derived mesenchymal stem cells (ADMSCs) and more significantly higher in LCA(BD) treated with EPCs (all $P < 0.001$). Gene expression of EC (CD31/vWF), EPC (SDF-1alpha/CXCR4) and angiogenesis (VEGF/VEGF-receptor/angiopoietin/eNOS) and EC intercellular junction (VE-cadherin) biomarkers were significantly lower in LCA(BD) than in groups LCA(BD) + Rosu to LCA(BD) + EPC (all $P < 0.001$). Conversely, the gene expression of inflammatory (VCAM-1/MMP-9/TNF-alpha), oxidative-stress (NOX-1/NOX-2), apoptosis (cleaved caspase-3/PARP) and thrombin cofactor (thrombomodulin) biomarkers were significantly higher in LCA(BD) than in other groups (all $P < 0.001$). By day 14, the neointimal-layer area and cellular expressions of (CD40+/CD68+) were highest in LCA(BD), lowest in SC, significantly higher in LCA(BD) + Val than in LCA(BD) + Rosu and LCA(BD) + EPC (all $P < 0.001$). In conclusion, EPCs were comparable to rosuvastatin and valsartan in upregulation of angiogenesis and repair of injured carotid ECs.

[4] *Perez-Martinez P, Katsiki N, Mikhailidis DP*. **The Role of n-3 Fatty Acids in Cardiovascular Disease: Back to the Future**. Angiology 2019:3319719842005.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30966756
ABSTRACT
Cardiovascular disease (CVD) remains the major cause of death and disability worldwide, and residual risk after implementing all current therapies is still high. In this context, the latest (2016) European Cardiology Society/European Atherosclerosis Society guidelines recommend that triglyceride (TG)-lowering drugs should be used in high-risk patients with TGs levels >2.3 mmol/L (200 mg/dL), after lifestyle measures fail to lower them. After several neutral CVD outcome trials with n-3 fatty acids, the Reduction of Cardiovascular Events with EPA-Intervention Trial met its primary end point, that is, among patients with elevated TGs levels

despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower in those who received 4 g of icosapent ethyl daily. In this review, we comment on the findings of previous and recently published randomized controlled CVD outcome trials assessing n-3 fatty acids supplementation. Both efficacy and safety, as well as future perspectives, are discussed.

[5] *Vuksic A, Lovric J, Konjevoda P et al.* **Effects of simvastatin and fenofibrate on butyrylcholinesterase activity in the brain, plasma, and liver of normolipidemic and hyperlipidemic rats**. Arhiv za higijenu rada i toksikologiju 2019; 70:30-35.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30956215
ABSTRACT
The study objective was to test the hypothesis that simvastatin and fenofibrate should cause an increase in butyrylcholinesterase (BuChE) activity not only in the plasma and liver but also in the brain of normolipidemic and hyperlipidemic rats. Catalytic enzyme activity was measured using acetylthiocholine (ATCh) and butyrylthiocholine (BTCh) as substrates. Normolipidemic and hyperlipidemic rats were divided in four groups receiving 50 mg/kg of simvastatin a day or 30 mg/kg of fenofibrate a day for three weeks and three control groups receiving saline. Simvastatin and fenofibrate caused an increase in brain BuChE activity in both normo- and hyperlipidemic rats regardless of the substrate. The increase with BTCh as substrate was significant and practically the same in normolipidemic and hyperlipidemic rats after simvastatin treatment (14-17% vs controls). Simvastatin and fenofibrate also increased liver and plasma BuChE activity in both normolipidemic and hyperlipidemic rats regardless of the substrate. In most cases the increase was significant. Considering the important role of BuChE in cholinergic transmission as well as its pharmacological function, it is necessary to continue investigations of the effects of lipid-lowering drugs on BuChE activity.

[6] *Wu X, Liu Y, Wei W, Liu ML*. **Extracellular vesicles in autoimmune vasculitis - Little dirts light the fire in blood vessels**. Autoimmunity reviews 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30959208
ABSTRACT
Systemic vasculitis is diverse group of autoimmune disorders which are characterized by inflammation of blood vessel walls with deep aching and burning pain. Their underlying etiology and pathophysiology still remain poorly understood. Extracellular vesicles (EVs), including exosomes, microvesicles (MVs), and apoptotic bodies, are membrane vesicular structures that are released either during cell activation, or when cells undergo programmed cell death, including apoptosis, necroptosis, and pyroptosis. Although EVs were thought as cell dusts, but now they have been found to be potently active since they harbor bioactive molecules, such as proteins, lipids, nucleic acids, or multi-molecular complexes. EVs can serve as novel mediators for cell-to-cell communications by delivery bioactive molecules from their parental cells to the recipient cells. Earlier studies mainly focused on MVs budding from membrane surface. Recent studies demonstrated that EVs may also carry molecules from cytoplasm or even from nucleus of their parental cells, and these EVs may carry autoantigens and are important in vasculitis. EVs may play important roles in vasculitis through their potential pathogenic involvements in inflammation, autoimmune responses, procoagulation, endothelial dysfunction/damage,

angiogenesis, and intimal hyperplasia. EVs have also been used as specific biomarkers for diagnostic use or disease severity monitoring. In this review, we have focused on the aspects of EV biology most relevant to the pathogenesis of vasculitis, discussed their perspective insights, and summarized the exist literature on EV relevant studies in vasculitis, therefore provides an integration of current knowledge regarding the novel role of EVs in systemic vasculitis.

[7] *Valkonen S, Holopainen M, Colas RA et al.* **Lipid mediators in platelet concentrate and extracellular vesicles: Molecular mechanisms from membrane glycerophospholipids to bioactive molecules**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30980920

ABSTRACT

Platelets are collected for transfusion to patients with different hematological disorders, and for logistical reasons, platelets are stored as concentrates. Despite the carefully controlled conditions, platelets become activated during storage, and platelet concentrates (PLCs) may cause adverse inflammatory reactions in the recipients. We studied by mass spectrometry the lipidomic changes during storage of the clinical PLCs, the platelets isolated from PLCs, and the extracellular vesicles (EVs) thereof. The release of EVs from platelets increased with the prolonged storage time. The molar percentages of arachidonic acid -containing species were increased during storage especially in the phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine classes of glycerophopholipids. The increase of these species in the membrane glycerophopholipid composition paralleled the production of both proinflammatory and proresolving lipid mediators (LMs) as the amount of the arachidonic acid-derived LMs such as thromboxane B2 and prostaglandin E2 also increased in time. Moreover, several monohydroxy pathway markers and functionally relevant proinflammatory and proresolving LMs were detected in the PLC and the EVs, and some of these clearly accumulated during storage. By Western blot, the key enzymes of these pathways were shown to be present in the platelets and in many cases also in the EVs. Since the EVs were enriched in the fatty acid precursors of LMs, harbored LM-producing enzymes, contained the related monohydroxy pathway markers, and also secreted the final LM products, the PLC-derived EVs appear to have the potential to regulate inflammation and healing, and may thereby aid the platelets in exerting their essential physiological functions.

[8] *Mohd Nor NS, Al-Khateeb AM, Chua YA et al.* **Heterozygous familial hypercholesterolaemia in a pair of identical twins: a case report and updated review**. BMC pediatrics 2019; 19:106.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30975109

ABSTRACT

BACKGROUND: Familial hypercholesterolaemia (FH) is the most common inherited metabolic disease with an autosomal dominant mode of inheritance. It is characterised by raised serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c), leading to premature coronary artery disease. Children with FH are subjected to early and enhanced atherosclerosis, leading to greater risk of coronary events, including premature coronary artery disease. To the best of our knowledge, this is the first report of a pair of monochorionic diamniotic identical twins with a diagnosis of heterozygous FH, resulting from mutations in both LDLR and ABCG8 genes. CASE PRESENTATION: This is a rare case of a pair of 8-year-old

monochorionic diamniotic identical twin, who on family cascade screening were diagnosed as definite FH, according to the Dutch Lipid Clinic Criteria (DLCC) with a score of 10. There were no lipid stigmata noted. Baseline lipid profiles revealed severe hypercholesterolaemia, (TC = 10.5 mmol/L, 10.6 mmol/L; LDL-c = 8.8 mmol/L, 8.6 mmol/L respectively). Their father is the index case who initially presented with premature CAD, and subsequently diagnosed as FH. Family cascade screening identified clinical FH in other family members including their paternal grandfather who also had premature CAD, and another elder brother, aged 10 years. Genetic analysis by targeted next-generation sequencing using MiSeq platform (Illumina) was performed to detect mutations in LDLR, APOB100, PCSK9, ABCG5, ABCG8, APOE and LDLRAP1 genes. Results revealed that the twin, their elder brother, father and grandfather are heterozygous for a missense mutation (c.530C > T) in LDLR that was previously reported as a pathogenic mutation. In addition, the twin has heterozygous ABCG8 gene mutation (c.55G > C). Their eldest brother aged 12 years and their mother both had normal lipid profiles with absence of LDLR gene mutation. CONCLUSION: A rare case of Asian monochorionic diamniotic identical twin, with clinically diagnosed and molecularly confirmed heterozygous FH, due to LDLR and ABCG8 gene mutations have been reported. Childhood FH may not present with the classical physical manifestations including the pathognomonic lipid stigmata as in adults. Therefore, childhood FH can be diagnosed early using a combination of clinical criteria and molecular analyses.

[9] *Qadi O, Marshall T, Adderley N, Bem D*. **Patients' and health professionals' attitudes and perceptions towards the initiation of preventive drugs for primary prevention of cardiovascular disease: protocol for a systematic review of qualitative studies**. BMJ open 2019; 9:e025587.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30975677
ABSTRACT
INTRODUCTION: Lipid-lowering drugs and antihypertensive agents can be prescribed for the primary prevention of cardiovascular disease. In some cases, patients eligible for primary prevention of cardiovascular disease according to the European guidelines are not always started on preventive drugs. Existing research explores the attitudes of health professionals and patients towards cardiovascular preventive drugs but does not always differentiate between the attitudes towards drug initiation for primary or secondary prevention. We aim to systematically review qualitative studies assessing health professionals' and patients' attitudes and perceptions towards drug initiation for primary prevention of cardiovascular disease. METHODS AND ANALYSIS: MEDLINE, MEDLINE In Process, EMBASE, PsycINFO, CINAHL, Applied Social Sciences Index and Abstracts, Conference Proceedings Citation Index (Web of Science), Healthcare Management Information Consortium, and Open Grey will be searched without restrictions on date or language of publication. Searches will be limited to studies of qualitative design, standalone or in the context of a mixed-method design, focusing on cardiovascular drug initiation for primary prevention. The primary outcome is the attitudes of health professionals and patients towards drug initiation for primary prevention of cardiovascular disease. Two reviewers will independently carry out the study selection, data extraction and quality assessment. The Critical Appraisal Skills Programme Qualitative Research Checklist will be used to assess the quality of included studies. The findings will be analysed using Thomas and

Harden's thematic synthesis approach. ETHICS AND DISSEMINATION: This systematic review does not require ethical approval as primary data will not be collected. The results of the study will be published in a peer-reviewed journal and presented at relevant conferences. PROSPERO REGISTRATION NUMBER: CRD42018095346.

[10] *Laube R, Liu K*. **An unwanted complement: Rare case of potential liver injury induced by an interaction between ginseng and atorvastatin**. British journal of clinical pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30980549
ABSTRACT

[11] *Giampietro L, Ammazzalorso A, Amoroso R, De Filippis B*. **Development of Fibrates as Important Scaffold in Medicinal Chemistry**. ChemMedChem 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30957432
ABSTRACT
Fibrates are a class of phenoxy-isobutyric acid derivatives mainly used as antihyperlipidemic agents. The fibrates scaffold has undergone a variety of chemical modifications providing a wide spectrum of biological activities. Within the last years, the majority of new synthetic fibrates derivatives have demonstrated hypolipidemic activity by the PPARalpha activation. However, some compounds containing fibrate scaffold have shown different pharmacological properties, also independent from PPARalpha activation, such as anti-inflammatory, analgesic, anti-oxidant and antiplatelet. The aim of this review is to highlight the structure-activity relationships (SAR) to evaluate the significance of fibrates in the field of medicinal chemistry.

[12] *Arnedo Hernandez S, Mosquera Lozano JD, Martinez de Narvajas Urra I et al.* **iPCSK9 treatment of Familial Hypercholesterolemia in a patient diagnosed as Congenital Muscular Dystrophy with contraindication for statin use**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30979437
ABSTRACT
Statins are contraindicated in patients with myopathies. Until a few years ago, in those patients with Familial Hypercholesterolemia who also presented muscular dystrophies and didnt reach adequate cholesterol plasmatic levels, the next therapeutic ladder was lipoapheresis. When iPCSK9 first appeared, lipoapheresis could be suspended in some of these patients, sustaining nevertheless proper levels of cholesterol. We present the case of a 27 year-old male, diagnosed with Congenital Muscular Dystrophy in the early childhood. He was referred to the Unit of Lipidology presenting hypercholesterolemia which, after genetic test, was assessed as Heterozygous Familial Hypercholesterolemia. Despite of treatment with diet and ezetimibe, cLDL blood levels abide high, being consequently included in lipoapheresis programme, therewith obtained levels of cLDL of 70mg/dl. In providing iPCSK9, lipoapheresis was withdrawn and treatment with alirocumab 150mg fortnightly introduced, unveiling a positive response, and sustaining cLDL levels around 75mg/dl.

[13] *Xin W, Lin Z, Zhang T, Jia S*. **Probucol for the prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography or percutaneous coronary intervention: A meta-analysis of randomized controlled trials**. Clinical nephrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30964433
ABSTRACT
BACKGROUND: The results of pilot randomized controlled trials (RCTs) evaluating probucol treatment on the risk of contrast-induced acute kidney injury (CI-AKI) are inconsistent. We aimed to perform a meta-analysis of RCTs to systematically evaluate the influence of probucol on the incidence of CI-AKI. MATERIALS AND METHODS: Related RCTs were identified via searching of PubMed, Embase, and Cochrane's Library databases. Results were pooled using a random-effect model or a fixed-effect model according to the heterogeneity. RESULTS: Five RCTs with 1,367 patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) were included. Meta-analysis indicated that probucol in addition to periprocedural hydration significantly reduced the incidence of CI-AKI (risk ratio (RR): 0.37, 95% confidence interval (CI): 0.24 - 0.56, $p < 0.001$) with insignificant heterogeneity ($I2 = 0\%$). Moreover, treatment with probucol significantly lowered the increment of serum creatinine (weighted mean difference (WMD): -0.04 mg/dL, 95% CI: -0.07 to -0.02 mg/dL, $p < 0.001$) and preserved the loss of estimated glomerular filtrating rate (WMD: 2.46 mL/min, 95% CI: 0.84 - 4.07 mL/min, $p = 0.003$) as compared with control treatment. No significant publication bias was noticed. CONCLUSION: Treatment with probucol reduces the incidence of CI-AKI in patients undergoing contrast exposure during CAG or PCI. The influence of probucol on the clinical outcome in these patients deserves further investigation..

[14] *Bogman K, Brumm J, Hofmann C et al.* **Assessment of Drug-Drug Interactions between Taspoglutide, a Glucagon-Like Peptide-1 Agonist, and Drugs Commonly Used in Type 2 Diabetes Mellitus: Results of Five Phase I Trials**. Clinical pharmacokinetics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30968335
ABSTRACT
BACKGROUND AND OBJECTIVE: Taspoglutide, a glucagon-like peptide-1 agonist, like native glucagon-like peptide-1, delays gastric emptying time and prolongs intestinal transit time, which may alter the pharmacokinetics of concomitantly administered oral drugs. The effect of taspoglutide on the pharmacokinetics of five oral drugs commonly used in patients with type 2 diabetes mellitus was assessed in healthy subjects. METHODS: Five clinical pharmacology studies evaluated the potential drug-drug interaction between multiple subcutaneous taspoglutide doses and a single dose of lisinopril, warfarin, and simvastatin and multiple doses of digoxin and an oral contraceptive containing ethinylestradiol and levonorgestrel. The extent of interaction was quantified using geometric mean ratios and 90% confidence intervals for the maximum plasma concentration and area under the plasma concentration-time curve. In addition to pharmacokinetics, pharmacodynamic effects were assessed for warfarin and the oral contraceptive. RESULTS: Among the tested drugs, the effect of taspoglutide on the pharmacokinetics of simvastatin was most pronounced, on the day of taspoglutide administration, the average exposure to simvastatin was decreased by - 26% and - 58% for the area under the plasma concentration-time curve and maximum plasma concentration, respectively, accompanied by an increase in average exposure to its active metabolite,

simvastatin beta-hydroxy acid (+ 74% and + 23% for area under the plasma concentration-time curve and maximum plasma concentration, respectively). Although statistically significant changes in exposure were observed for other test drugs, the 90% confidence intervals for the geometric mean ratio for maximum plasma concentration and area under the plasma concentration-time curve were within the 0.7-1.3 interval. No clinically relevant changes on coagulation (for warfarin) and ovulation-suppressing activity (for the oral contraceptive) were apparent. CONCLUSION: Overall, multiple doses of taspoglutide did not result in changes in the pharmacokinetics of digoxin, an oral contraceptive containing ethinylestradiol and levonorgestrel, lisinopril, warfarin, and simvastatin that would be considered of clinical relevance. Therefore, no dose adjustments are warranted upon co-administration.

[15] *Castilla-Guerra L, Fernandez-Moreno MDC, Leon-Jimenez D, Rico-Corral MA*. **Statins in Ischemic Stroke Prevention: What Have We Learned in the Post-SPARCL (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels) Decade?** Current treatment options in neurology 2019; 21:22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30957208
ABSTRACT
PURPOSE OF REVIEW: We describe the current status of lipid-lowering therapies for ischemic stroke prevention. The SPARCL trial published in 2006 has been a landmark study in vascular neurology. The trial demonstrated that high-dose atorvastatin prevents recurrent stroke, and led the AHA/ASA to recommend statin therapy for patients with stroke or TIA of atherosclerotic origin. RECENT FINDINGS: Recently, the J-STARS study demonstrated that therapy with low-dose pravastatin reduced atherothrombotic infarction incidence among patients with prior ischemic stroke. Besides, several trials have shown improved stroke outcomes with non-statin lipid-lowering medications: IMPROVE-IT with ezetimibe on top of simvastatin and PCSK9 inhibitors-FOURIER with evocolumab and ODYSSEY-OUTCOMES with alirocumab-on top of statin therapy. LDL-cholesterol remains the primary lipid treatment target for reduction of stroke risk. Randomized trials have shown that each reduction of 40 mg/dL in the level of LDL-cholesterol reduces the stroke risk by approximately one quarter, and further, reductions in LDL-cholesterol levels have shown to produce additional reductions in stroke risk. Currently, we have evidence of benefit for adding non-statin lipid-modifying therapies to statins to reduce stroke risk. Surely, these novel strategies to reduce residual lipidic risk will provide future benefits on stroke prevention.

[16] *Athyros VG, Polyzos SA, Kountouras J et al.* **Non-alcoholic fatty liver disease treatment in patients with type 2 diabetes mellitus; new kids on the block**. Current vascular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30961499
ABSTRACT
BACKGROUND: Non-alcoholic fatty liver disease (NAFLD), affecting over 25% of the general population worldwide, is characterized by a spectrum of clinical and histological manifestations ranging from simple steatosis (>5% hepatic fat accumulation without inflammation) to non-alcoholic steatohepatitis (NASH) which is characterized by inflammation, and finally fibrosis, often leading to liver cirrhosis, and hepatocellular carcinoma. Up to 70% of patients with type 2

diabetes mellitus (T2DM) have NAFLD, and diabetics have much higher rates of NASH compared with the general non-diabetic population. OBJECTIVE: The aim of this study is to report recent approaches to NAFLD/NASH treatment in T2DM patients. To-date, there are no approved treatments for NAFLD (apart from lifestyle measures). RESULTS: Current guidelines (2016) from 3 major Scientific Organizations suggest that pioglitazone and vitamin E may be useful in a subset of patients for adult NAFLD/NASH patients with T2DM. Newer selective PPAR-gamma modulators (SPPARMs, CHRS 131) have shown to have even better results with less side effects in both animal and human studies in T2DM. Newer antidiabetic drugs might also be useful, but detailed studies with histological outcomes are largely lacking. Nevertheless, prior animal and human studies on incretin mimetics, glucagon like peptide-1 receptor agonists (GLP-1 RA) approved for T2DM treatment, have provided indirect evidence that they may also ameliorate NAFLD/NASH, whereas dipeptidyl dipeptidase-4 inhibitors (DDP-4i) were not better than placebo in reducing liver fat in T2DM patients with NAFLD. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been reported to improve NAFLD/NASH. Statins, being necessary for most patients with T2DM, may also ameliorate NAFLD/NASH, and could potentially reinforce the beneficial effects of the newer antidiabetic drugs, if used in combination, but this remains to be shown. CONCLUSIONS: Newer antidiabetic drugs (SPPARMs, GLP-1 RA and SGLT2i) alone or in combination and acting alone or on the background of potent statin therapy which is recommended in T2DM, might contribute substantially to NAFLD/NASH amelioration, possibly reducing not only liver specific but also cardiovascular morbidity. These observations warrant long term placebo controlled randomized trials with appropriate power and outcomes, focusing on the general population and more specifically on T2DM with NAFLD/NASH. Certain statins may be useful for treating NAFLD/NASH, while they substantially reduce cardiovascular disease risk.

[17] *Papademetriou V, Alataki S, Stavropoulos K et al.* **Pharmacological Management of Diabetic Nephropathy**. Current vascular pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30961500
ABSTRACT
INTRODUCTION: Diabetes mellitus (DM) is one of the most common diseases worldwide. Its adverse effects on several body organs has made DM a priority to improve its treatment. One of the most serious complications of DM is diabetic nephropathy (DN). OBJECTIVE: The aim of this review is to critically discuss available data on the pharmacological management of DN. METHOD: A comprehensive review of the literature was performed to identify studies assessing the impact of several drug classes on DN. RESULTS: Several studies have been conducted in order to find a novel and effective treatment of DN. So far, the cornerstone therapy of DN consists of renin-angiotensin system (RAS) inhibitors, agents that decrease the synthesis of intrarenal angiotensin II or block its receptors. Their antiproteinuric and antihypertensive effects can not only decelerate the progress of DN but prevent its onset as well. Novel antidiabetic drugs, such as sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA), are promising agents in the therapy of DN, due to their positive effect on renal and cardiovascular adverse events. From lipid lowering agents atorvastatin improves DN up to stage 3 and substantially reduces CVD. CONCLUSION: RAS inhibitors, SGLT-2i and GLP-1 agonists were found to be beneficial for the treatment of DN.

Larger renal trials are needed in order to incorporate these drugs into the first line treatment of DN.

[18] *Gormsen LC, Sondergaard E, Christensen NL et al.* **Metformin increases endogenous glucose production in non-diabetic individuals and individuals with recent-onset type 2 diabetes**. Diabetologia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30976851
ABSTRACT
AIMS/HYPOTHESIS: Metformin is the endorsed first-line glucose-lowering drug for treating patients with type 2 diabetes but despite more than 50 years of use, no consensus has been reached on its mechanisms of action. In this study, we investigated the glucose-lowering effects of metformin in individuals with type 2 diabetes and non-diabetic individuals. METHODS: We performed a randomised, placebo-controlled trial in 24 individuals with recent-onset type 2 diabetes (diabetes duration 50 [48] months) who had good glycaemic control (HbA1c 48 mmol/mmol [6.5%]). The studies were conducted at Aarhus University Hospital between 2013 and 2016. Participants were randomised to receive either metformin (2000 mg/day, n = 12, MET group) or placebo (n = 12, PLA group) for 90 days, using block randomisation set up by an unblinded pharmacist. Two participants withdrew from the study prior to completion and were replaced with two new participants receiving the same treatment. In addition, we recruited a group of non-diabetic individuals with similar age and BMI (n = 12, CONT group), who were all treated with 2000 mg metformin daily. Before and after treatment all individuals underwent studies of whole-body glucose metabolism by non-steady-state [3-(3)H]glucose kinetics, hyperinsulinaemic-euglycaemic clamping, indirect calorimetry, metabolomics, dual x-ray absorptiometry and muscle biopsies. The primary study endpoint was the effect of metformin treatment on lipid kinetics as well as glucose rate of disappearance (Rd) and endogenous glucose production (EGP). RESULTS: One participant from the CONT group withdrew due to intolerable gastrointestinal side-effects and was excluded from analysis. As expected, metformin treatment lowered fasting plasma glucose (FPG) in the MET group (~1.5 mmol/l, $p < 0.01$), whereas no effect was observed in the PLA and CONT groups. Body weight and composition did not change in any of the groups. In both of the metformin-treated groups (MET and CONT), basal glucose Rd, EGP and glucagon levels increased by ~30% ($p < 0.05$) whereas this was not the case in the PLA group. CONCLUSIONS/INTERPRETATION: Ninety days of metformin treatment resulted in similar increases in EGP and glucose Rd in individuals with recent-onset type 2 diabetes and in non-diabetic control individuals. These results challenge the existing paradigm that metformin primarily acts in the liver by inhibiting EGP, at least in individuals with type 2 diabetes of short duration and who have discretely affected glycaemic status. Whether metformin increases basal glucose Rd by facilitating glucose uptake in other tissues such as the intestines remains to be further clarified. TRIAL REGISTRATION: ClinicalTrials.gov NCT01729156 FUNDING: This study was supported by grants from The Danish Council for Independent Research | Medical Sciences, Aase Danielsen Fund, the Novo Nordisk Foundation, the Danish Diabetes Association and the Danish Diabetes Academy supported by the Novo Nordisk Foundation.

Literature update week 15 (2019)

[19] *Coner A, Aydinalp A, Muderrisoglu H*. **Evaluation of hs-CRP and sLOX-1 Levels in Moderate-to-High Risk Acute Coronary Syndromes**. Endocrine, metabolic & immune disorders drug targets 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30961517
ABSTRACT
Objective: Risk stratification and prompt treatment are essential for the management of acute coronary syndromes (ACS) and prediction of future prognosis. Subclinical vascular inflammation and novel biomarkers play an important role in the clinical evaluation of ACS patients. Methods: We enrolled patients who were admitted to emergency service with unstable angina or non- ST segment elevated ACS (NSTE-ACS) in the study population. Coronary artery disease (CAD) com- plexity was determined via evaluation of angiographical views and peripheral venous blood samples were collected to measure highly sensitive C-reactive protein (hs-CRP) and soluble form of Lectin-like OxLDL receptor-1 (sLOX-1) levels. Results: A total of 40 patients were enrolled in the study population, mean age was 65.1+/-13.8 years and male gender percentage was 52.5%. Twenty-nine of patients had NSTE-ACS and 11 patients had unstable angina presentation. The modified Gensini scores were higher for patients with elevated hs-CRP and sLOX-1 levels. Conclusion: Vascular inflammation displays the onset of ACS and it is related to more complex CAD in these patients. An increase in sLOX-1 expression is closely related to anatomical complexity of CAD in ACS.

[20] *Arora S, Cavender MA, Chang PP et al.* **Outcomes of decreasing versus increasing cardiac troponin in patients admitted with non-ST-segment elevation myocardial infarction: the Atherosclerosis Risk in Communities Surveillance Study**. European heart journal. Acute cardiovascular care 2019:2048872619842983.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30958029
ABSTRACT
BACKGROUND: The fourth universal definition of myocardial infarction requires an increase or decrease in cardiac troponin for the classification of non-ST-segment elevation myocardial infarction. We sought to determine whether the characteristics, management, and outcomes of patients admitted with non-ST-segment elevation myocardial infarction differ by the initial biomarker pattern. METHODS: We identified patients in the Atherosclerosis Risk in Communities Surveillance Study admitted with chest pain and an initially elevated cardiac troponin I, who presented within 12 hours of symptom onset and were classified with non-ST-segment elevation myocardial infarction. A change in cardiac troponin I required an absolute difference of at least 0.02 ng/mL on the first day of hospitalization, prior to invasive cardiac procedures. RESULTS: A total of 1926 hospitalizations met the inclusion criteria, with increasing cardiac troponin I more commonly observed (78%). Patients with decreasing cardiac troponin I were more often black (45% vs. 35%) and women (54% vs. 40%), and were less likely to receive non-aspirin antiplatelets (44% vs. 63%), lipid-lowering agents (62% vs. 80%), and invasive angiography (38% vs. 64%). Inhospital mortality was 3%, irrespective of the cardiac troponin I pattern. However, patients with decreasing cardiac troponin I had twice the 28-day mortality (12% vs. 5%; P=0.01). Fatalities within 28 days were more often attributable to non-cardiovascular causes in those with decreasing versus increasing cardiac troponin I (75% vs. 38%; P=0.01). CONCLUSION: Patients presenting with chest pain and an initially elevated

cardiac troponin I which subsequently decreases are less often managed by evidence-based therapies and have greater mortality, primarily driven by non-cardiovascular causes. Whether associations are attributable to type 2 myocardial infarction or a subacute presentation merits further investigation.

[21] *Eleftheriadou I, Tentolouris A, Tentolouris N, Papanas N*. **Advancing pharmacotherapy for diabetic foot ulcers**. Expert opinion on pharmacotherapy 2019:1-8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30958725
ABSTRACT
INTRODUCTION: Standard treatment for diabetic foot ulcers (DFUs) includes off-loading, debridement, moisture balance, management of infection and peripheral arterial disease (PAD) as well as adequate glycemic control. The outcomes so far are unsatisfactory. Areas covered: Herein, the authors provide an outline of newer pharmacological agents for the management of DFUs and give their expert perspectives on future treatment strategies. Expert opinion: Evidence-based healthcare calls for high quality evidence from large RCTs before the implementation of new guidelines for the management of DFUs. Empagliflozin and liraglutide can be recommended for glucose control in patients with DFUs and PAD, while intensive lipid lowering therapy with evolocumab when primary cholesterol goals are not met could be offered to patients with DFUs. Further clinical studies are warranted to develop a structured algorithm for the treatment of DFUs that fail to heal after four weeks of current standard of care. Sucrose octasulfate dressings, becaplermin gel, and platelet-rich plasma (PRP) could also be considered as advanced treatment options for the management of hard to heal DFUs.

[22] *Onatibia-Astibia A, Malet-Larrea A, Larranaga B et al.* **Tailored interventions by community pharmacists and general practitioners improve adherence to statins in a Spanish randomized controlled trial**. Health services research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30957240
ABSTRACT
OBJECTIVE: To evaluate the impact of health professionals' intervention on adherence to statins, the influence on total cholesterol levels, and lifestyle patterns in patients with hypercholesterolemia and analyze the differences according to the center of recruitment. STUDY SETTING: Forty-six community pharmacies and 50 primary care centers of Spain. STUDY DESIGN: Randomized controlled trial design (n = 746). Patients were assigned into adherent (ADH) or nonadherent group depending on their initial adherence to statins. Nonadherent patients were randomly assigned to intervention (INT) or nonintervention (NOINT) group. Patients enrolled in the INT group received an intervention depending on the cause of nonadherence. Patients in the ADH and NOINT groups received usual care. Intention-to-treat (ITT) analysis was performed with multiple imputation to replace the missing data. DATA COLLECTION: Adherence, total cholesterol levels, and lifestyle behaviors. FINDINGS: The odds of becoming adherent during the 6 months was higher in the INT group compared to the NOINT group (OR = 1,49; 95% CI: 1.30-1.76; P < 0.001), especially in the community pharmacy group (OR = 2.34; 95% CI: 1.81-3.03; P < 0.001). Adherent patients showed lower values of total cholesterol compared with nonadherent patients at baseline (ADH: 200.3 mg/dL vs NOADH: 216.7 mg/dL; P < 0.001) and at the endpoint (ADH: 197.3 mg/dL vs NOADH: 212.2 mg/dL; P <

0.001). More patients enrolled in the INT group practices exercise at the end of the study (INT: +26.6 percent; P = 0.002), and a greater number of patients followed a diet to treat hypercholesterolemia (+30.2 percent; P < 0.001). CONCLUSIONS: The intervention performed by health professionals, especially by community pharmacists, improved adherence to statins by hypercholesterolemic patients, and this improvement in adherence was accompanied by a reduction in total cholesterol levels and a healthier lifestyle.

[23] *Yang F, Ma L, Zhang L et al.* **Association between serum lipoprotein-associated phospholipase A2, ischemic modified albumin and acute coronary syndrome: a cross-sectional study**. Heart Vessels 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30963302
ABSTRACT
Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a newly emerging biomarker with strong pro-inflammatory effects, and is an independent risk predictor of atherosclerotic plaque rupture and thrombosis. In addition, ischemic modified albumin (IMA) is another important marker for the evaluation of myocardial ischemia, and has been approved by the U.S. Food and Drug Administration. The objective of this study was to investigate serum Lp-PLA2 and IMA in the early diagnosis, progression and prognosis of acute coronary syndrome (ACS). Serum Lp-PLA2 and IMA were detected using an AU5800 automatic biochemical analyzer in samples from 180 patients with ACS [n = 60 with unstable angina pectoris (UA), n = 56 with non-ST segment elevation myocardial infarction (NSTEMI), and n = 64 with ST segment elevation myocardial infarction (STEMI)] and 60 healthy control subjects. The relationship between Lp-PLA2 and IMA with Gensini score and the number of coronary artery lesions was explored, and logistic regression was conducted to identify risk factors for major adverse cardiovascular events (MACE). Serum Lp-PLA2 and IMA were significantly higher in all ACS subgroups compared to the control group (P < 0.05), were positively associated with the severity of ACS based on the Gensini score (P < 0.05), and were significantly higher in patients with double- and triple-vessel lesions compared to those with single-vessel lesions and healthy controls (P < 0.05). Logistic regression identified Lp-PLA2, IMA, and troponin I levels as independent risk factors for MACE. Lp-PLA2 and IMA were predictive of the degree of myocardial ischemia in patients with ACS, and may provide important clinical significance for the early diagnosis of ACS and the choice of treatment strategy.

[24] *Rallidis LS*. **Tracing new atherogenic properties of PCSK9. Another insight into the pathogenesis of atherosclerosis "the Minotaur's labyrinth"**. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30974175
ABSTRACT

[25] *QiaoZhen X, AiGuo M, Tong W et al.* **Correlation between of small dense low-density lipoprotein cholesterol with acute cerebral infarction and carotid atherosclerotic plaque stability**. Journal of clinical laboratory analysis 2019:e22891.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30955225
ABSTRACT

BACKGROUND: Acute cerebral infarction (ACI) is seriously harmful to human health worldwide. However, at present, the risk of disease onset is still not accurately predicted for some people. METHODS: Five hundred and nineteen patients with ACI and 300 healthy controls were included in this study. We divided the patients into three groups according to the results of cervical artery contrast-enhanced ultrasound. Ninety-five patients were in the CAS without plaque group, 108 patients were in the stable plaque group, and 316 patients were in the unstable plaque group. TC, TG, HDL-C, LDL-C, and sdLDL-C were measured in all subjects. RESULTS: The level of small dense low-density lipoprotein cholesterol (sdLDL-C) in the ACI group was significantly higher than that in the control group ($P < 0.001$). Logistic regression analysis showed that sdLDL-C was an independent risk factor for ACI (OR = 1.067, 95% CI: 1.041-1.093, $P < 0.001$); serum sdLDL-C was significantly higher in the unstable plaque group than in the stable plaque group and plaque-free group ($P < 0.05$, $P < 0.001$); serum sdLDL-C was also higher in the stable plaque group than the plaque-free group ($P < 0.001$). Logistic regression analysis showed that sdLDL-C was an independent risk factor for unstable carotid plaques (OR = 1.053, 95% CI: 1.038-1.068, $P < 0.001$); Spearman correlation analysis showed that sdLDL-C test results were positively correlated with carotid plaque stability ($r = 0.363$, $P < 0.001$). CONCLUSION: Small dense low-density lipoprotein cholesterol is an independent risk factor for the onset of ACI and may be an early serum marker for this disease.

[26] *Csanyi G, Singla B*. **Arterial Lymphatics in Atherosclerosis: Old Questions, New Insights, and Remaining Challenges**. Journal of clinical medicine 2019; 8.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30979062
ABSTRACT
The lymphatic network is well known for its role in the maintenance of tissue fluid homeostasis, absorption of dietary lipids, trafficking of immune cells, and adaptive immunity. Aberrant lymphatic function has been linked to lymphedema and immune disorders for a long time. Discovery of lymphatic cell markers, novel insights into developmental and postnatal lymphangiogenesis, development of genetic mouse models, and the introduction of new imaging techniques have improved our understanding of lymphatic function in both health and disease, especially in the last decade. Previous studies linked the lymphatic vasculature to atherosclerosis through regulation of immune responses, reverse cholesterol transport, and inflammation. Despite extensive research, many aspects of the lymphatic circulation in atherosclerosis are still unknown and future studies are required to confirm that arterial lymphangiogenesis truly represents a therapeutic target in patients with cardiovascular disease. In this review article, we provide an overview of factors and mechanisms that regulate lymphangiogenesis, summarize recent findings on the role of lymphatics in macrophage reverse cholesterol transport, immune cell trafficking and pathogenesis of atherosclerosis, and present an overview of pharmacological and genetic strategies to modulate lymphatic vessel density in cardiovascular tissue.

[27] *Borja-Hart N, Graff JC, Nolan VG et al.* **Atherosclerotic cardiovascular disease risk assessment and predictors of statin use in Filipino-American Women**. Journal of clinical pharmacy and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30963623

ABSTRACT
WHAT IS KNOWN AND OBJECTIVE: Race and gender disparities in the context of appropriate treatment with lipid-lowering therapies do exist. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines outlined four groups, three for primary prevention and one for secondary prevention, whom would benefit from statin therapy to target atherosclerotic cardiovascular disease (ASCVD). The application of these recommendations in Filipino women living in the United States is unknown; however, this population is known to have elevated cardiovascular risk. Socio-economic and clinical characteristics that predict statin utilization of this Asian American subgroup need to be explored. METHODS: This was an exploratory analysis of data collected during a cross-sectional study of Filipino-American Women (FAW). The Pooled Cohort equation was used to estimate 10-year ASCVD risk. Bivariate analysis was employed to determine the association between statin treatment and clinical and socio-economic factors. Data were analysed using SAS((R)) 9.4; statistical significance was set at $P < 0.05$. RESULTS AND DISCUSSION: A total of 384 women (mean age 56.3 years) were included in the original study, and the average 10-year ASCVD risk was 3.5 +/- 3.7%. Upon applying the 2013 ACC/AHA guidelines, 97 FAW were categorized into one of the primary prevention groups. Women considered to benefit from a statin based on the guideline criteria but were not prescribed a statin were considered the not statin treated group ($n = 55$). From the original cohort, 93 FAW reported current statin therapy use and were categorized as statin treated. The clinical characteristics associated with not being statin treated were as follows: untreated blood pressure ($P = 0.012$), higher diastolic blood pressure ($P = 0.015$), higher total cholesterol ($P < 0.001$), higher triglycerides ($P = 0.041$), higher low-density lipoprotein ($P < 0.001$) and higher glucose ($P = 0.011$). The socio-economic factor associated with not being statin treated was having two or more insurance payers ($P = 0.005$). Overall, this population had a waist circumference and body mass index (BMI) that exceeds guidelines for Asian women (31.5 or 80 cm). WHAT IS NEW AND CONCLUSION: Predictors of statin utilization in FAW are not well documented in the literature. These findings emphasize room for improvement for the prescribing of statins in primary prevention for this study population. Applying culturally appropriate screening strategies to identify cardiovascular risk factors early such as BMI or waist circumference may assist with quantifying patients into one of the statin benefit groups if eligible.

[28] *Li IH, Shih JH, Tsai CS et al.* **Inverse Association of Fibrates and Liver Cancer: A Population-Based Case-Control Study in Taiwan**. Journal of clinical pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30964561

ABSTRACT
This large-scale case-control study in Taiwan elucidated the potential connection between fibrate use and liver cancer by using the Longitudinal Health Insurance Database 2005 with a propensity-score-matching design. In total, 4173 patients diagnosed as having liver cancer were included as cases, and 4173 propensity-score-matched patients without liver cancer were identified as controls. The association between previous fibrate use and liver cancer occurrence was demonstrated using conditional logistic regression. Fibrate use was noted in 371 (8.89%) cases and 481 (11.53%) controls. After adjustments, the cases had significantly lower odds of previous fibrate use than did the controls (adjusted odds ratio 0.70, 95%CI 0.60-0.82);

moreover, regardless of the patients' sex, age group, and comorbidities, the cases were less likely to have used fibrates than were the controls. Dose-dependent analysis revealed that 1-695 cumulative defined daily doses of fibrates may significantly induce a protective effect for liver cancer. Although other fibrate dose intervals did not reach statistical significance, the dose-response curve presented the trend of a protective effect for liver cancer among the fibrate users. In summary, fibrate use had a significant protective effect against liver cancer in this Asian population.

[29] *Porcu M, Anzidei M, Suri JS et al.* **Carotid artery imaging: the study of intra-plaque vascularization and hemorrhage in the era of the "vulnerable" plaque**. Journal of neuroradiology. Journal de neuroradiologie 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30954549
ABSTRACT
Intraplaque hemorrhage (IPH) is one of the main factors involved in atherosclerotic plaque (AP) instability. Its recognition is crucial for the correct staging and management of patients with carotid artery plaques to limit ischemic stroke. Imaging plays a crucial role in identifying IPH, even if the great variability of intraplaque vascularization and the limitations of our current imaging technologies make it difficult. The intent of this review is to give a general overview of the main features of intraplaque vascularization and IPH on Ultrasound (US), Computed Tomography (CT), Magnetic Resonance (MR) and Nuclear Medicine, and a brief description on the future prospectives.

[30] *D'Andrea E, Hey SP, Ramirez CL, Kesselheim AS*. **Assessment of the Role of Niacin in Managing Cardiovascular Disease Outcomes: A Systematic Review and Meta-analysis**. JAMA network open 2019; 2:e192224.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30977858
ABSTRACT
Importance: Niacin remains a therapeutic option for patients with cardiovascular disease, but recent studies have called into question the effectiveness of other drugs that increase high-density lipoprotein cholesterol levels. Objective: To systematically review and evaluate the evidence supporting current US Food and Drug Administration-approved uses of niacin in cardiovascular disease prevention settings. Data Sources: MEDLINE, Embase, Cochrane Controlled Clinical Trial Register (Central), ClinicalTrials.gov, and TrialResults-center, from database inception to October 2017. Study Selection: The systematic review included clinical trials involving niacin as a treatment for cardiovascular disease. The meta-analysis included randomized clinical trials reporting niacin's effect, as exposure, on at least 1 long-term cardiovascular disease outcome. Data Extraction and Synthesis: Aggregate study-level data were extracted between November 2017 and January 2018 by 3 independent reviewers, and the analysis was performed in February 2018. Inverse-variance weighted methods were used to produce pooled risk ratios using random-effects models for between-study heterogeneity. Random effects-weighted metaregression analysis was used to assess the association of change in high-density lipoprotein cholesterol levels with the log risk ratio of the pooled results. Main Outcomes and Measures: Cardiovascular disease, coronary heart disease mortality, and other cardiovascular events, including acute coronary syndrome, fatal and nonfatal stroke,

revascularization, and major adverse cardiac events. Results: Of 119 clinical trials, 17 documented niacin's effect on at least 1 cardiovascular disease outcome. The meta-analysis included 35760 patients with histories of cardiovascular disease or dyslipidemia. Cumulative evidence found no preventive association of niacin with cardiovascular outcomes in secondary prevention. Stratified meta-analysis showed an association of niacin monotherapy with reduction of some cardiovascular events among patients without statin treatment (acute coronary syndrome: relative risk, 0.74; 95% CI, 0.58-0.96; stroke: relative risk, 0.74; 95% CI, 0.59-0.94; revascularization: relative risk, 0.51; 95% CI, 0.37-0.72). These results were mainly derived from 2 trials conducted in the 1970s and 1980s. Conclusions and Relevance: Niacin may have some use in lipid control for secondary prevention as monotherapy, perhaps in patients intolerant to statins, but evidence is from older studies on a population potentially not representative of current-day patients.

[31] *Lee C, Cui Y, Song J et al.* **Effects of familial hypercholesterolemia-associated genes on the phenotype of premature myocardial infarction**. Lipids in health and disease 2019; 18:95.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30971288
ABSTRACT
BACKGROUND: The incidence of premature myocardial infarction (PMI) has gradually increased in recent years. Genetics plays a central role in the development of PMI. Familial hypercholesterolemia (FH) is one of the most common genetic disorders of cholesterol metabolism leading to PMI. OBJECTIVE: This study investigated the relationship between FH-associated genes and the phenotype of PMI to clarify the genetic spectrum of PMI diseases. METHOD: This study enrolled PMI patients (n = 225) and detected the mutations in their FH-associated genes (LDLR, APOB, PCSK9, LDLRAP1) by Sanger sequencing. At the same time, patients free of PMI (non-FH patients, n = 56) were enrolled as control, and a logistic regression analysis was used to identify risk factors associated with PMI. The diagnosis of FH was confirmed using "2018 Chinese expert consensus of FH screening and diagnosis" before the prevalence and clinical features of FH were analyzed. RESULTS: Pathogenic mutations in LDLR, APOB, PCSK9 and LDLRAP1 genes were found in 17 of 225 subjects (7.6%), and all mutations were loss of function (LOF) and heterozygous. The genotype-phenotype relationship of patients carrying FH-associated mutations showed high heterogeneity. The logistic regression analysis showed that the smoking history, obesity and the family history of premature CHD were independent risk factors of PMI. In this study, a total of 19 patients (8.4%) were diagnosed as FH, and the proportion of smoking subjects in FH patients was higher than that in non-FH patients. CONCLUSIONS: FH-associated gene mutations were present in about 7.6% of Chinese patients with PMI. In addition to genetic factors, smoking history, lifestyle and other environmental factors may play a synergistic role in determining the phenotype of PMI. TRIAL REGISTRATION: Essential gene mutation of cholesterol metabolism in patients with premature myocardial infarction. ChiCTR-OCH-12002349.Registered 26 December 2014, http://www.chictr.org.cn/showproj.aspx?proj=7201 .

[32] *Simental-Mendia LE, Simental-Mendia M, Sanchez-Garcia A et al.* **Impact of ursodeoxycholic acid on circulating lipid concentrations: a systematic review and meta-analysis of randomized placebo-controlled trials**. Lipids in health and disease 2019; 18:88.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30954082

ABSTRACT

OBJECTIVE: The aim of this meta-analysis of randomized placebo-controlled trials was to examine whether ursodeoxycholic acid treatment is an effective lipid-lowering agent. METHODS: PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched in order to find randomized controlled trials evaluating the effect of ursodeoxycholic acid on lipid profile. A random-effect model and the generic inverse variance weighting method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. A random-effects meta-regression model was performed to explore the association between potential confounders and the estimated effect size on plasma lipid concentrations. RESULTS: Meta-analysis of 20 treatment arms revealed a significant reduction of total cholesterol following ursodeoxycholic acid treatment (WMD: - 13.85 mg/dL, 95% CI: -21.45, - 6.25, p < 0.001). Nonetheless, LDL-C (WMD: -6.66 mg/dL, 95% CI: -13.99, 0.67, p = 0.075), triglycerides (WMD: - 1.42 mg/dL, 95% CI: -7.51, 4.67, p = 0.648) and HDL-C (WMD: -0.18 mg/dL, 95% CI: -5.23, 4.87, p = 0.944) were not found to be significantly altered by ursodeoxycholic acid administration. In the subgroup of patients with primary biliary cirrhosis, ursodeoxycholic acid reduced total cholesterol (WMD: - 29.86 mg/dL, 95% CI: -47.39, - 12.33, p = 0.001) and LDL-C (WMD: -37.27 mg/dL, 95% CI: -54.16, - 20.38, p < 0.001) concentrations without affecting TG and HDL-C. CONCLUSION: This meta-analysis suggests that ursodeoxycholic acid therapy might be associated with significant total cholesterol lowering particularly in patients with primary biliary cirrhosis.

[33] *van den Berg EH, Wolters AAB, Dullaart RPF et al.* **Prescription of statins in suspected non-alcoholic fatty liver disease and high cardiovascular risk, a population-based study**. Liver international : official journal of the International Association for the Study of the Liver 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30968536

ABSTRACT

BACKGROUND & AIMS: The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing, with concomitant high incidence of lipoprotein abnormalities. Cardiovascular disease (CVD) is the main cause of death in subjects with NAFLD and management of dyslipidemia is pivotal for prevention. We aimed to determine cardiovascular risk and indication for statin therapy in subjects with NAFLD. METHODS: Cross sectional analysis of the population-based Lifelines Cohort Study of 34,240 adult individuals. Subjects with reported use of lipid-lowering drugs were excluded. Suspected NAFLD was defined as Fatty Liver Index (FLI) >/=60 and advanced hepatic fibrosis as NAFLD fibrosis score (NFS) >0.676. Cardiovascular risk and indication for statin therapy were defined according to the European Society of Cardiology and European Atherosclerosis Society Guideline for the Management of Dyslipidemias. RESULTS: FLI>/=60 was present in 7,067 (20.6%) participants and coincided with increased prevalence of type 2 diabetes mellitus, metabolic syndrome, CVD and impaired renal function (all P<0.001). 10-Year predicted cardiovascular risk was significantly increased in subjects with elevated FLI and NFS (both P<0.001). Indication for statin use was significantly increased in subjects with FLI>/=60 (31.0% vs. 15.6%, P<0.001) and NFS>0.676 (73.2% vs. 30.6%, P<0.001). In multivariable analyses FLI>/=60 (OR 1.26, 95%CI: 1.13-1.41%, P<0.001) and NFS>0.676 (OR 5.03, 95%CI: 2.76-9.17%, P<0.001) were independent predictors for indication regarding statin therapy.

CONCLUSIONS: Because of increased cardiovascular risk, substantial proportions of subjects with suspected NAFLD and/or fibrosis have an indication for lipid-lowering treatment and could benefit from statin therapy.

[34] *Zhang Q, Qiao H, Dou J et al.* **Plaque components segmentation in carotid artery on simultaneous non-contrast angiography and intraplaque hemorrhage imaging using machine learning**. Magnetic resonance imaging 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30959178
ABSTRACT
PURPOSE: This study sought to determine the feasibility of using Simultaneous Non-contrast Angiography and intraPlaque Hemorrhage (SNAP) to detect the lipid-rich/necrotic core (LRNC), and develop a machine learning based algorithm to segment plaque components on SNAP images. METHODS: Sixty-eight patients (age: 58+/-9years, 24 males) with carotid artery atherosclerotic plaque were imaged on a 3T MR scanner with both traditional multi-contrast vessel wall MR sequences (TOF, T1W, and T2W) and 3D SNAP sequence. The manual segmentations of carotid plaque components including LRNC, intraplaque hemorrhage (IPH), calcification (CA) and fibrous tissue (FT) on traditional multi-contrast images were used as reference. By utilizing the intensity and morphological information from SNAP, a machine learning based two steps algorithm was developed to firstly identify LRNC (with or without IPH), CA and FT, and then segmented IPH from LRNC. Ten-fold cross-validation was used to evaluate the performance of proposed method. The overall pixel-wise accuracy, the slice-wise sensitivity & specificity & Youden's index, and the Pearson's correlation coefficient of the component area between the proposed method and the manual segmentation were reported. RESULTS: In the first step, all tested classifiers (Naive Bayes (NB), Support Vector Machine (SVM), Random Forest (RF), Gradient Boosting Decision Tree (GBDT) and Artificial Neural Network (ANN)) had overall pixel-wise accuracy higher than 0.88. For RF, GBDT and ANN classifiers, the correlation coefficients of areas were all higher than 0.82 ($p<0.001$) for LRNC and 0.79 for CA ($p<0.001$), and the Youden's indexes were all higher than 0.79 for LRNC and 0.76 for CA, which were better than that of NB and SVM. In the second step, the overall pixel-wise accuracy was higher than 0.78 for the five classifiers, and RF achieved the highest Youden's index (0.69) with the correlation coefficients as 0.63 ($p<0.001$). CONCLUSIONS: The RF is the overall best classifier for our proposed method, and the feasibility of using SNAP to identify plaque components, including LRNC, IPH, CA, and FT has been validated. The proposed segmentation method using a single SNAP sequence might be a promising tool for atherosclerotic plaque components assessment.

[35] *Arthur RS, Kirsh VA, Rohan TE*. **Dietary B-Vitamin Intake and Risk of Breast, Endometrial, Ovarian and Colorectal Cancer among Canadians**. Nutrition and cancer 2019:1-11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30955365
ABSTRACT
Few studies have explored the associations of thiamin, niacin and riboflavin with risk of cancer despite their role in potentially cancer-associated one-carbon metabolism. Using multivariable Cox proportional hazards regression models modified for the case-cohort design, we examined the associations of dietary intake of the above-mentioned B vitamins, as well as folate, and

vitamins B6 and B12, with risk of the breast (n = 922), endometrial (n = 180), ovarian (n = 104) and colorectal (n = 266) cancers among age-stratified subcohorts of 3,185 women who were randomly selected from a cohort of 73,909 participants. None of the B-vitamins were associated with risk of breast or colorectal cancers. However, relatively high dietary intake of folate intake was inversely associated with risk of endometrial (HRq4 vs q1: 0.52; 95% CI: 0.29-0.93) and ovarian (HRq3 vs q1: 0.39; 95% CI: 0.19-0.80) cancers while relatively high dietary intake of vitamin B6 was inversely associated with ovarian cancer risk (HRq3 vs q1: 0.49; 95% CI: 0.24-0.98). These findings suggest that dietary intake of folate may reduce risk of endometrial and ovarian cancers and dietary intake of vitamin B6 may reduce risk of ovarian cancer.

[36] *Cicero AFG, Toth PP, Fogacci F et al.* **Improvement in arterial stiffness after short-term treatment with PCSK9 inhibitors**. Nutrition, metabolism, and cardiovascular diseases : NMCD 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30954414
ABSTRACT

[37] *Balakumar P, Sambathkumar R, Mahadevan N et al.* **Molecular targets of fenofibrate in the cardiovascular-renal axis: a unifying perspective of its pleiotropic benefits**.
Pharmacological research : the official journal of the Italian Pharmacological Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30970278
ABSTRACT
The activation of peroxisome proliferator-activated receptor alpha (PPARalpha) is a key pharmacological drug target for dyslipidemic management. Dyslipidemia is associated with abnormal serum lipid profiles viz. elevated total cholesterol, high triglyceride, elevated low-density lipoprotein cholesterol, and reduced high-density lipoprotein cholesterol levels. Fenofibrate, a third-generation fibric acid derivative, is an activator of PPARalpha indicated for the treatment of mixed dyslipidemia and hypertriglyceridemia in adults. Fenofibrate is considered an important lipid-lowering medication employed in patients afflicted with atherogenic dyslipidemia. Intriguingly, recent bench studies have demonstrated an array of cardiovascular and renal pleiotropic beneficial activities of fenofibrate, besides its foremost lipid-lowering action. The activation of PPARalpha by fenofibrate could negatively regulate the cardiomyocyte hypertrophy. In addition, fenofibrate has been suggested to have a protective effect against experimental ischemia/reperfusion injury in the myocardium in part via endoplasmic reticulum stress inhibition. Fenofibrate has also been shown to suppress arrhythmias in isolated rat hearts subjected to ischemic/reperfusion-induced cardiac injury. Moreover, in a rat model of metabolic syndrome and myocardial ischemia, fenofibrate therapy has been shown to restore antioxidant protection and improve myocardial insulin resistance. Furthermore, studies have highlighted the pleiotropic vascular endothelial protective and antihypertensive actions of fenofibrate. Interestingly, recent bench studies have demonstrated renoprotective actions of fenofibrate by implicating diverse mechanisms. This review sheds light on the current perspectives and molecular mechanistic aspects pertaining to the cardiovascular pleiotropic actions of fenofibrate. Additionally, the renal pleiotropic actions of fenofibrate by focusing its possible modulatory role on renal fibrosis, inflammation and renal epithelial-to-mesenchymal transition have been enlightened.

[38] *Cho O, Kim HS, Park KY, Heo TH*. **A Comparison of the Anti-Inflammatory Effects of Four Combined Statin and Antiplatelet Therapies on Tumor Necrosis Factor-Mediated Acute Inflammation in vivo**. Pharmacology 2019; 104:21-27.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30970359

ABSTRACT

BACKGROUND: Combination therapy has been administered to patients with chronic or complex diseases due to its improved therapeutic effects compared with the results of monotherapy. Due to the pleiotropic effects of statins and antiplatelets, these drugs have been studied in combination with other drugs, but not all combinations exerted obvious beneficial effects compared with individual drugs. In this study, we aimed to compare the anti-inflammatory effects of 4 different combination therapies of statins and antiplatelets on the tumor necrosis factor (TNF)-mediated inflammation in vivo. METHODS: Mice were orally administered cilostazol plus pravastatin (CILOP) or cilostazol plus rosuvastatin (CILOR), clopidogrel plus pravastatin (CLOP), or clopidogrel plus rosuvastatin (CLOR); then, acute inflammation was induced by the injection of lipopolysaccharide (LPS) or TNF. Serum TNF levels, macrophage accumulation in the lesioned aortas, and mouse mortality were observed to be comparable to the anti-inflammatory effects of the combination therapies. RESULTS: In mice with LPS-induced inflammation, CILOP and CILOR substantially reduced macrophage infiltration of aortic lesions and the serum TNF levels compared with CLOP and CLOR. Moreover, among the 4 combinations, CILOP significantly improved the survival rate of mice with TNF-mediated acute lethal inflammation. CONCLUSIONS: The combination therapy comprising cilostazol and statins, particularly pravastatin, exerted the best anti-TNF effect compared with clopidogrel and statin therapy; thus, a suitable combination therapy, such as CILOP, can be a potential remedy to cure TNF-related diseases.

[39] *Oztas E, Yilmaz TE, Guzel E et al.* **Gliclazide alone or in combination with atorvastatin ameliorated reproductive damage in streptozotocin-induced type 2 diabetic male rats**. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 2019; 27:422-431.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30976187

ABSTRACT

Objectives: Type 2 diabetes (T2DM) is one of the most serious challenges of the 21th century with life-threatening complications and excessive health care costs. In diabetic patients, the main goal in T2DM treatment is the regulation of both blood glucose and lipid levels. For that, Gliclazide (GLZ), an oral antidiabetic, and Atorvastatin (ATV), a lipid lowering agent, are widely used drugs as combination. Diabetes has been reported severe impacts on male reproductive system; however, data obtained about ATV and GLZ treatment alone or in combination are conflicted or insufficient. Herein the effects of ATV and GLZ on male reproductive system in type 2 diabetic male rats have been investigated in the present study. Methods: T2DM was induced by high-fat diet and single injection of streptozotocin (STZ) (35mg/kg) in young adult male Sprague-Dawley rats. The diabetic rats were given ATV (10mg/kg), GLZ (10mg/kg) and ATV/GLZ (1:1, 10mg/kg) combination by oral gavage for 28days. The hormone levels were determined in the cardiac blood samples; and the histopathological and ultrastructural analyses

were conducted in the testicular tissues and epididymal sperms. Results: It was observed that diabetes had severe effects on testicular tissue and spermatogenesis. ATV treatment did not affect sperm count and testes structure ($p>0.05$), however ameliorated sperm morphology ($p<0.05$). GLZ treatment increased sperm count, and improved sperm morphology, testes structure and spermatogenesis ($p<0.05$). ATV/GLZ combination treatment enhanced sperm morphology and improved testicular structure ($p<0.05$) while did not affect sperm count ($p>0.05$). Conclusion: GLZ treatment regenerated testicular damage and sperm parameters whether alone or in combination with ATV in diabetic rats without affecting hypothalamic-pituitary-gonadal axis.

[40] *Vallejo J, Duner P, To F et al.* **Activation of immune responses against the basement membrane component collagen type IV does not affect the development of atherosclerosis in ApoE-deficient mice**. Scientific reports 2019; 9:5964.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30979943
ABSTRACT
Oxidation of low-density lipoprotein (LDL) in the arterial extracellular matrix results in malondialdehyde (MDA)-modifications of surrounding matrix proteins. We have recently demonstrated an association between high levels of autoantibodies against MDA-modified collagen type IV and risk for development of myocardial infarction. Collagen type IV is an important component of the endothelial basement membrane and influences smooth muscle cell function. We hypothesized that immune responses against collagen type IV could contribute to vascular injury affecting the development of atherosclerosis. To investigate this possibility, we induced an antibody-response against collagen type IV in apolipoprotein E (Apo E)-deficient mice. Female ApoE(-/-) mice on C57BL/6 background were immunized with alpha1alpha2 type IV collagen chain peptides linked to the immune-enhancer PADRE, PADRE alone or PBS at 12 weeks of age with three subsequent booster injections before the mice were killed at 23 weeks of age. Immunization of PADRE alone induced autoantibodies against PADRE, increased IL-4 secretion from splenocytes and reduced SMC content in the subvalvular plaques. Immunization with peptides of alpha1alpha2 type IV collagen chains induced a strong IgG1antibody response against collagen type IV peptides without affecting the distribution of T cell populations, plasma cytokine or lipid levels. There were no differences in atherosclerotic plaque development between collagen alpha1alpha2(IV)-PADRE immunized mice and control mice. Our findings demonstrate that the presence of antibodies against the basement membrane component collagen type IV does not affect atherosclerosis development in ApoE(-/-) mice. This suggests that the association between autoantibodies against collagen type IV and risk for myocardial infarction found in humans does not reflect a pathogenic role of these autoantibodies.

[41] Bajaj T, Giwa AO. Rosuvastatin. In: StatPearls. Treasure Island (FL): StatPearls Publishing StatPearls Publishing LLC.; 2019.
[42] Rucker D, Dhamoon AS. Physiology, Thromboxane A2. In: StatPearls. Treasure Island (FL): StatPearls Publishing
StatPearls Publishing LLC.; 2019.

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[43] *Libby P*. **Arson in the artery: Who set the atheroma aflame?** Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30956033
ABSTRACT
Inflammation drives the formation, evolution, and complication of atherosclerotic plaques. Yet, we have not yet captured the culprits who light the fire that burns within the atherosclerotic plaque. The arsonist remains at large. A rigorous analysis exculpates many of the usual suspects. Low-density lipoprotein (LDL) itself engenders little inflammation. Clinical trials do not support an actionable role of oxidized LDL in atherothrombosis. In contrast, triglyceride-rich lipoproteins do promote inflammation, and provide a promising target for intervention. Obese adipose tissue -especially visceral or ectopic lipid deposits -also incite inflammation. A newly recognized cardiovascular risk factor, clonal hematopoiesis provides a novel link between inflammatory pathways and atherosclerotic risk. Despite this progress, the jury is still out on who lit the plaque afire. The rigorous observer must still consider this an unsolved act of arson. We remain in "hot" pursuit of the causal culprit, the arsonist, and accomplices who set the artery wall ablaze.

[44] *Wascher TC, Paulweber B, Toplak H et al.* **[Lipids-Diagnosis and therapy in diabetes mellitus (Update 2019)]**. Wien Klin Wochenschr 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30980157
ABSTRACT
Hyper- and dyslipidemia contribute to cardiovascular morbidity and mortality in diabetic patients. Pharmacological therapy to lower LDL cholesterol has convincingly shown to reduce cardiovascular risk in diabetic patients. The present article represents the recommendations of the Austrian Diabetes Association for the use of lipid-lowering drugs in diabetic patients according to current scientific evidence.