

Literature update week 12 (2019)

[1] Zarganes-Tzitzikas T, Neochoritis CG, Domling A. **Atorvastatin (Lipitor) by MCR.** ACS medicinal chemistry letters 2019; 10:389-392.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30891146>

ABSTRACT

A concise and convergent synthesis of the atorvastatin, the best-selling cardiovascular drug of all time, is presented. Our approach is based on an Ugi reaction, which shortens the current synthetic route and is advantageous over the published syntheses.

[2] De Vloo C, Nevens F. **Cholestatic pruritus : an update.** Acta gastro-enterologica Belgica 2019; 82:75-82.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30888758>

ABSTRACT

Pruritus is a common, troublesome symptom in patients with cholestatic liver diseases, especially frequent in intrahepatic cholestasis of pregnancy (ICP) and in primary biliary cholangitis (PBC). Cholestatic associated pruritus can have profound effects on the quality of life. The underlying mechanism is still poorly understood. Severe potential pruritogens have been discussed, such as bile salts, opioids, steroid and lysophosphatidic acid (LPA), but none of these are considered as key mediators. Because of this unraveling pathophysiology the treatment of hepatogenic pruritus often represents a clinical challenge. The EASL guidelines have suggested a step-wise approach, starting with elimination of pruritogens by bile acid sequestrants (cholestyramine), in second line managing the metabolism of pruritogens (rifampicin) and in third-line and fourth- line by modifying the itch perception with mu-opioid antagonist or selective serotonin reuptake inhibitors (SSRI). In treatment-refractory pruritus interruption of the enterohepatic cycle by molecular absorbent recirculating system (MARS), nasobiliary drainage or experimental therapy such as Ultraviolet B light therapy can be considered. Liver transplantation may be reserved for intractable pruritus. Clinical trials with novel agents are ongoing, potentially providing efficacious options in the future.

[3] Saxena A, Tiwari P, Wahi N et al. **Transcriptome profiling reveals association of peripheral adipose tissue pathology with type-2 diabetes in asian Indians.** Adipocyte 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30894049>

ABSTRACT

Type 2 Diabetes (T2D) is a complex disease with an elusive link between its molecular etiology and clinical presentation. Although, the role of visceral adipose tissue in the pathogenesis of insulin resistance and T2D is well known, only a limited information is available on the role of peripheral subcutaneous adipose tissue especially in Asian Indians. In this microarray based study of diabetic and normal glucose tolerant (NGT) Asian Indians, we generated the transcription profile of their thigh subcutaneous adipose tissue and further analyzed the differentially expressed genes (DEGs) using weighted gene co-expression network analysis (WGCNA) approach. Through WGCNA, we identified the perturbed pathways implicated by these DEGs in relevant co-expression modules by using a topology-based enrichment method. We also attempted to link these pathways with known aspects of T2D pathophysiology in terms of their association with some of their intermediate traits, namely; clinical

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diagnosis of diabetes, adipocyte size, HOMA-B, and HOMA-R, glycated hemoglobin (Hb1Ac), insulin, glucose level, proinflammatory markers - TNF-alpha, IL-6, lipid profile markers - Very Low Density Lipids (VLDL), Low Density Lipids (LDL), High Density Lipids (HDL), and Non Esterified Fatty Acids (NEFA). It was observed in this study that several modules of co-expressed genes show an association with diabetes and some of its intermediate phenotypic traits mentioned above. Therefore, these findings suggest a role of peripheral subcutaneous adipose tissue in the pathophysiology of T2D in Asian Indians. Additionally, our study indicated that the peripheral subcutaneous adipose tissue in diabetics shows pathologic changes characterized by adipocyte hypertrophy and upregulation of inflammation related pathways. Graphical Abstract.

[4] *Giles JT, Wasko MCM, Chung CP et al. Exploring the Lipid Paradox Theory in Rheumatoid Arthritis: Associations of Low Circulating Low Density Lipoprotein Concentration with Subclinical Coronary Atherosclerosis. Arthritis & rheumatology (Hoboken, N.J.) 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30883031>

ABSTRACT

BACKGROUND/PURPOSE: Rheumatoid arthritis (RA) patients with the lowest circulating low-density lipoprotein concentrations (LDL-C) are at heightened risk for cardiovascular disease (CVD) events. However, atherosclerotic burden within this subgroup is unknown. METHODS: RA patients pooled from 4 cohort studies of CVD (n=546) were compared with non-RA controls from the Multi-Ethnic Study of Atherosclerosis (MESA; n=5,279). Those on lipid lowering medications were excluded. Differences in cardiac computed tomography-derived coronary arterial calcium (CAC) Agatston scores between the RA and control groups were compared across strata of LDL-C. RESULTS: Among those with low LDL-C (LDL-C<70 mg/dL), mean adjusted CAC scores were 3-fold higher for RA patients compared with controls (18.6 vs. 4.6 Agatston units, respectively; p<0.001), a difference significantly greater than that of any other LDL-C stratum except LDL-C>160 mg/dL. Similarly, 32% of the RA patients with low LDL-C had a CAC score \geq 100 Agatston units compared with only 7% of controls in the same LDL-C stratum (OR=5.97; p<0.001), a difference significantly greater than all of the other LDL-C strata. Low LDL-C was most strongly associated with higher CAC among RA patients who were white race, ever smokers, and the non-obese. Other than a higher frequency of current smokers, RA patients with low LDL-C did not have more CVD risk factors or higher measures of RA disease activity or severity when compared with RA patients with higher LDL-C. CONCLUSIONS: RA patients with low LDL-C may represent a group appropriate for heightened screening and prevention of atherosclerotic CVD. This article is protected by copyright. All rights reserved.

[5] *Ruscica M, Watts GF, Sirtori CR. PCSK9 in HIV infection: New opportunity or red herring? Atherosclerosis 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30890266>

ABSTRACT

[6] *Al'Aref SJ, Pena JM, Min JK. High-risk atherosclerotic plaque features for cardiovascular risk assessment in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain trial. Cardiovascular diagnosis and therapy 2019; 9:89-93.*

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30881885>

ABSTRACT

[7] Quintanilha BJ, Pinto Ferreira LR, Ferreira FM et al. **Circulating plasma microRNAs dysregulation and metabolic endotoxemia induced by a high-fat high-saturated diet.** *Clinical nutrition (Edinburgh, Scotland)* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30885503>

ABSTRACT

High-fat diet increase two to three times the plasma lipopolysaccharide (LPS) levels and induce subclinical inflammation. Diet can modify gene expression due to epigenetic processes related to MicroRNAs (miRNAs). MicroRNAs (miRNAs) play important role in the post-transcriptional mechanisms involved in regulation of expression of genes related to the inflammatory response. Also, diet can indirectly induce post-transcriptional regulation of gene expression by miRNAs, which may affect the risk for the development of chronic diseases. OBJECTIVE: This study investigated the effect of high-fat high-saturated meal ingestion on plasma miRNA expression and LPS levels during the postprandial period in healthy women. METHODS: An interventional study was carried out in which a high-fat breakfast (1067.45 kcal), composed mainly of saturated fatty acids (56 g), and 500 mL of water, was offered. Blood samples were collected at baseline and 1, 3 and 5 h after meal intake. The studied population consisted of healthy women (n = 11), aged between 20 and 40 years, and body mass index (BMI) between 18.5 and 25 kg/m². Plasma levels of lipid profile, cytokines, adhesion molecules, and LPS were measured at the 3 time points. A profile of 752 human plasma miRNA expression was analyzed by real-time PCR assay. These analyzes were performed for all blood collection time-points. RESULTS: Expression profile analysis revealed 33 differentially expressed plasma circulating miRNAs compared to that of the control group. MiR-145-5p and miR-200 were differentially modulated in all time-points post meal consumption. In addition, there was a significant increase in plasma LPS, triglycerides, myristic and palmitic saturated fatty acids levels at the 3 time-points in comparison with the control basal levels. We also observed increased levels of the plasma tumor necrosis factor alpha (TNF-alpha) cytokine and the vascular cell adhesion molecule 1 (VCAM-1) levels after 5 h post meal ingestion. CONCLUSION: Ingestion of high-fat high-saturated meal was able to induce metabolic endotoxemia and increase the expression of pro-inflammatory molecules such as TNF-alpha and VCAM-1, as well as modulating circulating miRNAs possibly controlling inflammatory and lipid metabolism proteins at the postprandial period.

[8] Struik D, Dommerholt MB, Jonker JW. **Fibroblast growth factors in control of lipid metabolism: from biological function to clinical application.** *Current opinion in lipidology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30893110>

ABSTRACT

PURPOSE OF THE REVIEW: Several members of the fibroblast growth factor (FGF) family have been identified as key regulators of energy metabolism in rodents and nonhuman primates. Translational studies show that their metabolic actions are largely conserved in humans, which led to the development of various FGF-based drugs, including FGF21-mimetics LY2405319, PF-05231023, and pegbelfermin, and the FGF19-mimetic NGM282. Recently, a number of clinical trials have been published that examined the safety and efficacy of these novel therapeutic proteins in the treatment of

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obesity, type 2 diabetes (T2D), nonalcoholic steatohepatitis (NASH), and cholestatic liver disease. In this review, we discuss the current understanding of FGFs in metabolic regulation and their clinical potential. **RECENT FINDINGS:** FGF21-based drugs induce weight loss and improve dyslipidemia in patients with obesity and T2D, and reduce steatosis in patients with NASH. FGF19-based drugs reduce steatosis in patients with NASH, and ameliorate bile acid-induced liver damage in patients with cholestasis. In contrast to their potent antidiabetic effects in rodents and nonhuman primates, FGF-based drugs do not appear to improve glycemia in humans. In addition, various safety concerns, including elevation of low-density lipoprotein cholesterol, modulation of bone homeostasis, and increased blood pressure, have been reported as well. **SUMMARY:** Clinical trials with FGF-based drugs report beneficial effects in lipid and bile acid metabolism, with clinical improvements in dyslipidemia, steatosis, weight loss, and liver damage. In contrast, glucose-lowering effects, as observed in preclinical models, are currently lacking.

[9] *Brack MC, Lienau J, Kuebler WM, Witzenrath M. Cardiovascular sequelae of pneumonia. Current opinion in pulmonary medicine* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30893107>

ABSTRACT

PURPOSE OF REVIEW: In this brief review, we discuss the current epidemiological data and latest results from basic research on the cardiovascular sequelae after lower respiratory tract infection. **RECENT FINDINGS:** Novel epidemiological evidence substantiates the association between pneumonia and subsequent cardiovascular events (CVEs) in the short- and long-term after viral or bacterial acute infection. Biomarkers such as cardiac troponin or coronary artery calcium may represent useful predictive tools for the detection of cardiac involvement during and after pneumonia. Particularly, *Streptococcus pneumoniae* directly cause cardiac damage by invasion into the myocardium and formation of microscopic lesions finally leading to the development of cardiac scarring in rodents and nonhuman primates. In addition, a causal relationship between pulmonary inflammation and atherosclerotic plaque formation in systemic arteries has emerged that appears to involve a mechanistic role for neutrophil granulocytes. However, many key pathomechanisms by which pneumonia may trigger or promote subsequent CVEs still remain unclear. **SUMMARY:** Pneumonia may deleteriously impact cardiovascular function. Direct cardiomyocyte destruction by pathogens as well as host inflammatory response associated effects including atherosclerotic plaque development and/or rupture have been observed. Details of underlying mechanisms need to be further investigated to deliver future perspectives for the prevention of CVEs subsequent to pneumonia.

[10] *da Rocha AL, Pinto AP, Kohama EB et al. The proinflammatory effects of chronic excessive exercise. Cytokine* 2019; 119:57-61.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30884427>

ABSTRACT

Chronic moderate-intensity exercise is an efficient non-pharmacological strategy to prevent and treat several diseases such as type 2 diabetes mellitus, cardiovascular and chronic obstructive pulmonary diseases, cancers, and Parkinson's disease. On the other hand, improving an athlete's performance requires completing high-intensity and volume exercise sessions. When the delicate balance between high-load exercise sessions and adequate recovery periods is disrupted, excessive training (known as overtraining) can lead to performance decline. The cytokine hypothesis considers that an imbalance

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involving excessive exercise and inadequate recovery induces musculoskeletal trauma, increasing the production and release of proinflammatory cytokines, mainly interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interleukin 1beta (IL-1beta), which interact with different organic systems, initiating most of the signs and symptoms linked to performance decrement. This leading article used recent data to discuss the scientific basis of Smith's cytokine theory and highlighted that the adverse effects of excessive exercise go beyond performance decline, proposing a multi-organ approach for this issue. These recent insights will allow coaches and exercise physiologists to develop strategies to avoid chronic excessive exercise-induced adverse outcomes.

[11] *Grodzinsky A, Pokharel Y, Myadam R. Don't Stop at Statins: Complementary PCSK9 Use In Patients at High Risk for Recurrent Cardiac Events. European heart journal. Quality of care & clinical outcomes* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30882136>

ABSTRACT

[12] *Li B, Lei SS, Su J et al. Alcohol Induces More Severe Fatty Liver Disease by Influencing Cholesterol Metabolism. Evidence-based complementary and alternative medicine : eCAM* 2019; 2019:7095684.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30891077>

ABSTRACT

Objectives. Fatty liver disease (FLD) is a major cause of morbidity and mortality worldwide. Dietary cholesterol and alcohol consumption are important risk factors for the progression of FLD, but whether and how alcohol induces more severe FLD with cholesterol ingestion remain unclear. Herein, we mainly used the Lieber-DeCarli diet to establish the FLD mouse model to investigate the synergistic effects of alcohol and cholesterol metabolism on liver damage. The indices of aspartate transaminase (AST), alanine transaminase (ALT), low-density lipoprotein cholesterol (LDL-c), and total cholesterol (TC) levels, inflammation foci, and pathogenesis by hematoxylin and eosin (H&E) and Oil Red O staining revealed that alcohol induces more severe liver damage by influencing cholesterol metabolism, which might be primarily related to the influence of cholesterol absorption, synthesis, and excretion on the liver or small intestine. Moreover, inhibition of absorption of intestinal cholesterol, but not of fat, sucrose, and alcohol, absorption into the body's metabolism by Ezetimibe, significantly improved FLD in rats fed with the high fat-cholesterol-sucrose and alcohol diet. These results showed that alcohol plays an important role in cholesterol metabolism in FLD.

[13] *Wong ND, Shapiro MD. Interpreting the Findings From the Recent PCSK9 Monoclonal Antibody Cardiovascular Outcomes Trials. Frontiers in cardiovascular medicine* 2019; 6:14.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30895178>

ABSTRACT

The recent development of monoclonal antibodies targeted to proprotein convertase subtilisin/kexin type 9 (PCSK9), e.g., PCSK9 inhibitors has revolutionized the landscape of lipid management. Many clinical trials assessing this class have demonstrated remarkable and consistent reductions in low-density lipoprotein-cholesterol. Moreover, the GLAGOV trial demonstrated the efficacy of evolocumab,

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when added to statin therapy, in reducing the progression of atherosclerosis measured by serial intravascular ultrasound, with the first suggestion of continued benefit down to LDL-C levels of 0.5 mmol/L (20 mg/dL). This trial was followed by the FOURIER Cardiovascular Outcomes trial in more than 27,000 patients with stable atherosclerotic cardiovascular disease (ASCVD) where evolocumab reduced the primary endpoint of atherosclerotic events by 15%, without significant safety differences between treatment groups. Furthermore, subgroup analyses suggested greater benefits seen in those with longer exposure to evolocumab recent acute coronary syndrome, multiple myocardial infarctions, multivessel coronary artery disease, peripheral arterial disease, as well as the subgroup who achieved very low low-density lipoprotein-cholesterol levels of below 0.3 mmol/L (10 mg/dL). Moreover, the EBBINGHAUS substudy demonstrated no differences in objectively measured cognitive function between treatment groups. The SPIRE 2 trial evaluating bococizumab in high-risk patients with baseline LDL-C \geq 2.6 mmol/L (100 mg/dL) demonstrated significant atherosclerotic risk reduction, but the trial and further development of the drug was prematurely discontinued due to substantial attenuation of the LDL-C effect over time due to the development of neutralizing antibodies. Finally, the ODYSSEY Cardiovascular Outcomes trial testing alirocumab in subjects with recent (<1 year) acute coronary syndrome demonstrated a 15% relative risk reduction in the primary composite outcome, as well as a significant reduction in total mortality. Greater benefits were noted in those whose LDL-C at baseline was 2.6 mmol/L (100 mg/dL) or greater. These trials collectively demonstrate the added efficacy of PCSK9 inhibitors over moderate and high-intensity statin therapy for unprecedented low-density lipoprotein-cholesterol reduction and incremental ASCVD risk reduction.

[14] Hopkin SJ, Lewis JW, Krautter F et al. **Triggering the Resolution of Immune Mediated Inflammatory Diseases: Can Targeting Leukocyte Migration Be the Answer?** *Frontiers in pharmacology* 2019; 10:184.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30881306>

ABSTRACT

Leukocyte recruitment is a pivotal process in the regulation and resolution of an inflammatory episode. It is vital for the protective responses to microbial infection and tissue damage, but is the unwanted reaction contributing to pathology in many immune mediated inflammatory diseases (IMIDs). Indeed, it is now recognized that patients with IMIDs have defects in at least one, if not multiple, check-points regulating the entry and exit of leukocytes from the inflamed site. In this review, we will explore our understanding of the imbalance in recruitment that permits the accumulation and persistence of leukocytes in IMIDs. We will highlight old and novel pharmacological tools targeting these processes in an attempt to trigger resolution of the inflammatory response. In this context, we will focus on cytokines, chemokines, known pro-resolving lipid mediators and potential novel lipids (e.g., sphingosine-1-phosphate), along with the actions of glucocorticoids mediated by 11-beta hydroxysteroid dehydrogenase 1 and 2.

[15] Aguglia A, Solano P, Giacomini G et al. **The Association Between Dyslipidemia and Lethality of Suicide Attempts: A Case-Control Study.** *Frontiers in psychiatry* 2019; 10:70.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30881317>

ABSTRACT

Evidence supports the existence of an association between dyslipidemia, psychiatric disorders, and suicide risk due to the effects of altered lipid profiles on serotonergic neuron membranes. The aim of

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this study was to investigate the differences in c-reactive protein (CRP), thyroid functioning, total cholesterol, high lipoprotein density cholesterol (HDL-c), low-lipoprotein density cholesterol (LDL-c), and triglycerides (TG) serum levels in low lethality (LLSA) vs. high lethality suicide attempters (HLSA) within 24 h from the suicide attempt and inpatients who never attempted suicide (NAS). After attempting suicide, subjects were admitted to the emergency ward of the IRCCS Ospedale Policlinico San Martino and later to the section of Psychiatry from 1st August 2013 to 31st July 2018. Socio-demographic and clinical characteristics, serum lipids profile, CRP, and thyroid functioning were collected. The sample consisted of 133 individuals with a HLSA, 299 subjects with LLSA, and 200 patients NAS. HLSA subjects were more likely to be males and diagnosed as having a bipolar disorder. Furthermore, HLSA subgroup showed significantly lower total cholesterol and LDL-c levels and higher CRP serum levels compared to LLSA and control group, respectively. LLSA subgroup showed higher HDL-c levels compared to HLSA subgroup (no differences between HLSA and control group were observed). Additionally, the control group reported higher triglycerides levels compared to patients admitted to psychiatric ward for a suicide attempt. Only male gender, having a diagnosis of bipolar disorder, lower total cholesterol, and higher CRP serum levels predicted HLSA. Investigating the relation between dyslipidemia and the severity of suicide attempts may contribute to reveal the complex determinants underlying at-risk behaviors such as suicide, thus playing a relevant role in the possible prevention of this disabling phenomenon.

[16] *Lavecchia A, Cerchia C. Recent advances in developing PCSK9 inhibitors for lipid-lowering therapy. Future medicinal chemistry 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30892945>

ABSTRACT

Cardiovascular disease is the major cause of death globally, with hypercholesterolemia being an important risk factor. The PCSK9 represents an attractive therapeutic target for hypercholesterolemia treatment and is currently in the spotlight of the scientific community. After autocatalytic activation in the hepatocyte endoplasmic reticulum, this convertase binds to the LDLR and channels it to the degradation pathway. This review gives an overview on the latest developments in the inhibition of PCSK9, including disruption of the protein-protein interaction (PPI) between PCSK9 and LDLR by peptidomimetics, adnectins and monoclonal antibodies and the suppression of PCSK9 expression by small molecules, siRNA and genome editing techniques. In addition, we discuss alternative approaches, such as anti-PCSK9 active vaccination and heparin mimetics.

[17] *Bertolotti M, Lancellotti G, Mussi C. Management of high cholesterol levels in older people. Geriatrics & gerontology international 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30900369>

ABSTRACT

The management of hypercholesterolemia in older adults still represents a challenge in clinical medicine. The pathophysiological alterations of cholesterol metabolism associated with aging are still incompletely understood, even if epidemiological evidence suggests that serum cholesterol levels increase with ongoing age, possibly with a plateau after the age of 80 years. Age is also one of the main determinants of cardiovascular disease, according to all cardiovascular risk estimate tools. Cholesterol-lowering treatment, therefore, would be expected to bring significant protection, even in these patients.

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Unfortunately, direct experimental evidence is extremely limited, particularly in the very old age strata of the population; a clinical benefit still seems to be present, but the risk for drug-related adverse events is clearly higher. At any rate, at the present time, definite guidelines for the correct management of hypercholesterolemia in older patients are not available. Therefore, the decision whether or not a pharmacological treatment should be set up, and the choice of the drug, need to be tailored to the individual patient, and requires accurate clinical judgment. The specific aspects of frailty and disability, along with the actual age of the patients, have to be considered together, with a comprehensive assessment approach. The present review summarizes the evidence regarding the modifications of cholesterol metabolism in older patients, the impact of lipid-lowering drugs on cardiovascular outcomes and focuses on the considerations that can help to define the most appropriate treatment strategy, in view of the individual functional profile. *Geriatr Gerontol Int* 2019; **: **_**.

[18] *de Miranda JR, Choi IGG, Moreira MS et al. Histologic Evaluation of Early Bone Regeneration Treated with Simvastatin Associated with Low-Level Laser Therapy. The International journal of oral & maxillofacial implants* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30892287>

ABSTRACT

PURPOSE: This histologic study aimed at assessing bone healing after treatment with simvastatin in association with low-level laser therapy (LLLT). **METHODS:** Twenty-four male rats (Wistar) were submitted to surgery to create a bone defect of 5 mm in diameter in the parietal bone. These rats were randomly and equally divided into four treatment groups (n = 6): control (C), in which no treatment was performed; simvastatin (SIM), in which rats received daily subcutaneous doses of 2.5 mg/kg of simvastatin; LLLT, which was daily applied to the bone defect; and SIM-LLLT, in which both SIM and LLLT were daily applied. All laser irradiations were carried out with a 830-nm infrared diode laser (GaAlAs) with maximum output of 100 mW and a dose of 4 J, totaling 16 J per session. Rats were euthanized on the 12th postoperative day. Formalin-fixed paraffin-embedded bone samples were obtained and stained with hematoxylin-eosin (HE) and toluidine blue for optical microscope analysis. Degree of inflammation, new vascular formation, tissue repair, and osteoblastic activity were assessed. **RESULTS:** Categorical analysis of the histologic slides revealed newly formed bone reaching the center of the surgical wound in two animals from the SIM group, two from the LLLT group, and three from the SIM-LLLT group. Greater new bone formation and a lower degree of inflammation were observed in the animals that had bone neoformation at the center of the defect, especially in the LLLT and SIM-LLLT groups. SIM and C groups presented greater angiogenesis than LLLT and SIM-LLLT. SIM-LLLT therapy showed a statistically significant reduction in the degree of inflammation when compared to the control group (P < .05). **CONCLUSION:** Within the limitations of this study, the present results suggest that a combination of simvastatin and low-level laser therapy may stimulate better bone formation.

[19] *Cheung YM, O'Brien R, Ekinici EI. What's new in lipid lowering therapies in diabetes? Internal medicine journal* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30887650>

ABSTRACT

Diabetes can lead to myriad of microvascular and macrovascular complications - with the leading cause of mortality in diabetes being cardiovascular disease (CVD). Low-density lipoprotein cholesterol (LDL-C),

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along with non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TGs) are proven, modifiable risk factors for CVD. This article will focus on lipid lowering agents in individuals with diabetes. It will summarise relevant changes in the latest guidelines for dyslipidemia, and will also review the mechanisms of action of lipid lowering agents along with the latest cardiovascular outcomes data specific to individuals with diabetes. Older agents such as statins, ezetimibe, fibrates and nicotinic acid will be reviewed with a focus on new diabetes-specific evidence. Similarly, a relatively novel agent proprotein-convertase subtilisin-kexin type 9 (PCSK9) will be reviewed and details around the Pharmaceutical Benefits Scheme (PBS) criteria governing its usage in Australia will be included. Finally, this review will touch on agents still on the horizon such as icosapent ethyl, high-density lipoprotein (HDL) mimetics, bempedoic acid, omega-3 free fatty acids, bromodomain and extra-terminal proteins (BET) inhibitors and inclisiran - a long-acting RNA interference agent. In the appropriately selected population of individuals with diabetes, these agents can assist to further improve lipid profile and reduce cardiovascular events. This article is protected by copyright. All rights reserved.

[20] *Jukema JW, Szarek M, Zijlstra LE et al. Patients with Recent Acute Coronary Syndrome and Polyvascular Disease Derive Large Absolute Benefit from Alirocumab: ODYSSEY OUTCOMES Trial. Journal of the American College of Cardiology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30898609>

ABSTRACT

BACKGROUND: Patients with acute coronary syndrome (ACS) and concomitant noncoronary atherosclerosis have a high risk of major adverse cardiovascular events (MACE) and death. The impact of lipid-lowering by proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibition in such patients is undetermined. **OBJECTIVES:** This pre-specified analysis from ODYSSEY OUTCOMES determined whether polyvascular disease (polyVD) influenced risks of MACE and death and their modification by alirocumab in patients with recent ACS and dyslipidemia despite intensive statin therapy. **METHODS:** Patients were randomized to alirocumab or placebo 1-12 months after ACS. The primary MACE endpoint was the composite of coronary heart disease death, nonfatal myocardial infarction, fatal/nonfatal ischemic stroke, or unstable angina requiring hospitalization. All-cause death was a secondary endpoint. **RESULTS:** Median follow-up was 2.8 years. Of 18,924 patients, 17,370 had monovascular (coronary) disease, 1,405 had polyVD in two beds (coronary and peripheral artery or cerebrovascular), and 149 had polyVD in three beds (coronary, peripheral artery, cerebrovascular). With placebo, the incidence of MACE by respective vascular categories was 10.0%, 22.2%, and 39.7%. With alirocumab, corresponding absolute risk reduction (ARR [95% confidence interval]) was 1.4% (0.6, 2.3), 1.9% (-2.4%, 6.2%), and 13.0% (-2.0, 28.0). With placebo, the incidence of death by respective vascular categories was 3.5%, 10.0%, and 21.8%; ARR with alirocumab was 0.4% (-0.1, 1.0), 1.3% (-1.8%, 4.3%), and 16.2% (5.5, 26.8). **CONCLUSIONS:** In patients with recent ACS and dyslipidemia despite intensive statin therapy, polyVD is associated with high risks of MACE and death. The large absolute reductions in those risks with alirocumab are a potential benefit for this population.

[21] *Chan DC, Watts GF, Coll B et al. Lipoprotein(a) Particle Production as a Determinant of Plasma Lipoprotein(a) Concentration Across Varying Apolipoprotein(a) Isoform Sizes and Background Cholesterol-Lowering Therapy. Journal of the American Heart Association 2019; 8:e011781.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30897995>

ABSTRACT

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Background Elevated lipoprotein(a) (Lp(a)), a low-density lipoprotein-like particle bound to the polymorphic apolipoprotein(a) (apo(a)), may be causal for cardiovascular disease. However, the metabolism of Lp(a) in humans is poorly understood. **Methods and Results** We investigated the kinetics of Lp(a)-apo(a) and low-density lipoprotein-apoB-100 in 63 normolipidemic men. The fractional catabolic rate (FCR) and production rate (PR) were studied. Plasma apo(a) concentration was significantly and inversely associated with apo(a) isoform size ($r=-0.536$, $P<0.001$) and apo(a) FCR ($r=-0.363$, $P<0.01$), and positively with apo(a) PR ($r=0.877$, $P<0.001$). There were no significant associations between the FCRs of apo(a) and low-density lipoprotein-apoB-100. Subjects with smaller apo(a) isoform sizes (≤ 22 kringle IV repeats) had significantly higher apo(a) PR ($P<0.05$) and lower apo(a) FCR ($P<0.01$) than those with larger sizes. Plasma apo(a) concentration was significantly associated with apo(a) PR ($r=0.930$, $P<0.001$), but not with FCR ($r=-0.012$, $P>0.05$) in subjects with smaller apo(a) isoform size. In contrast, both apo(a) PR and FCR were significantly associated with plasma apo(a) concentrations ($r=0.744$ and -0.389 , respectively, $P<0.05$) in subjects with larger isoforms. In multiple regression analysis, apo(a) PR and apo(a) isoform size were significant predictors of plasma apo(a) concentration independent of low-density lipoprotein-apoB-100 FCR and background therapy with atorvastatin and evolocumab. **Conclusions** In normolipidemic men, the plasma Lp(a) concentration is predominantly determined by the rate of production of Lp(a) particles, irrespective of apo(a) isoform size and background therapy with a statin and a proprotein convertase subtilisin-kexin type 9 inhibitor. Our findings underscore the importance of therapeutic targeting of the hepatic synthesis and secretion of Lp(a) particles. Lp(a) particle catabolism may only play a modest role in determining Lp(a) concentration in subjects with larger apo(a) isoform size. Clinical Trial Registration URL : <http://www.clinicaltrials.gov> . Unique identifier: NCT 02189837.

[22] Khan SU, Rahman H, Okunrintemi V et al. **Association of Lowering Low-Density Lipoprotein Cholesterol With Contemporary Lipid-Lowering Therapies and Risk of Diabetes Mellitus: A Systematic Review and Meta-Analysis.** *Journal of the American Heart Association* 2019; 8:e011581.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30898075>

ABSTRACT

Background The relationship between lowering LDL (low-density lipoprotein) cholesterol with contemporary lipid-lowering therapies and incident diabetes mellitus (DM) remains uncertain. **Methods and Results** Thirty-three randomized controlled trials (21 of statins, 12 of PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors, and 0 of ezetimibe) were selected using Medline, Embase, and the Cochrane Central Register of Controlled Trials (inception through November 15, 2018). A total of 163 688 nondiabetic patients were randomly assigned to more intensive (83 123 patients) or less intensive (80 565 patients) lipid-lowering therapy. More intensive lipid-lowering therapy was defined as the more potent pharmacological strategy (PCSK 9 inhibitors, higher intensity statins, or statins), whereas less intensive therapy corresponded to active control group or placebo/usual care of the trial. Metaregression and meta-analyses were conducted using a random-effects model. No significant association was noted between 1-mmol/L reduction in LDL cholesterol and incident DM for more intensive lipid-lowering therapy (risk ratio: 0.95; 95% CI, 0.87-1.04; $P=0.30$; $I^2=14\%$) or for statins or PCSK 9 inhibitors. More intensive lipid-lowering therapy was associated with a higher risk of incident DM compared with less intensive therapy (risk ratio: 1.07; 95% CI, 1.03-1.11; $P<0.001$; $I^2=0\%$). These results were driven by higher risk of incident DM with statins (risk ratio: 1.10; 95% CI, 1.05-1.15; $P<0.001$; $I^2=0\%$), whereas PCSK 9 inhibitors were not associated with incident DM (risk ratio: 1.00; 95% CI, 0.93-1.07; $P=0.96$; $I^2=0\%$; $P=0.02$ for interaction). **Conclusions** Among intensive lipid-lowering

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therapies, there was no independent association between reduction in LDL cholesterol and incident DM . The risk of incident DM was higher with statins, whereas PCSK 9 inhibitors had no association with risk of incident DM .

[23] Stewart RAH, Held C, Krug-Gourley S et al. **Cardiovascular and Lifestyle Risk Factors and Cognitive Function in Patients With Stable Coronary Heart Disease.** Journal of the American Heart Association 2019; 8:e010641.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30897999>

ABSTRACT

Background Vascular risk factors have been associated with differences in cognitive performance in epidemiological studies, but evidence in patients with coronary heart disease is more limited. Methods and Results The Montreal Cognitive Assessment score obtained 3.2+/-0.37 years after randomization to darapladib, a reversible inhibitor of lipoprotein phospholipase A2 or placebo was evaluated for 10 634 patients with coronary heart disease from 38 countries in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial. The Montreal Cognitive Assessment scores for darapladib and placebo groups were similar (mean+/- SD , 25.3+/-3.84 versus 25.4+/-3.73, respectively; P=0.27) and the adjusted odds ratio (OR) for mild cognitive impairment (Montreal Cognitive Assessment score <26) was 1.00 (95% CI , 0.93-1.09). Mild cognitive impairment was more likely with increasing age (OR , 1.33 [1.27-1.41], +5 years after 65). For other baseline clinical characteristics, the strongest independent predictors of cognitive impairment were education (<=8 years versus college/university, OR , 2.95 [2.60-3.35]; >8 years/trade school versus college/university, OR , 1.38 [1.25-1.52] and geographic grouping). Cardiovascular risk factors independently associated with cognitive impairment were history of stroke (OR , 1.43 [1.20-1.71]); <2.5 hours of moderate or vigorous intensity exercise/week (OR , 1.19 [1.04-1.37]); high-density lipoprotein cholesterol <1.16 mmol/L (OR , 1.19 [1.04-1.37]); diabetes mellitus requiring treatment (OR , yes versus no: 1.15 [1.05-1.26]); and history of hypertension (OR , 1.12 [1.02-1.23]). Conclusions In patients with stable coronary heart disease, cognitive performance was associated with modifiable cardiovascular risk factors, educational level, and global region, but was not influenced by darapladib. Clinical Trial Registration URL : <http://www.clinicaltrials.gov> . Unique identifier: NCT 00799903.

[24] Lu W, He X, Su L, Miao J. **Long Noncoding RNA-CERNA1 Stabilized Atherosclerotic Plaques in apolipoprotein E(-/-) Mice.** Journal of cardiovascular translational research 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30888631>

ABSTRACT

Atherosclerosis is predicted to be the primary cause of death in the world by 2020. Changes in atherosclerotic plaque composition will lead to acute coronary syndromes. Although the studies on the molecular mechanisms of long noncoding RNA (lncRNA) are in-depth in molecular and cell levels, the in vivo research which studied the knowledge about lncRNAs in the regulation of plaque composition is still sparse. In this study, in order to investigate how a new lncRNA, CERNA1, regulates the composition of atherosclerotic plaques, we overexpressed CERNA1 in apolipoprotein E(-/-) (Apo E(-/-)) mice and analyzed the role of CERNA1 in atherosclerotic plaque stabilization. The results showed that CERNA1 inhibited the apoptosis of VSMCs and anti-inflammatory macrophages through increasing API5 level and

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further stabilized the atherosclerotic plaques. This discovery provided a novel therapeutic target for atherosclerosis.

[25] *Marquina C, Mousa A, Belski R et al. Increased Inflammation and Cardiometabolic Risk in Individuals with Low AMY1 Copy Numbers. Journal of clinical medicine* 2019; 8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30893908>

ABSTRACT

Lower copy number variations (CNVs) in the salivary amylase gene (AMY1) have been associated with obesity and insulin resistance; however, the relationship between AMY1 and cardiometabolic risk has not been fully elucidated. Using gold-standard measures, we aimed to examine whether AMY1 CNVs are associated with cardiometabolic risk factors in an overweight or obese, otherwise healthy population. Fifty-seven adults (58% male) aged 31.17 +/- 8.44 years with a body mass index (BMI) ≥ 25 kg/m² were included in the study. We measured AMY1 CNVs (qPCR); anthropometry (BMI; body composition by dual-energy X-ray absorptiometry); cardiovascular parameters (blood pressure, serum lipids by ELISA); insulin sensitivity (hyperinsulinaemic(-)euglycaemic clamp), insulin secretion (intravenous glucose tolerance test), and serum inflammation markers (multiplex assays). Based on previous studies and median values, participants were divided into low (≤ 4) and high (> 4) AMY1 CNV groups. Low AMY1 carriers (n = 29) had a higher fat mass (40.76 +/- 12.11 versus 33.33 +/- 8.50 kg, p = 0.009) and LDL-cholesterol (3.27 +/- 0.80 versus 2.87 +/- 0.69 mmol/L, p = 0.038), and higher serum levels of interleukin [IL]-6, IL-1beta, tumour necrosis factor-alpha and monocyte chemoattractant protein-1 (MCP-1) (all p < 0.05) compared with high AMY1 carriers (n = 28), but there were no differences in glycaemic measures, including insulin sensitivity or secretion (all p > 0.1). Except for MCP-1, the results remained significant in multivariable models adjusted for age, sex, and fat mass (all p < 0.05). Our findings suggest that low AMY1 CNVs are associated with increased cardiovascular disease risk and inflammation, but not glucose metabolism, in overweight or obese adults.

[26] *Chikowore T, Sahibdeen V, Hendry LM et al. C679X loss-of-function PCSK9 variant is associated with lower fasting glucose in black South African adolescents: Birth to Twenty Plus Cohort. Journal of clinical & translational endocrinology* 2019; 16:100186.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30899674>

ABSTRACT

Aim: To evaluate the association between loss-of-function (LOF) PCSK9 variants (A433T/rs28362263 and C679X/rs28362286) and biomarkers of cardiometabolic risk, specifically fasting glucose and low density lipoprotein cholesterol (LDL-C) concentrations. Methods: Our study comprised 757 male and female black South African adolescents (mean age 18.0 +/- 0.5 years) who are part of the Birth to Twenty Plus Cohort and had been genotyped for the two above-mentioned variants. Anthropometric measures were completed and fasting plasma glucose and lipid analysis were performed using standard procedures. Results: The median and interquartile range of fasting glucose and LDL-C for the whole group were 4.60 (4.36-4.88) mmol/L and 1.67 (1.25-2.14) mmol/L, respectively. After adjusting for sex, association between the biomarkers and A443T was not significant. However, C679X carriers displayed 0.30 [95% CI (-0.57, -0.02); p=0.035] mmol/L lower fasting glucose and 0.50 [95% CI (-0.74, -0.26); p<0.001] mmol/L lower LDL-C concentrations compared to non-carriers. Conclusions: Our results indicate for the first that the C679X variants associated with low fasting glucose levels during adolescents as had been known for

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LDL-C. In view that a similar finding was reported in older black South African adults, therefore, the correlation of lower fasting glucose and LDL-C levels with C679X is observed from an early age to adulthood.

[27] Li Y, Xu K, Xu K *et al.* **Roles of Identified Long Noncoding RNA in Diabetic Nephropathy.** Journal of diabetes research 2019; 2019:5383010.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30891461>

ABSTRACT

Diabetes mellitus is the leading chronic disease in the world, and diabetic nephropathy (DN) as one of its complications could increase the mortality. The development of DN is associated to abnormal hemodynamic factors like cytokine networks and the intervention of metabolic risk factors like blood pressure, blood glucose, and blood lipid. However, the pathogenesis of DN is still poorly understood. Although glucose-lowering drugs and insulins have significant effects on blood glucose, the fluctuation of blood glucose or other risk factors could continuously damage the kidney. Recent studies reported that the progression of DN is closely related to the expression of long noncoding RNA (lncRNA), which is important for the early diagnosis and targeted intervention of DN. In this review, we briefly summarize the published studies on the functions and potential mechanism of reported lncRNA in the regulation of DN.

[28] Ala S, Alvandipour M, Saeedi M *et al.* **Evaluation of Cholestyramine 15% Ointment in Relieving Pruritus and Burning After Ileostomy: A Rrandomized, Double-Blind Placebo-Controlled Clinical Trial.** Journal of investigative surgery : the official journal of the Academy of Surgical Research 2019:1-8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30892108>

ABSTRACT

Purpose/Aims: Skin irritation is a common ileostomy problem that causes burning and pruritus among patients due to the leakage of intestinal discharge around the stoma. This clinical trial was performed to evaluate the efficacy of topical cholestyramine (15%) on the reduction of the levels of burning and pruritus after an ileostomy. MATERIAL AND METHODS: The patients were randomly divided into two groups of treatment and control (n = 15). The intervention group was subjected to one fingertip of cholestyramine, whereas the other group received the placebo ointment (approximately 0.5 g) on the skin immediately after the surgery and twice a day for 2 months. The primary outcome measure was the severity of burning and pruritus measured by a visual analog scale at different times after an ileostomy. RESULTS: Out of 34 patients, four cases were excluded due to the inappropriate completion of the questionnaire (n = 2) and unwillingness to attend the follow-up visits (n = 2). Therefore, 30 patients were included in the study. The levels of burning among patients in the cholestyramine were lower in weeks 3, 4, and 8 compared to the placebo group. Moreover, lower levels of pruritus were observed among patients in the treatment group in weeks 4 and 8 after an ileostomy. No side effects were reported among the patients. CONCLUSIONS: Topical cholestyramine was found to be effective in the management of burning and pruritus resulting from an ileostomy among the population under study.

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[29] Judge C, Rutledge S, Costello M et al. **Lipid Lowering Therapy, Low-Density Lipoprotein Level and Risk of Intracerebral Hemorrhage - A Meta-Analysis.** Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30878368>

ABSTRACT

BACKGROUND: The association of lipid lowering therapy and intracerebral hemorrhage risk is controversial. METHODS: We performed a cumulative meta-analysis of lipid lowering trials that reported intracerebral hemorrhage. Statin, fibrates, ezetimibe, PCSK9, and CETP trials were included. We explored whether the association of lipid lowering therapy and risk of intracerebral hemorrhage may vary by baseline low-density lipoprotein (LDL) level, mean change in LDL or baseline cardiovascular risk of population. RESULTS: Among 39 trials (287,651 participants), lipid lowering therapy was not associated with a statistically significant increased risk of intracerebral hemorrhage (ICH) in primary and secondary prevention trials combined (odds ratio [OR], 1.12; 95% confidence interval [CI], .98-1.28). Lipid lowering was associated with an increased risk of ICH in secondary prevention trials (OR, 1.18; 95% CI, 1.00-1.38), but not in primary prevention trials (OR, 1.01; 95% CI, .78-1.30), but the test for interaction was not significant (P for interaction=.31). Meta-regression of baseline LDL or difference in LDL reduction between active and control did not explain significant heterogeneity between studies for ICH risk. Of 1000 individuals treated for 1 year for secondary prevention, we estimated 9.17 (95% CI, 5.78-12.66) fewer ischemic strokes and .48 (95% CI, .06-1.02) more ICH, and a net reduction of 8.69 in all stroke per 1000 person-years. CONCLUSIONS: The benefits of lipid lowering therapy in prevention of ischemic stroke greatly exceed the risk of ICH. Concern about ICH should not discourage stroke clinicians from prescribing lipid lowering therapy for secondary prevention of ischemic stroke.

[30] Melin EO, Thulesius HO, Hillman M et al. **Lower HDL-cholesterol, a known marker of cardiovascular risk, was associated with depression in type 1 diabetes: a cross sectional study.** Lipids in health and disease 2019; 18:65.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30885233>

ABSTRACT

BACKGROUND: Depression, metabolic disturbances and inflammation have been linked to cardiovascular disease and mortality. Low levels of high-density lipoprotein cholesterol (HDL-cholesterol), a known marker of cardiovascular risk, have been observed in patients with major depression in psychiatric populations. Our main aim was to explore associations between depression, antidepressants, and metabolic and inflammatory variables in patients with type 1 diabetes (T1D). A secondary aim was to explore variables associated with HDL-cholesterol. METHODS: Cross-sectional design. T1D patients (n = 292, men 55%, age 18-59 years, diabetes duration \geq 1 year) were consecutively recruited from one specialist diabetes clinic. Depression was defined as \geq 8 points for Hospital Anxiety and Depression Scale-Depression sub scale. Blood samples, anthropometrics, blood pressure, and data regarding medication and life style were collected from electronic health records. Non-parametric tests, multiple logistic and linear regression analyses were performed. RESULTS: The depression prevalence was 10 and 8% used antidepressants. Median (q1, q3) HDL-cholesterol (mmol/l) was for the depressed 1.3 (1.2, 1.5) and for the non-depressed 1.6 (1.3, 1.8), p = 0.001. HDL-cholesterol levels (per mmol/l) were negatively associated with depression (Adjusted odds ratio (AOR) 0.2, p = 0.007), and the use of antidepressants was positively associated with depression (AOR 8.1, p < 0.001). No other metabolic or inflammatory variables, or life style factors, were associated with depression

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when adjusted for antidepressants. Abdominal obesity was associated with antidepressants in women (AOR 4.6, $p = 0.029$). Decreasing HDL-cholesterol levels were associated with increasing triglyceride levels ($p < 0.001$), increasing high-sensitive C-reactive protein (hs-CRP) levels ($p = 0.021$), younger age ($p < 0.001$), male sex ($p < 0.001$), and depression ($p = 0.045$). CONCLUSIONS: Lower HDL-cholesterol levels, known predictors of cardiovascular disease, were associated with depression in patients with T1D. The use of antidepressants was associated with abdominal obesity in women. Depression, low-grade inflammation measured as hs-CRP, higher triglycerides, male sex, and lower age were independently associated with lower HDL-cholesterol levels.

[31] *Pasina L, Brignolo Ottolini B, Cortesi L et al. Need for De-Prescribing in Hospital Elderly Patients Discharged with Limited Life Expectancy: The REPOSI Study. Medical principles and practice : international journal of the Kuwait University, Health Science Centre 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30889568>

ABSTRACT

OBJECTIVE: Older people approaching the end of life are at high risk for adverse drug reactions. Approaching end of life should change the therapeutic aims, triggering a reduction in the number of drugs. The main aim of this study was to describe the preventive and symptomatic drug treatments prescribed to patients discharged from internal medicine and geriatric wards, with limited life expectancy. The secondary aim was to describe the potentially severe DDIs. MATERIALS AND METHODS: We analyzed Registry of Polytherapies Societa Italiana di Medicina Interna (REPOSI), a network of internal medicine and geriatric wards, to describe the drug therapy of patients discharged with limited life expectancy. RESULTS: The study sample comprised 55 patients discharged with limited life expectancy. Patients with at least one preventive medication that could be considered for de-prescription at end-of-life were significantly fewer from admission to discharge (30; 54.5% and 21; 38.2%, $p = 0.02$). ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, lipid-lowering drugs and clonidine were the most frequent potentially avoidable medications prescribed at discharge, followed by xanthine oxidase inhibitors and drugs to prevent fractures. Thirty-seven (67.3%) patients were also exposed to at least one potentially severe drug-drug interaction at discharge. CONCLUSION: Hospital discharge is associated with small reductions in the use of commonly prescribed preventive medications in patients discharged with limited life expectancy. Cardiovascular drugs are the most frequent potentially avoidable preventive medications. A consensus framework, or shared criteria for potentially inappropriate medication in elderly patients with limited life expectancy could be useful to further improve drug prescription.

[32] *Yan J, Qiao L, Tian J et al. Effect of statins on Parkinson's disease: A systematic review and meta-analysis. Medicine (Baltimore) 2019; 98:e14852.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30896628>

ABSTRACT

BACKGROUND: Statins have key lipid-lowering, anti-inflammatory, and anti-oxidative effects. However, it remains unclear whether statins are beneficial to patients with Parkinson's disease (PD). This study aimed to evaluate the relationship between statins and PD through a systematic review. METHODS: This study adhered to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Potentially relevant case-control or cohort studies published before March 2018 were

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identified by searching the MEDLINE (PubMed), EMBASE (OVID), CENTRAL (Cochrane Library), CNKI, WANGANG, VIP, CBM, CMCC, Clinicaltrials.gov, ProQuest, Opengray, and ISI Proceedings databases and conducting a manual search. Summarized relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a fixed effect model. Sensitivity and subgroup analyses were also performed. RESULTS: The meta-analysis included 17 studies (3,845,303 patients; 8 case-control and 9 cohort studies), including 5 articles not cited by other studies. We searched the Chinese database, but unfortunately, no Chinese literature can be included in the study. Briefly, statins could decrease the risk of PD, with a summary OR of 0.92 (95% CI: 0.86-0.99). A sensitivity analysis demonstrated the robustness of the results. Subgroup analyses revealed heterogeneity across the studies in terms of subject race, study type, reporting style, quality, statins type, and time for taking statins. CONCLUSION: Our study provides evidence that statins, especially atorvastatin, can reduce the risk of PD. Different time of statins using has different effects on PD. However, additional randomized controlled trials and observational studies are needed to confirm this conclusion. REGISTRATION ID: PROSPERO CRD: 42018095580.

[33] *Malinowski B, Zalewska K, Wesierska A et al. Intermittent Fasting in Cardiovascular Disorders-An Overview. Nutrients* 2019; 11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30897855>

ABSTRACT

Intermittent fasting is a form of time restricted eating (typically 16 h fasting and 8 h eating), which has gained popularity in recent years and shows promise as a possible new paradigm in the approach to weight loss and the reduction of inflammation, and has many potential long term health benefits. In this review, the authors will incorporate many aspects of fasting, mainly focusing on its effects on the cardiovascular system, involving atherosclerosis progression, benefits for diabetes mellitus type 2, lowering of blood pressure, and exploring other cardiovascular risk factors (such as lipid profile and inflammation).

[34] *Droz-Perroteau C, Blin P, Dureau-Pournin C et al. Six-year survival study after myocardial infarction: The EOLE prospective cohort study. Long-term survival after MI. Therapie* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30878144>

ABSTRACT

BACKGROUND: Studies of survival after myocardial infarction (MI) are often based on intention to treat analyses of controlled trials. OBJECTIVES: Describe long-term survival after MI in France. METHODS: Six-year cohort study of patients recruited within 3 months after MI. Primary outcome was all-cause death. Vital status was verified in the national death registry. Analysis used Cox models with time-dependent variables and propensity scores. RESULTS: Five thousand five hundred and twenty-seven (5527) subjects were included, 62.1±13 years old, 77.6% male, 9.6% smokers, 16.7% diabetic, 13.3% with previous MI. Up to 99% of patients were initially prescribed secondary prevention drugs (aspirin and/or other antiplatelet agents, beta-blockers, statins or other lipid-lowering agents, angiotensin converting enzyme inhibitors or angiotensin receptor blockers); 73% had all four classes. Overall 6-year mortality was 13.1% [95% confidence interval 12.3 to 14.0%], 2.34 per hundred patient-years (% PY); 49% returned all or all but one of the possible questionnaires (compliant [C]), 50.8% did not (non-compliant [NC]). The main predictors for death were non-compliance with study protocol (death rates NC 2.98% PY, C 1.69%PY, hazard ratio (HR) 3.13 [2.63-3.57]); increasing age at inclusion (HR up to 15.7 [10.7-23.2] for age ≥80);

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diabetes (1.39 [1.17-1.65]); smoking at inclusion (1.76 [1.27-2.44]), previous MI (1.46 [1.22-1.75]). Beta-blockers (0.79 [0.64-0.96]), statins (0.68 [0.51-0.90]), and enrolment in physical rehabilitation programs (0.74 [0.62-0.89]) were associated with a lower death rate. CONCLUSION: Association of mortality with non-compliance to study protocol probably indicates general non-compliance with prevention. Analyses of treatment effects were hindered by paucity of events and of unexposed patients.

[35] *van Dijk AC, Donkel SJ, Zadi T et al. Association between fibrinogen and fibrinogen gamma' and atherosclerotic plaque morphology and composition in symptomatic carotid artery stenosis: Plaque-At-RISK study. Thrombosis research* 2019; 177:130-135.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30897531>

ABSTRACT

INTRODUCTION: Von Willebrand Factor (VWF), ADAMTS13, fibrinogen and fibrinogen gamma' are associated with an increased risk of ischemic stroke. Carotid atherosclerosis is an important risk factor for ischemic stroke. Characteristics of the vulnerable plaque; intraplaque hemorrhage (IPH), plaque ulceration and lipid-rich necrotic core (LRNC) can be visualized with imaging techniques. Since atherosclerosis might attribute to the association between coagulation factors and ischemic stroke risk, the aim of this study is to investigate the association between coagulation factors and atherosclerotic plaque characteristics in more detail. MATERIALS AND METHODS: In 182 patients of the Plaque-At-RISK study (prospective multicenter cohort study) with a recent transient ischemic attack (TIA) or ischemic stroke and a symptomatic mild-to-moderate carotid artery stenosis, we measured VWF antigen (VWF:Ag), ADAMTS13 activity, fibrinogen (Clauss), and fibrinogen gamma'. Presence of plaque ulceration, IPH volume and LRNC volume were determined by Multidetector-Row Computed Tomography (MDCTA, n=160) and Magnetic Resonance Imaging (MRI, n=172). Linear regression analysis was used to assess the association between imaging biomarkers and coagulation factors. RESULTS: VWF:Ag or ADAMTS13 levels were not significantly associated with plaque ulceration, IPH and LRNC. We found an inverse association between fibrinogen and fibrinogen gamma' and IPH volume (B=-23.40mm(3)/g/L, p=0.01 and B=-161.73mm(3)/g/L, p=0.01) and between fibrinogen and fibrinogen gamma' and LRNC volume (B=-38.89mm(3)/g/L, p<0.01 and B=-227.06mm(3)/g/L, p=0.01). Additional adjustments for C-reactive protein (CRP) did not change the results. CONCLUSIONS: Fibrinogen and fibrinogen gamma' are inversely associated with IPH volume and LRNC volume, independent of inflammation. CLINICAL TRIAL REGISTRATION: clinicaltrials.gov/NCT01208025.

[36] *Milanesi LH, Rossato DR, Dias VT et al. Mediterranean X Western based diets: opposite influences on opioid reinstatement. Toxicology letters* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30898663>

ABSTRACT

Opioids are addictive drugs, whose misuse evoke withdrawal and relapse. Mediterranean-based diet (MBD) is rich in n-3 polyunsaturated fatty acids (PUFA), while Western based diets (WBDs) contain saturated fatty acids including interesterified fat (IF) and palm oil (PO), influencing neural functions. We compared MBD and WBDs on morphine-induced addiction parameters. Rats fed with MBD (chow plus 20% soybean- and fish-oil- n-6/n-3 PUFA 1:1) or WBD (WBD- PO or WBD-IF: chow plus 20% of palm oil or interesterified fat, respectively; high n-6/n-3 PUFA ratio) were exposed to morphine in conditioned place preference (CPP) paradigm. Anxiety-like behavior, locomotion and thermal sensitivity were

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evaluated during withdrawal. After morphine-CPP extinction, animals were challenged to morphine-reinstatement to induce relapse. All groups showed morphine-CPP, WBDs favored anxiety-like behaviors per se, locomotor sensitization and thermal hypersensitivity during withdrawal, resulting in increased morphine-reinstatement in comparison to MBD, which did not show relapse. WBDs increased glucocorticoid receptor immunoreactivity in the pre-frontal cortex, increasing corticosterone (CORT) and adrenocorticotrophic hormone (ACTH) per se and after morphine-reinstatement. In the nucleus accumbens, WBDs increased dopamine transporter (DAT) and dopamine receptor-2 (D2R) immunoreactivity and decreased dopamine receptor-1 (D1R). These findings indicate that WBDs facilitate morphine-reinstatement, unlike MBD, preserving the DA system mesolimbic neuroplasticity.

[37] *Qu G, Wu Q, Zhao B et al. The promotion effect of novel magnetic nanoparticles on atherosclerotic plaque vulnerability in apolipoprotein E(-/-) mice. Toxicology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30898670>

ABSTRACT

Although manufactured magnetic nanoparticles (NPs) are currently used in many fields, NPs have potential toxicity on cardiovascular system especially atherosclerosis. In our previous study, we prepared novel Fe₃O₄ nanoparticles surface-coated with aminoguanidine (Fe₃O₄-AG NPs) which could remove acid dyes from aqueous solution efficiently. To understand its biocompatibility to atherosclerotic plaque vulnerability, we investigated the effects of the nanoparticles on human umbilical vein endothelial cells (HUVECs) in vitro and plaque stability in vivo. Fe₃O₄-AG NPs were taken up by HUVECs and induced HUVEC apoptosis. Fe₃O₄-AG NP injection remarkably promoted plaque vulnerability at low-dose (0.5 mg/kg) but not high-dose (5.0 mg/kg) in apolipoprotein E(-/-) (ApoE(-/-)) mice. Further study indicated that Fe₃O₄-AG NP-induced atherosclerotic plaque vulnerability was tightly linked to bioactivity of nitric oxide (NO). A significant decrease in NO production was induced which coincided with the inhibition of endothelial nitric oxide synthase (eNOS) activity in serum and endothelium of plaque in ApoE(-/-) mice injected with low-dose Fe₃O₄-AG NPs in vivo and HUVECs treated with low-dose Fe₃O₄-AG NPs in vitro. Thus, the low concentration of Fe₃O₄-AG NPs presented toxicity to atherosclerosis. Our results indicated that the use of Fe₃O₄-AG NPs to improve aqueous solution pollution should be cautious due to the potential toxicity.

[38] *Melloni C, Roe MT. Androgen deprivation therapy and cardiovascular disease. Urologic oncology 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30879969>

ABSTRACT

Prostate cancer (PCa) is the most common cancer among men. Advances in early detection and successful treatments have improved cancer-specific survival. With prolonged survival, PCa patients now suffer from the effects of aging and are at increasing risk for the development of cardiovascular (CV) risk factors and CV disease. Androgen deprivation therapy (ADT) is the mainstay treatment of advanced PCa. There is conflicting evidence about whether or not ADT is associated with increased CV morbidity and mortality. Metabolic abnormalities such as increasing body weight, reduced insulin sensitivity, dyslipidemia, and activation of T cells to the Th1 phenotype, resulting in atherosclerotic plaque destabilization, have been proposed as possible mechanisms by which ADT may increase the risk of CV events. Type of ADT and preexisting CV history also seem to play a major role in the risk of subsequent

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CV events. Ongoing prospective clinical trials will help define whether there is any difference between gonadotropin-releasing hormone agonists and antagonists in terms of CV morbidity and mortality.