

Literature update week 41 (2018)

[1] *Ballantyne CM, Bhatt DL, Cannon CP et al. Raising the Bar by Lowering the Target: Integrating PCSK9 Inhibitors Into Hypercholesterolemia Management. The American journal of cardiology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30301542>

ABSTRACT

This CME-accredited CME Snapshot seven-part series is intended for interventional cardiologists, other cardiologists, lipidologists, endocrinologists, and other diabetologist physicians involved in the ongoing management of patients with persistent hypercholesterolemia. During these activities, expert faculty will participate in a series of interactive discussions on the latest evidence and their clinical experience managing patients with persistently elevated low-density lipoprotein cholesterol levels using nonstatin lipid-lowering medications, including inhibitors of the enzyme protein convertase subtilisin or kexin type 9 (PCSK9). (Online access: <https://lipidsnapshotcme.elsevierresource.com/>).

[2] *Sedki M, Khalil IA, El-Sherbiny IM. Hybrid nanocarrier system for guiding and augmenting simvastatin cytotoxic activity against prostate cancer. Artificial cells, nanomedicine, and biotechnology 2018:1-10.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30295086>

ABSTRACT

Prostate cancer is the most common non-skin cancer among men. Though statins are mainly used as antihyperlipidemic drugs, many studies have reported their proapoptotic and antimetastatic activities on prostate cancer. However, the poor solubility and insufficient delivery of statins in tumor site limit their anticancer activity. The present study introduces an efficient hybrid drug delivery system for the treatment of prostate cancer. The system involves the chemical conjugation of Simvastatin (SMV), a statin compound, to acid-terminated poly(D, L-lactic-co-glycolic acid), PLGA chains followed by its conversion into nanoparticles (NPs), with in situ physical incorporation of more SMV and superparamagnetic iron oxide nanoparticles (SPIONS) into the PLGA NPs. The PLGA-based hybrid nanocarrier system has been designed in such a way to evade the low bioavailability of SMV, confer sustained release of both encapsulated and chemically conjugated SMV, as well as enhancing the anti-cancer effect of the formula via the magnetic targeting with the aid of the encapsulated SPIONS. Magnetism, morphological and physicochemical characterizations, as well as in-vitro release studies were performed. Besides, cytotoxicity on human prostate cancer cell line (PC-3) was evaluated using MTT assay, cell cycle arrest analysis, annexin V/propidium iodide apoptosis assay and ELISA immunoassay for apoptotic enzyme. Optimum PLGA-based hybrid nanocarrier significantly improved the SMV anticancer activity against human prostate cancer cell line through both apoptosis mechanism and retardation of G2-M phase of cell cycle. Also, the up-regulation of the Caspase 3 was aligned with cytotoxicity study's findings.

[3] *Farnier M, Hovingh GK, Langslet G et al. Long-term safety and efficacy of alirocumab in patients with heterozygous familial hypercholesterolemia: An open-label extension of the ODYSSEY program. Atherosclerosis 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293878>

ABSTRACT

Literature update week 41 (2018)

BACKGROUND AND AIMS: ODYSSEY OLE (open-label extension; NCT01954394) included patients diagnosed with heterozygous familial hypercholesterolemia (HeFH), receiving maximally tolerated statins, who had completed one of four Phase 3 double-blind parent studies (all 18 months' duration), with the aim to assess longer-term safety and efficacy of alirocumab. **METHODS:** Patients received starting dose alirocumab 75mg every 2 weeks (Q2W; patients from FH I, FH II, and LONG TERM) or alirocumab 150mg Q2W (patients from HIGH FH). Low-density lipoprotein cholesterol (LDL-C) levels were blinded to the patient and physician until Week 8; from Week 8, LDL-C levels were communicated to physicians. From Week 12, dose adjustment from 75 to 150mg Q2W, or vice versa, was possible per physician's clinical judgment according to patient's LDL-C levels. **RESULTS:** Patients who had received alirocumab (n=655) compared with placebo (n=330) in the parent studies exhibited similar rates of treatment-emergent adverse events (TEAEs; 87.3% vs. 83.9%) during OLE (2.5 years median alirocumab exposure). Overall, 33 patients (3.4%) experienced TEAEs leading to permanent treatment discontinuation. At Week 8, alirocumab reduced mean LDL-C by 44.2% (reduction from 151.9mg/dL at parent study baseline to 84.9mg/dL); reduction in LDL-C was consistent to Week 96 of OLE. Reductions in lipid parameters were similar regardless of treatment allocation in the parent study. **CONCLUSIONS:** In patients with HeFH, no unexpected long-term safety concerns were observed with alirocumab compared with previously published data; durability of LDL-C-lowering over 3 years (including 1.5 years of parent trials) was demonstrated.

[4] *Ibarretxe D, Rodriguez-Borjabad C, Feliu A et al. Detecting familial hypercholesterolemia earlier in life by actively searching for affected children: The DECOPIN project. Atherosclerosis 2018; 278:210-216.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30312929>

ABSTRACT

BACKGROUND AND AIMS: Familial hypercholesterolemia (FH) is underdiagnosed in children. We assessed a combination of two screening methods. The first method was to detect hypercholesterolaemic children and then study the parents (Ch-P pathway), and the second one was to study the offspring of FH-affected parents (P-Ch pathway). **METHODS:** In the Ch-P path, primary care paediatricians were asked to include lipid profiling or, at least, total cholesterol (TC) and then lipid profiling if TC was higher than 5.2mmol/L in any clinically indicated blood test. Children with LDL-C \geq 3.5mmol/L, plus either a family history of early cardiovascular disease or one parent with severe hypercholesterolemia, were referred to the lipid unit where the parents, rather than their children, were studied. In parents with definite, clinical FH, a genetic study was performed. Focused genetic testing was performed on all offspring of genetically positive parents. The P-Ch path consisted of the active study of children from definite FH adults. **RESULTS:** Fifty-nine paediatricians covering a total population of 63,616 children agreed to participate in the project. Of the 216 children (122 Ch-P and 94P-Ch) who were ultimately referred to the lipid unit, 87 children with FH (84% genetically positive) were identified. Additionally, 41 parents (from 40 families) were newly diagnosed with FH (63% genetically positive). Forty-nine different mutations were detected: 46 in the LDLR, 2 in the PCSK9 and 1 in APOB gene. **CONCLUSIONS:** The implementation of active strategies to detect FH in children, in close collaboration with primary care paediatricians, provides a high-performance method for early FH detection.

Literature update week 41 (2018)

[5] Presa N, Clugston RD, Lingrell S et al. **Vitamin E alleviates non-alcoholic fatty liver disease in phosphatidylethanolamine N-methyltransferase deficient mice.** Biochimica et biophysica acta. Molecular basis of disease 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30300671>

ABSTRACT

Phosphatidylethanolamine N-methyltransferase (PEMT) converts phosphatidylethanolamine (PE) to phosphatidylcholine (PC), mainly in the liver. Pemt(-/-) mice are protected from high-fat diet (HFD)-induced obesity and insulin resistance, but develop severe non-alcoholic fatty liver disease (NAFLD) when fed a HFD, mostly due to impaired VLDL secretion. Oxidative stress is thought to be an essential factor in the progression from simple steatosis to steatohepatitis. Vitamin E is an antioxidant that has been clinically used to improve NAFLD pathology. Our aim was to determine whether supplementation of the diet with vitamin E could attenuate HFD-induced hepatic steatosis and its progression to NASH in Pemt(-/-) mice. Treatment with vitamin E (0.5g/kg) for 3weeks improved VLDL-TG secretion and normalized cholesterol metabolism, but failed to reduce hepatic TG content. Moreover, vitamin E treatment was able to reduce hepatic oxidative stress, inflammation and fibrosis. We also observed abnormal ceramide metabolism in Pemt(-/-) mice fed a HFD, with elevation of ceramides and other sphingolipids and higher expression of mRNAs for acid ceramidase (Asah1) and ceramide kinase (Cerk). Interestingly, vitamin E supplementation restored Asah1 and Cerk mRNA and sphingolipid levels. Together this study shows that vitamin E treatment efficiently prevented the progression from simple steatosis to steatohepatitis in mice lacking PEMT.

[6] Feng S, Dai Z, Liu AB et al. **Intake of stigmasterol and beta-sitosterol alters lipid metabolism and alleviates NAFLD in mice fed a high-fat western-style diet.** Biochimica et biophysica acta. Molecular and cell biology of lipids 2018; 1863:1274-1284.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30305244>

ABSTRACT

OBJECTIVE: To investigate and compare the effects of two common dietary phytosterols, stigmasterol and beta-sitosterol, in altering lipid metabolism and attenuating nonalcoholic fatty liver disease (NAFLD). METHODS: Stigmasterol and beta-sitosterol were administered to mice at 0.4% in a high-fat western-style diet (HFWD) for 17weeks. RESULTS: Stigmasterol and beta-sitosterol significantly ameliorated HFWD-induced fatty liver and metabolic abnormalities, including elevated levels of hepatic total lipids, triacylglycerols, cholesterol and liver histopathology. Both phytosterols decreased the levels of intestinal bile acids, accompanied by markedly increased fecal lipid levels. In addition, they altered the expression of genes involved in lipid metabolism. beta-Sitosterol was less effective in affecting most of these parameters. Lipidomic analysis of liver and serum samples showed that stigmasterol prevented the HFWD-induced elevation of some di- and triacylglycerol species and lowering of some phospholipid species. Stigmasterol also decreased serum levels of ceramides. CONCLUSION: Stigmasterol and beta-sitosterol, at a dose corresponding to that suggested for humans by the FDA for lowering cholesterol levels, are shown to alleviate HFWD-induced NAFLD. Stigmasterol was more effective than beta-sitosterol, possibly because of its suppression of hepatic lipogenic gene expression and modulation of circulating ceramide levels.

Literature update week 41 (2018)

[7] Carita P, Guaricci AI, Muscogiuri G et al. **Prognostic Value and Therapeutic Perspectives of Coronary CT Angiography: A Literature Review.** BioMed research international 2018; 2018:6528238.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30306089>

ABSTRACT

Coronary stenosis severity is both a powerful and a still debated predictor of prognosis in coronary artery disease. Coronary computed tomographic angiography (CCTA) has emerged as a noninvasive technique that enables anatomic visualization of coronary artery disease (CAD). CCTA with newer applications, plaque characterization and physiologic/functional evaluation, allows a comprehensive diagnostic and prognostic assessment of otherwise low-intermediate subjects for primary prevention. CCTA measures the overall plaque burden, differentiates plaque subtypes, and identifies high-risk plaque with good reproducibility. Research in this field may also advance towards an era of personalized risk prediction and individualized medical therapy. It has been demonstrated that statins may delay plaque progression and change some plaque features. The potential effects on plaque modifications induced by other medical therapies have also been investigated. Although it is not currently possible to recommend routinely serial scans to monitor the therapeutic efficacy of medical interventions, the plaque modulation, as a part of risk modification, appears a feasible strategy. In this review we summarize the current evidence regarding vulnerable plaque and effects of lipid lowering therapy on morphological features of CAD. We also discuss the potential ability of CCTA to characterize coronary atherosclerosis, stratify prognosis of asymptomatic subjects, and guide medical therapy.

[8] Chen A, Sun Y, Cui J et al. **Associations of sclerostin with carotid artery atherosclerosis and all-cause mortality in Chinese patients undergoing maintenance hemodialysis.** BMC Nephrol 2018; 19:264.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30314461>

ABSTRACT

BACKGROUND: Previous clinical studies found inconsistent relationship between circulating sclerostin levels and treatment outcome in patients undergoing maintenance hemodialysis (MHD). Therefore, this study aimed to assess the associations of sclerostin with carotid artery atherosclerosis and all-cause mortality in Chinese patients undergoing MHD. **METHODS:** This retrospective study assessed 84 patients undergoing MHD at the Nephrology Department of Beijing Hospital from January to April 2012, with a median follow-up of 61.2 months (range: 11.5 to 63 months). Carotid artery intima-media thicknesses (CIMTs) and atherosclerotic plaques were measured by B-mode Doppler ultrasound at baseline. Blood samples were collected for measuring serum sclerostin and soluble klotho (s-klotho) levels. The associations of sclerostin levels with carotid artery atherosclerosis was evaluated by correlation methods. Predictive factors of mortality were assessed by multivariate COX regression. **RESULTS:** Baseline serum sclerostin averaged 162.01 pmol/L, with an interquartile range of 121.69 to 225.22 pmol/L, while CIMT values were 1.35 +/- 0.39 mm. Carotid artery atherosclerotic plaques were detected in 68 subjects (81%). Subjects with sclerostin levels above the median value had higher CIMT ($p = 0.038$) and higher prevalence of atherosclerotic plaque ($p = 0.025$). During

Literature update week 41 (2018)

follow-up, 27 patients died; Kaplan-Meier curves indicated that subjects with high sclerostin levels (above the median value at baseline) had shorter survival (log rank $p = 0.011$). In multivariate COX regression analysis, serum sclerostin (HR, 1.095; 95% confidence interval [CI] 1.022-1.174, $p = 0.010$) and albumin (HR, 0.742; 95%CI 0.612-0.900, $p = 0.002$) levels were independent predictors of all-cause mortality. CONCLUSIONS: Sclerostin is positively associated with CIMT. In addition, patients with low baseline serum sclerostin undergoing MHD show better survival.

[9] Zhao Q, Liu F, Wang YH et al. **LDL-C:HDL-C ratio and common carotid plaque in Xinjiang Uygur obese adults: a cross-sectional study.** *BMJ open* 2018; 8:e022757.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30297348>

ABSTRACT

OBJECTIVE: The aim of this study was to explore the relationship between low-density lipoprotein cholesterol:high-density lipoprotein cholesterol (LDL-C:HDL-C) ratio and common carotid atherosclerotic plaque (CCAP) among obese adults of Uygur community in Xinjiang, China. DESIGN: A hospital-based cross-sectional study. SETTING: First Affiliated Hospital of Xinjiang Medical University. PARTICIPANTS: A total of 1449 obese adults of Uygur population who were free of coronary artery disease were included in our study from 1 January 2014 to 31 December 2016. METHODOLOGY: Lipid profiles, other routine laboratory parameters and intima-media thickness of the common carotid artery were measured in all participants. Multivariate logistic regression analysis was used to examine the association between LDL-C:HDL-C ratio and CCAP. RESULTS: Four hundred and fifteen (28.64%) participants had CCAP. Participants with CCAP had significantly higher LDL-C:HDL-C ratio compared with those without CCAP (3.21 [2.50, 3.88] vs 2.33 [1.95, 2.97], $p < 0.001$). Multivariate logistic regression analysis showed high LDL-C:HDL-C ratio as independent predictor of CCAP after adjusting for conventional cardiovascular risk factors. The top LDL-C:HDL-C ratio quartile (≥ 3.25) had an OR of 9.355 (95% CI 6.181 to 14.157) compared with the bottom quartile (< 2.07) of LDL-C:HDL-C ratio ($p < 0.001$) after adjustment for age, body mass index, smoking, diabetes mellitus and serum level of total cholesterol. CONCLUSION: CCAP is highly prevalent in Uygur obese adults. A high LDL-C:HDL-C ratio is an independent predictor of CCAP. It may help identify obese individuals who are at high risk of CCAP and who may benefit from intensive LDL-lowering therapy.

[10] Abdollahimajd F, Rajabi F, Shahidi-Dadras M et al. **Pachyonychia congenita: A case report of a successful treatment with rosuvastatin in a patient with a KRT6A mutation.** *The British journal of dermatology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307612>

ABSTRACT

Pachyonychia congenita (PC) is a rare autosomal dominant disorder characterized by nail dystrophy and palmoplantar keratoderma with severe plantar pain affecting the quality of life. There is no effective treatment. Heterozygous mutations in the keratin 6A, 6B, 6C, 16 and 17 genes have been reported as a cause of PC. Herein we present a female patient with an amino acid substitution mutation in KRT6A (c.1381G>A, p.Glu461Lys in exon 7) and classic features of PC associated with oral leukokeratosis and follicular hyperkeratosis. We also demonstrate

Literature update week 41 (2018)

successful treatment of the patient with rosuvastatin. A 3.6 millimeter reduction in plantar callosity thickness was demonstrated by sonography. Our patient also experienced significant pain relief that allowed her to increase physical activity (CDLQI score dropped nine points following treatment). Collectively, rosuvastatin may offer a promising treatment for PC. This article is protected by copyright. All rights reserved.

[11] *Ambrozewicz E, Wojcik P, Wronski A et al. Pathophysiological Alterations of Redox Signaling and Endocannabinoid System in Granulocytes and Plasma of Psoriatic Patients. Cells 2018; 7.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30301214>

ABSTRACT

Inflammatory granulocytes are characterized by an oxidative burst, which may promote oxidative stress and lipid modification both in affected tissues and on a systemic level. On the other hand, redox signaling involving lipid peroxidation products acting as second messengers of free radicals play important yet not fully understood roles in the pathophysiology of inflammation and various stress-associated disorders. Therefore, the aim of this study was to evaluate the onset of oxidative stress and alterations of enzyme-dependent lipid metabolism resulting from redox imbalance in granulocytes and plasma obtained from patients with psoriasis vulgaris or psoriatic arthritis in comparison to the healthy subjects. The results obtained revealed enhanced activity of pro-oxidant enzymes nicotinamide adenine dinucleotide phosphate (NADPH) and xanthine oxidases in granulocytes with a decrease of enzymatic and non-enzymatic antioxidants in the plasma of psoriatic patients. The nuclear factor erythroid 2(-)related factor 2 (Nrf2) and its regulators were increased in both forms of psoriasis while heme oxygenase 1 levels were increased only in psoriasis vulgaris. The redox imbalance was associated with decreased levels of phospholipids and of free polyunsaturated fatty acids but with enhanced activity of enzymes involved in lipid metabolism (phospholipase A2, acetylhydrolase PAF, cyclooxygenases 1 and 2) and increased lipid peroxidation products 4-hydroxynonenal, isoprostanes, and neuroprostanes. Increased endocannabinoids and G protein-coupled receptor 55 were observed in both forms of the disease while expression of the cannabinoid type 1 receptor (CB1) was increased only in patients with psoriatic arthritis, which is opposite to the cannabinoid type 2 receptor. This receptor was increased only in psoriasis vulgaris. Changes in protein expression promoted the apoptosis of granulocytes by increased caspases mainly in psoriasis vulgaris. This study indicates that inhibition of the Nrf2 pathway in psoriatic arthritis promotes a redox imbalance. In addition, increased expression of CB1 receptors leads to increased oxidative stress, lipid modifications, and inflammation, which, in turn, may promote the progression of psoriasis into the advanced, arthritic form of the disease.

[12] *Blanco-Vaca F, Martin-Campos JM, Perez A, Fuentes-Prior P. A rare STAP1 mutation incompletely associated with familial hypercholesterolemia. Clinica chimica acta; international journal of clinical chemistry 2018; 487:270-274.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30308187>

ABSTRACT

Literature update week 41 (2018)

Autosomal dominant hypercholesterolemia, being referred to as familial hypercholesterolemia (FH), is mainly due to defective LDL receptor (LDLR) function, but is also associated with variants in genes encoding APOB (LDLR ligand) and PCSK9, the catabolic regulator of LDLR. The signal-transducing adaptor family member 1 (STAP1) gene has been recently linked to FH. We describe the case of a 56-year-old male patient found to have hypercholesterolemia at age 34, but who did not continue follow-up nor received treatment with lipid-lowering drugs. At age 55 he suffered a myocardial infarction. A systematic NGS analysis did not show point mutations in the LDLR, APOB, LDLRAP1, or PCSK9 genes, nor large rearrangements of the LDLR gene, but revealed the heterozygous missense variant rs199787258 of STAP1 (c.526C>T; p.Pro176Ser). This variant was also found in heterozygosity in the two siblings of the index case, who also had hypercholesterolemia, but did not cosegregate in his progeny. A bioinformatics analysis and available structural information predicts p.Pro176Ser as the most damaging of all STAP1 missense variants associated with familial hypercholesterolemia. Our findings confirm and extend the linkage between STAP1 variants and FH, and point to an important role of this adaptor protein within a signaling pathway that affects cholesterol homeostasis.

[13] *Parra-Virto A, Torres do Rego A, Demelo-Rodriguez P et al. Usefulness of compounds with monacolin K in a case of statins intolerance. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30309697>

ABSTRACT

Many patients with familial hypercholesterolaemia (FH) or in secondary prevention situations and with statin intolerance do not achieve LDL-C targets, and require treatment with PCSK9 inhibitors (iPCSK9) and ezetimibe. The case is presented on a patient with FH and total intolerance to statins. Treatment with iPCSK9 and ezetimibe failed to achieve her LDL-C target. A compound with red yeast rice derivatives containing 3mg of monacolin K was added, with good therapeutic compliance, and a very good control of LDL-C. The addition of red yeast rice derivatives containing low doses of monacolin K, together with IPCSK9 in patients with total intolerance to statins, may open a new path to obtain LDL-C targets in patients with high/very high cardiovascular risk.

[14] *Lorenzi M, Ambegaonkar B, Baxter CA et al. Ezetimibe in high-risk, previously treated statin patients: a systematic review and network meta-analysis of lipid efficacy. Clinical research in cardiology : official journal of the German Cardiac Society* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30302558>

ABSTRACT

PURPOSE: While statins are used as first-line treatments for high-risk patients with hypercholesterolemia, statin monotherapy is often insufficient to achieve target low-density lipoprotein cholesterol (LDL-C) levels. Second-line treatment options include up-titration of statin dose, switching to a more potent statin, or combination therapy, e.g., with ezetimibe. The aim of this study was to evaluate the efficacy of adding ezetimibe to simvastatin, atorvastatin, or rosuvastatin monotherapy versus doubling the dosage or switching to a higher-potency statin in a population of patients with hypocholesterolemia at high risk of cardiovascular disease (CVD) and who had been previously treated with a statin. METHODS: A

Literature update week 41 (2018)

systematic literature search was performed and evidence bases were established for populations of atorvastatin-, simvastatin-, and rosuvastatin-experienced patients using eligible randomized controlled trials (RCTs). Based on the available data, we constructed networks of evidence and conducted a Bayesian network meta-analysis (NMA) within each statin population. The primary outcome of interest was percent change from baseline in LDL-C. Changes in total cholesterol were explored as a secondary outcome. FINDINGS: Across all patient populations, 35 RCTs were identified and included in the evidence base. Among patients on simvastatin therapy, the addition of ezetimibe resulted in a mean difference (MD) in LDL-C of - 13.62% (95% CrI - 19.99, - 6.91; see table below) compared to doubling the starting dose of simvastatin. In the population of patients on atorvastatin therapy, the addition of ezetimibe resulted in an MD in LDL-C of - 14.71% (95% CrI - 16.46, - 12.95) compared to doubling the starting dose of atorvastatin. The addition of ezetimibe to rosuvastatin resulted in an MD in LDL-C of - 14.96% (95% CrI - 17.79, - 12.11), compared to doubling the starting rosuvastatin dose. Similar trends were observed for changes in total cholesterol. IMPLICATIONS: Given the available data, the addition of ezetimibe to ongoing simvastatin, atorvastatin, or rosuvastatin monotherapy offers greater reduction in LDL-C among patients at high risk of CVD compared to doubling the initial statin dose.

[15] *Alves BC, Bruch-Bertani JP, Galinatti CBM et al. Obesity, dynapenia and high cardiovascular risk co-exist in post-liver transplant setting: results of a cross-sectional study. Clinics and research in hepatology and gastroenterology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30301681>

ABSTRACT

BACKGROUND: Cardiovascular disease is a major cause of death in post-liver transplantation (LT). The aim of this study was to evaluate LT patients as to the carotid intima-media thickness (CIMT) and its association with nutritional status, dietary intake, metabolic profile and cardiovascular risk factors. METHODS: In this cross-sectional study, adult patients with more than 12 months of post-transplant follow-up underwent clinical, laboratory, functional and nutritional evaluation by 3-day-diet-record, anthropometry and dynamometry. CIMT was evaluated by Doppler ultrasonography. RESULTS: Sixty-nine post-LT patients [males 61%, median of age 59 (51-64) years were included; median time post-liver transplantation 2.8 (1.4-6.3) years]. High prevalence of malnutrition was found (45% of arm muscle area < p15 and 71% of handgrip strength < p30). Excess weight was present in 72% of patients, body mass index \geq 30 kg/m² in 35% and metabolic syndrome in 51%. Abnormal CIMT was found in 54% of the sample. Patients with abnormal CIMT presented higher cardiovascular risk Score, LDL cholesterol, higher prevalence of high-sensitive C-reactive protein \geq 1 mg/L and higher intake of saturated and trans fatty acids (P < 0.05 for all). CONCLUSIONS: Abnormal IMT was commonly found in LT patients presenting at the same time with overweight and dynapemia. These results were associated with higher LDL-cholesterol levels, high-sensitive C-reactive protein \geq 1 mg/L and higher intake of saturated and trans fatty acids. Preventive measures, including dietary advice, are required for all post-liver transplantation patients to minimize cardiovascular risk.

Literature update week 41 (2018)

[16] *Warraich HJ, Rana JS. Diabetic Dyslipidemia: Epidemiology and Prevention of Cardiovascular Disease and Implications of Newer Therapies. Current cardiology reports* 2018; 20:125.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30311078>

ABSTRACT

PURPOSE OF REVIEW: Dyslipidemia in patients with T2DM confers significant additional risk of adverse outcomes to patients with cardiovascular disease (CVD). These patients carry residual risk of adverse outcomes despite optimal management with conventional therapy such as lifestyle changes and statin therapy. The role of both nonstatin monotherapy in statin-intolerant patients and combination therapy with statins in patients with high risk of CVD events has been well studied. We sought to review the role of newer therapies in risk reduction in these patients. RECENT FINDINGS: Traditionally, non-statin options have included medications such as niacin, ezetimibe, fenofibrate, and n-3 fatty acids. Recently, drugs such as ezetimibe, inclisiran, and PCSK9 inhibitors have been studied with favorable results without an increased risk of developing new-onset diabetes. These medications hold the promise of increasing options to reduce cardiovascular risk in patients with T2DM. The role of newer non-statin therapies in patients with diabetic dyslipidemia in combination with statins needs to be further explored.

[17] *Sakamoto A, Virmani R, Finn AV. Coronary artery calcification: recent developments in our understanding of its pathologic and clinical significance. Current opinion in cardiology* 2018; 33:645-652.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307412>

ABSTRACT

PURPOSE OF REVIEW: Prior investigations have shown the close association between coronary artery calcification (CAC) and total atherosclerotic plaque burden as well as the risk of cardiovascular and all-cause mortality. However, recent pathologic and imaging-based studies suggested that massive dense calcifications are usually associated with stable plaque; whereas, micro calcifications, especially in the thin fibrous cap, are related to vulnerable characteristics. Further, the molecular mechanisms for initiation/progression of vascular calcification are highly complex and still need to be elucidated. In this manuscript, we discuss recent advancement in our understanding of CAC from the basic, pathologic, and clinical perspectives. RECENT FINDINGS: Research on the relationship between genetic polymorphisms and CAC has been growing and may potentially lead to future precision-based medicine. In basic research field, more attention has been focused on the relationship between inflammation and vascular calcification. Large-scale imaging based studies support the association between statin and calcification progression, maybe one of the ways by which statins prevent cardiovascular events. Nevertheless, the mechanism responsible for this effect is still not fully understood. Optical coherence tomography has improved resolution to detect CAC over traditional CT and may be especially promising for the detection of calcified nodules. SUMMARY: A better understanding of CAC in all of its forms will advance our understanding of its natural history of atherosclerosis. More work is needed to understand the basic molecular mechanisms responsible for the initiation/progression of CAC, which may eventually lead to the development of effective treatments for atherosclerosis.

Literature update week 41 (2018)

[18] *Athyros VG, Katsiki N, Dimakopoulou A et al. Drugs that mimic the effect of gene mutations for the prevention or the treatment of atherosclerotic disease: from PCSK9 inhibition to ANGPTL3 inactivation. Current pharmaceutical design* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30306859>

ABSTRACT

BACKGROUND: Drugs mimicking natural beneficial mutations, including that for familial hypercholesterolemia (FH), might represent the future of hypolipidemic drug treatment. **OBJECTIVE:** The aim of this review is to review the properties and the effects of these drugs, which are either already commercially available or are in the process to be approved for the treatment of dyslipidemia. **RESULTS:** More than a decade ago, it was accidentally discovered that proprotein convertase subtilisin/kexin type 9 (PCSK9) loss-of-function mutations resulted in marked lifelong reduction of LDL-C and the incidence of cardiovascular disease (CVD). This provided the idea for a human anti-PCSK9 antibody. Along with dozens of phase II and III studies demonstrating unprecedented reductions in LDL-C levels, two large clinical trials established the substantial benefits of evolocumab and alirocumab on cardiovascular morbidity and mortality, on top of standard treatment. Evolocumab and alirocumab are now approved and used in clinical practice for the treatment of FH, statin intolerance, and high risk patients not achieving LDL-C targets. Anti RNA, small molecules, peptides and also protein fragments against PCSK9 are in phase 1 trials. Angiotensin-like protein 3 (ANGPTL3) regulates lipid metabolism increasing triglycerides (TGs), remnants, and LDL-C. In a huge study, ANGPTL3 deficiency due to gene(s) loss-of-function was associated with substantial reductions in circulating TGs, LDL-C, and CVD. Evinacumab, an ANGPTL3 antibody, caused a dose-dependent reduction in fasting TG levels of up to 76% and LDL-C of up to 23% and CVD risk by 41%. There is also antisense oligonucleotide and micro-RNA-27b (miR-27b) against ANGPTL3. Two naturally occurring mutations in apo3 gene, A23T and K58E, reduce TGs and CVD risk. A monoclonal antibody targeting apoC-III has the same effect. **CONCLUSIONS:** Mimicking the beneficial naturally happening mutations in lipid metabolism pathways with biological drugs is probably the future of hypolipidemic drug treatment.

[19] *Faselis C, Imprialos K, Grassos H et al. Is very low LDL-C harmful? Current pharmaceutical design* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30295187>

ABSTRACT

BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) is a major cardiovascular (CV) risk factor. Accumulating evidence supports a linear association between LDL-C levels and CV risk. However, the lower limit of LDL-C that might offer CV benefits without any safety concerns is still a topic of debate. **OBJECTIVE:** The purpose of this review is to present the safety of reducing LDL-C to low levels as it comes from major lipid-lowering drug studies, and to discuss data on several safety events that have been associated with low LDL-C levels. **METHODS:** A comprehensive literature search was performed to identify available data from clinical studies evaluating the association of low LDL-C with safety outcomes. **RESULTS:** Several large trials have evaluated the safety of reducing LDL-C to levels lower than 50 mg/dl or even lower than 25 mg/dl, more commonly with the use of combination of statins with ezetimibe or proprotein

Literature update week 41 (2018)

convertase subtilisin kexin 9 inhibitors. In almost all trials, CV benefits were observed with LDL-C levels of 50 mg/dl or less compared with higher levels. In terms of safety, reduction of LDL-C to such levels was not associated with any significant adverse event. Of importance, cancer and hemorrhagic stroke incidences were not increased in patients attaining LDL-C lower than 40-50 mg/dl. Data regarding the impact of lowering LDL-C with neurocognitive disorders are contradictory; nevertheless, most studies stand in favor of neurocognitive safety with LDL-C reductions to low levels. CONCLUSION: Achieving an LDL-C of 40-50 mg/dl seems to be safe, and importantly might offer CV beneficial effects. Data for attaining levels below 25 mg/dl is limited, however in favor of such reductions.

[20] *Gossios T, Zografou I, Simoulidou V et al. Multimodal treatment of homozygous familial hypercholesterolemia. Current pharmaceutical design 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30306858>

ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disease, associated with premature atherosclerotic cardiovascular disease (CVD), especially in its homozygous type (HoFH). OBJECTIVE: The aim of this review is to discuss the safety and efficacy of combination treatments (procedures and drugs) for HoFH. RESULTS: Historically, liver transplantation was used first; however, it is currently considered only as a last resort for some patients. In the mid 70's, LDL aphaeresis was introduced and remains up today the treatment of choice for patients of any age, despite its significant cost. The use of Ezetimibe results in additive 15-20% reductions in LDL-C regardless of therapeutic approach, while statins are modestly effective in patients with class 4 or 5 mutations, in which LDL receptors (LDLR) are present. One of the novel drugs for HoFH is Lomitapide, which is a highly effective oral agent, but is also exceedingly expensive (\$350,000/year). Mipomersen is administered every week subcutaneously, is also effective but has been approved only in US mainly due to injection site reactions up to 80%. Both Lomitapide (mainly) and Mipomersen have been found to promote fat accumulation in the liver, resulting in subsequent serum transaminases elevations. PCSK9 inhibitors are effective in those with partial LDLR presence and function by reducing frequency of LDL apheresis, improve cost effectiveness of treatment. CONCLUSION: Pediatric and adult HoFH treatment needs combination of procedures and drugs. The main treatment is LDL-C apheresis aided by ezetimibe and PCSK9 inhibitors. Lomitapide needs caution, and liver transplantation is an alternative as the last resort.

[21] *Viigimaa M, Heinsar S, Lovic D et al. New horizons in the pathogenesis, pathophysiology and treatment of familial hypercholesterolaemia. Current pharmaceutical design 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30306860>

ABSTRACT

BACKGROUND: Familial hypercholesterolaemia (FH) is an autosomal-dominant genetic disease and represents the most common genetic disorder: heterozygous 1/250 births, homozygous 1/300,000 births. FH is characterized by high to very high low density lipoprotein cholesterol (LDL-C), which is the main cause of increased incidence of premature atherosclerotic cardiovascular disease (CVD) or aortic stenosis. OBJECTIVE: The aim of the review was to investigate the pathogenesis and the pathophysiology of FH. RESULTS: The most common (60-

Literature update week 41 (2018)

80%) FH cause is mutations of the LDL receptor (LDLR) protein (6 classes with different number of receptors and functionality). Moreover, mutations in apolipoprotein B (APOB) (<5%) and gain-of function mutations of proprotein convertase subtilisin/kexin type 9 genes (PCSK9) (<1%) contribute to its pathogenesis. An autosomal recessive hypercholesterolaemia (ARH) is another cause, very rare (1/2.500 births), mainly in Sardinia. The remaining patients with a clinical diagnosis of monogenic hypercholesterolaemia do not present any known genetic cause. Since FH is a significant public health problem, early diagnosis and treatment are of utmost importance. Recent studies demonstrated the influence of the LDLR mutation type in the FH phenotype, associating a more severe clinical phenotype and worse advanced CVD in patients with null mutation than those with receptor-defective mutations. This analysis completes the adequate clinical diagnosis. CONCLUSION: Both homozygous and heterozygous FH are related to mutations of LDLR (mainly), APOB, PCSK9, while other rare forms exist. All aberrations lead to the impaired removal of LDL-C from the blood leading to its accumulation and subsequent CVD earlier than in the general population.

[22] Archibugi L, Arcidiacono PG, Capurso G. **Statin use is associated to a reduced risk of pancreatic cancer: A meta-analysis.** Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30314951>

ABSTRACT

BACKGROUND: Previous studies investigating the association between statin use and pancreatic cancer (PDAC) risk for a possible chemopreventive effect gathered heterogeneous results. AIMS: To conduct a systematic review and meta-analysis to clarify this association. METHODS: Comprehensive literature search of articles published up to February 2018, including case-control (CC), cohort studies (C), randomized controlled trials (RCTs) assessing association between statin use and PDAC risk. Studies had to report odds ratio (OR)/relative risk (RR), estimates with 95% confidence interval (CI), or provide data for their calculation. Pooled ORs with 95% CIs were calculated using random effects model, publication bias through Begg and Mazumdar test and heterogeneity by I(2) value. RESULTS: 27 studies (13 CC, 9C, 5 RCTs) for a total population of 11,975 PDAC/3,433,175 controls contributed to the analysis. The overall pooled result demonstrated a reduced PDAC risk among statin users (OR 0.70; 95% CI 0.60-0.82; $p < 0.0001$), compared to non-users. Sensitivity analyses suggested the risk reduction to be more important in CC studies, studies conducted in Asia and Europe, in males and atorvastatin users. No publication bias found. CONCLUSIONS: The present meta-analysis suggests that statin use is associated with an overall PDAC risk reduction of 30%. Further studies are needed to clarify the association.

[23] Korani S, Korani M, Bahrami S et al. **Application of nanotechnology to improve the therapeutic benefits of statins.** Drug discovery today 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30292917>

ABSTRACT

Hyperlipidemia is defined as an elevated level of lipids and lipoproteins in the blood and is considered to be a significant risk factor for accelerating the process of atherosclerosis and, consequently, cardiovascular disease. The level of cholesterol, especially low-density

Literature update week 41 (2018)

lipoprotein cholesterol (LDL-C), is commonly elevated in hyperlipidemia and represents the primary therapeutic target. Statins are a group of drugs that function by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are extremely efficacious in reducing elevated LDL-C in the serum and preventing atherosclerotic cardiovascular disease. However, statins have some limitations, such as poor aqueous solubility, low oral absorption, and, consequently, limited bioavailability when administered by the oral route. The field of nanotechnology is now well developed and some of these newer nanotechnology strategies offer systems with enhanced aqueous solubility of the statin, increased absorption, bioavailability, and controlled release of the statin at the site of administration. Here, we discuss nano-sized drug delivery systems to enhance the therapeutic potential of statins.

[24] Sandesara PB, Virani SS, Fazio S, Shapiro MD. **The Forgotten Lipids: Triglycerides, Remnant Cholesterol, and Atherosclerotic Cardiovascular Disease Risk.** *Endocrine reviews* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30312399>

ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide. Low-density lipoprotein cholesterol (LDL-C) is a well-established mediator of atherosclerosis and a key target for intervention for the primary and secondary prevention of ASCVD. However, despite significant reduction in LDL-C, patients continue to have recurrent ASCVD events. Hypertriglyceridemia maybe an important contributor of this residual risk. Observational and genetic epidemiological data strongly support a causal role of triglycerides and the cholesterol content within triglyceride-rich lipoproteins (TGRL) and/or remnant cholesterol (RC) in the development of ASCVD. TGRL are comprised of hepatically derived very low-density lipoprotein (VLDL) and intestinally derived chylomicrons. RC is the cholesterol content of all TGRL and plasma triglycerides serve as a surrogate measure of TGRL and RC. Although lifestyle modification remains the cornerstone for management of hypertriglyceridemia, many novel drugs are in development and have shown impressive TG lowering efficacy. Several ongoing randomized controlled trials are under way to examine the impact of these novel agents on ASCVD outcomes. In this comprehensive review, we provide an overview of the biology, epidemiology and genetics of triglycerides and ASCVD and discuss current and novel triglyceride lowering therapies under development.

[25] Abdullah K, Rohatgi A. **Statins: Practical Considerations - A Review.** *European cardiology* 2014; 9:71-75.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310489>

ABSTRACT

Statins are currently the most efficacious and widely prescribed lipid-lowering medications. The 2013 ACC/AHA cholesterol guidelines provide a dramatic shift in treatment approach with a focus on fixed-dose statins matched to individual risk scores. Statin intolerance is not uncommon and can be challenging to diagnose and manage; however, several therapeutic strategies have been successful in achieving statin tolerance. Statin use is also associated with liver enzyme elevations and increased risk of incident diabetes, but studies show these individuals benefit from statins. Several guidelines exist and statin use is expected to increase with the new cholesterol guidelines bringing along new challenges for prescribers. This review

Literature update week 41 (2018)

article will provide practical considerations for statin use and management of statin intolerance.

[26] *Alonso R, Perez de Isla L, Muniz-Grijalvo O et al. Familial Hypercholesterolaemia Diagnosis and Management. European cardiology 2018; 13:14-20.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310464>

ABSTRACT

Familial hypercholesterolaemia is the most common monogenic disorder associated with premature coronary artery disease. Mutations are most frequently found in the LDL receptor gene. Clinical criteria can be used to make the diagnosis; however, genetic testing will confirm the disorder and is very useful for cascade screening. Early identification and adequate treatment can improve prognosis, reducing negative clinical cardiovascular outcomes. Patients with familial hypercholesterolaemia are considered at high cardiovascular risk and the treatment target is LDL cholesterol <2.6 mmol/l or at least a 50 % reduction in LDL cholesterol. Patients require intensive treatment with statins and ezetimibe and/or colesvelam. Recently, proprotein convertase subtilisin/kexin type 9 inhibitors have been approved for the management of familial hypercholesterolaemia on top of statins.

[27] *Cifkova R. Antiplatelet and Lipid-lowering Drugs in Hypertension. European cardiology 2014; 9:16-20.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310480>

ABSTRACT

Antiplatelet therapy, and low-dose acetylsalicylic acid (ASA) in particular, is recommended in hypertensive patients with previous cardiovascular events and is considered in hypertensive patients with reduced renal function or a high cardiovascular (CV) risk, provided blood pressure is well-controlled. Acetylsalicylic acid is not recommended in low-to-moderate risk hypertensive patients in whom absolute benefit and harm are equivalent. Further trials evaluating antithrombotic therapy including newer agents in hypertension are needed. Women at high and moderate risk of pre-eclampsia are advised to take a low dose of ASA daily from 12 weeks of gestation until delivery. In addition to their lipid-lowering effects, statins induce a small blood pressure reduction. The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines recommend using statin therapy in hypertensive patients at moderate-to-high CV risk to achieve the target low-density lipoprotein (LDL) cholesterol value <3 mmol/l (115 mg/dl). For individuals with manifest CV disease or at very high CV risk, a more aggressive LDL target of <1.8 mmol/l (70 mg/dl) is recommended.

[28] *Lambert CT, Sandesara P, Isiadinso I et al. Current Treatment of Familial Hypercholesterolaemia. European cardiology 2014; 9:76-81.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310490>

ABSTRACT

Familial hypercholesterolaemia is an autosomal-dominant disorder associated with mutations in the LDL receptor gene resulting in markedly elevated plasma low-density lipoprotein cholesterol levels. FH is significantly underrecognised with as many as 1 in 300 having the heterozygous form and 1 in 1 million having the homozygous form of the disease. Early

Literature update week 41 (2018)

diagnosis and treatment of FH is paramount to reduce the risk of premature atherosclerotic cardiovascular disease and death. The goal of treatment is to reduce LDL-C by 50 % from baseline levels with lifestyle modification, pharmacologic lipid-lowering therapy, LDL apheresis and in rare cases, liver transplantation. Pharmacologic treatment ranges from statin medications to newer agents such as lomitapide, mipomersin and PCSK9 inhibitors. Combination therapy is frequently required to achieve goal lipoprotein level reductions and prevent complications.

[29] *Nicholls SJ. Management of Severe Dyslipidaemia: Role of PCSK9 Inhibitors. European cardiology 2018; 13:9-13.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310463>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in regulation of LDL receptors on the hepatocyte surface and therefore is essential for effective removal of LDL particles from circulation. Genetic and biochemical studies have established that altered PCSK9 functionality influences both LDL cholesterol levels and cardiovascular risk. This has prompted development of inhibitory strategies targeting PCSK9. Study of monoclonal PCSK9 antibodies has progressed to the clinic, where they have been found to lower LDL cholesterol levels and reduce cardiovascular event rates in large, clinical outcome trials. The use of PCSK9 inhibitors in the setting of dyslipidaemia is reviewed.

[30] *Pitts RN, Eckel RH. The Emerging Role of PCSK9 Inhibitors in Preventive Cardiology. European cardiology 2014; 9:65-70.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310488>

ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) is a most important risk factor for developing coronary artery disease (CAD) and other forms of atherosclerotic cardiovascular disease (CVD) and a major focus of CVD risk reduction with lifestyle and statins. Unfortunately residual risk of CVD remains in patients with familial hypercholesterolaemia and/or statin intolerance in whom adequate LDL-C lowering is not accomplished with lifestyle and statins. PCSK9 is a serine protease that binds the LDL receptor (LDL-R) and acts as a chaperone for endocytosis and shuttling the PCSK9-LDLR complex to lysosomes for degradation. In the absence of PCSK9 the LDLR-LDL-C complex dissociates and LDL-R is recycled back to the cell surface. Humanised monoclonal antibodies (evolcumab, alirocumab, bocolicumab) have been developed that increase LDL-R by ~2-fold and lower LDL-C by up to 75 percent. This effect is synergistic to that of statins with the only common adverse effect is a local injection site reaction. At present, ongoing Phase III CVD outcome trials with PCSK9 inhibitors offer promise that patients with LDL-C levels that remain elevated can decrease CVD events and related mortality.

[31] *Vallejo-Vaz AJ. Guest Editorial: Reducing Risk in Familial Hypercholesterolaemia and Severe Dyslipidaemia: Novel Drugs Targeting PCSK9. European cardiology 2018; 13:7-8.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30310462>

ABSTRACT

Literature update week 41 (2018)

[32] *Bucerius J, Dijkgraaf I, Mottaghy FM, Schurgers LJ. Target identification for the diagnosis and intervention of vulnerable atherosclerotic plaques beyond (18)F-fluorodeoxyglucose positron emission tomography imaging: promising tracers on the horizon. European journal of nuclear medicine and molecular imaging 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30302506>

ABSTRACT

Cardiovascular disease is the major cause of morbidity and mortality in developed countries and atherosclerosis is the major cause of cardiovascular disease. Atherosclerotic lesions obstruct blood flow in the arterial vessel wall and can rupture leading to the formation of occlusive thrombi. Conventional diagnostic tools are still of limited value for identifying the vulnerable arterial plaque and for predicting its risk of rupture and of releasing thromboembolic material. Knowledge of the molecular and biological processes implicated in the process of atherosclerosis will advance the development of imaging probes to differentiate the vulnerable plaque. The development of imaging probes with high sensitivity and specificity in identifying high-risk atherosclerotic vessel wall changes and plaques is crucial for improving knowledge-based decisions and tailored individual interventions. Arterial PET imaging with (18)F-FDG has shown promising results in identifying inflammatory vessel wall changes in numerous studies and clinical trials. However, due to its limited specificity in general and its intense physiological uptake in the left ventricular myocardium that impair imaging of the coronary arteries, different PET tracers for the molecular imaging of atherosclerosis have been evaluated. This review describes biological, chemical and medical expertise supporting a translational approach that will enable the development of new or the evaluation of existing PET tracers for the identification of vulnerable atherosclerotic plaques for better risk prediction and benefit to patients.

[33] *Balk EM, Adams GP, Langberg V et al. Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review. Evidence report/technology assessment 2016:1-1252.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307737>

ABSTRACT

BACKGROUND: The effect and association of omega-3 fatty acids (n-3 FA) intake and biomarker levels with cardiovascular (CV) clinical and intermediate outcomes remains controversial. We update prior Evidence Reports of n-3 FA and clinical and intermediate CV disease (CVD) outcomes. **OBJECTIVES:** Evaluate the effect of n-3 FA on clinical and selected intermediate CV outcomes and the association of n-3 FA intake and biomarkers with CV outcomes. The n-3 FA under review include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), stearidonic acid (SDA), and algalinolenic acid (ALA). **DATA SOURCES:** MEDLINE(R), Embase(R), the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CAB Abstracts from 2000 or 2002 to June 8, 2015, and eligible studies from the original reports and relevant existing systematic reviews. **REVIEW METHODS:** We included randomized controlled trials (RCTs) of any n-3 FA intake compared to no, lower, or other n-3 FA intake with an outcome of interest conducted in healthy adults, those at risk for CVD, or those with CVD. We also included prospective observational studies of the association between baseline n-3 FA intake or biomarker level and followup outcomes. We required 1 year or more of followup for clinical outcomes and 4 weeks for intermediate

Literature update week 41 (2018)

outcomes (blood pressure [BP] and lipids). RESULTS: From 11,440 citations (from electronic literature searches and existing systematic reviews), 829 abstracts met basic eligibility criteria; 61 RCTs and 37 longitudinal observational studies (in 147 articles) were included. Most RCTs and observational studies had few risk-of-bias concerns. Total n-3 FA: There is low strength of evidence (SoE) of no association between total n-3 FA intake and stroke death or myocardial infarction. There is insufficient evidence for other outcomes. Marine oils, total: There is moderate to high SoE that higher marine oil intake lowers triglycerides (Tg), raises high density lipoprotein cholesterol (HDL-c), and lowers the ratio of total cholesterol to HDL-c but raises low density lipoprotein cholesterol (LDL-c); also that higher marine oil intake does not affect major adverse CV events, all-cause death, total stroke, sudden cardiac death, coronary revascularization, atrial fibrillation, or BP. There is low SoE of associations between higher marine oil intake and decreased risk of CVD death, coronary heart disease (CHD), myocardial infarction, ischemic stroke, and congestive heart failure (CHF). There is low SoE of no association with CHD death or hemorrhagic stroke. There is insufficient evidence for other outcomes. Marine oil FA individually: There is low SoE of no associations between EPA or DHA intake (separately) and CHD, and between EPA or DHA and atrial fibrillation. There is low SoE of no association between EPA biomarkers and atrial fibrillation, but moderate SoE of no effect of purified DHA supplementation on BP or LDL-c. There is insufficient evidence for other specific marine oil FA and outcomes. ALA: There is moderate SoE of no effect of ALA intake on BP, LDL-c, HDL-c, or Tg. There is low SoE of no association between ALA intake or biomarker level and CHD, CHD death, atrial fibrillation, and CHF. There is insufficient evidence for other outcomes. Other n-3 FA analyses: There is insufficient evidence comparing n-3 FA with each other or for SDA. Subgroup analyses: Nineteen of 22 studies found no interaction of sex on any effect of n-3 FA. Likewise, 19 of 20 studies found no differential effect by statin co-use. Within 16 studies evaluating diabetes subgroups, 2 found statistically significant beneficial effects of n-3 FA in those with diabetes but not in those without diabetes, but no test of interaction was reported. CONCLUSIONS: The 61 RCTs mostly compared marine oil supplements with placebo on CVD outcomes in populations at risk for CVD or with CVD, while the 37 observational studies mostly examined associations between various individual n-3 FA and long-term CVD events in generally healthy populations. Compared with the prior report on n-3 FA and CVD, there is more robust RCT evidence on ALA and on clinical CV outcomes; also, by design there are newly added data on associations between n-3 FA biomarkers and CV outcomes. However, conclusions regarding the effect of n-3 FA intake on CV outcomes or associations with outcomes remain substantially unchanged. Marine oils statistically significantly raise HDL-c and LDL-c by similar amounts (\approx 2 mg/dL), while lowering Tg in a dose-dependent manner, particularly in individuals with elevated Tg; they have no significant effect on BP. ALA has no significant effect on intermediate outcomes. Limited data were available from RCTs on the effect of n-3 FA on clinical CVD outcomes. Observational studies suggest that higher marine oil intake (including from dietary fish) is associated with lower risk of several CVD outcomes. No clear differences in effects or associations were evident based on population, demographic features, or cointerventions. Future RCTs would be needed to establish adequate evidence of the effect of n-3 FA on CVD outcomes or to clarify differential effects in different groups of people. However, future trials are unlikely to alter conclusions about the effects of n-3 FA supplementation on intermediate cardiovascular outcomes (BP, LDL-c, HDL-c, or Tg).

Literature update week 41 (2018)

[34] Newberry SJ, Chung M, Booth M et al. **Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review.** Evidence report/technology assessment 2016:1-826. PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307735>

ABSTRACT

OBJECTIVES: To update a prior systematic review on the effects of omega-3 fatty acids (n-3 FA) on maternal and child health and to assess the evidence for their effects on, and associations with, additional outcomes. **DATA SOURCES:** MEDLINE(R), Embase(R), the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Centre for Agriculture and Biosciences (CAB) Abstracts from 2000 to August 2015; eligible studies from the original report; and relevant systematic reviews. **REVIEW METHODS:** We included randomized controlled trials (RCTs) of any defined dose of n-3 FA (or combination) compared to placebo, any other n-3 FA, or alternative dose with an outcome of interest conducted in pregnant or breastfeeding women or neonates (preterm or term). We also included prospective observational studies that analyzed the association between baseline n-3 FA intake or biomarker level and followup outcomes. Postnatal interventions began within a week of birth for term infants and within a week of beginning enteral or oral feeding for preterm infants. Standard methods were used for data abstraction and analysis, according to the Evidence-based Practice Center Methods Guide. **RESULTS:** We identified 4,275 potentially relevant titles from our searches, of which 95 RCTs and 48 observational studies met the inclusion criteria. Risk of bias was a concern with both RCTs and observational studies. Outcomes for which evidence was sufficient to draw a conclusion are summarized here with the Strength of Evidence (SoE). (Outcomes for which the evidence was insufficient to draw a conclusion are summarized in Appendix G of the report.) **Maternal Exposures and Outcomes:** Gestational length and risk for preterm birth: Prenatal algal docosahexaenoic acid (DHA) or DHA-enriched fish oil supplementation had a small positive effect on length of gestation (moderate SoE), but no effect on risk for preterm birth (low SoE). Prenatal EPA (eicosapentaenoic acid) plus DHA-containing fish oil supplementation has no effect on length of gestation (low SoE). Supplementation with DHA, or EPA plus DHA-, or DHA-enriched fish oil does not decrease risk for preterm birth (low SoE). **Birth weight and risk for low birth weight:** Changes in maternal n-3 FA biomarkers were significantly associated with birth weight. Prenatal algal DHA or DHA-enriched fish oil supplementation had a positive effect on birth weight among healthy term infants (moderate SoE), but prenatal DHA supplementation had no effect on risk for low birth weight (low SoE). Prenatal EPA plus DHA or alpha-linolenic acid (ALA) supplementation had no effect on birth weight (low SoE). **Risk for peripartum depression:** Maternal n-3 FA biomarkers had no association with risk for peripartum depression. Maternal DHA, EPA, or DHA-enriched fish oil supplementation had no effect on risk for peripartum depression (low SoE). **Risk for gestational hypertension/preeclampsia:** Prenatal DHA supplementation among high-risk pregnant women had no effect on the risk for gestational hypertension or preeclampsia (moderate SoE). Prenatal supplementation of any n-3 FA in normal-risk women also had no significant effect on risk for gestational hypertension or preeclampsia (low SoE). **Fetal, Infant, and Child Exposures and Outcomes:** Postnatal growth patterns: Maternal fish oil or DHA plus EPA supplementation had no effect on postnatal growth patterns (attainment of weight, length, and head circumference) when administered prenatally (moderate SoE) or both pre- and

Literature update week 41 (2018)

postnatally (low SoE). Fortification of infant formulas with DHA plus arachidonic acid (AA, an n-6 FA) had no effect on growth patterns of preterm or term infants (low SoE). Visual acuity: Prenatal supplementation with DHA had no effect on development of visual acuity (low SoE). Supplementing or fortifying preterm infant formula with any n-3 FA had no significant effect on visual acuity assessed by visual evoked potentials (VEP) at 4 or 6 months corrected age (low SoE). Data conflicted on the effectiveness of supplementing infant formula for term infants with n-3 FA depending on when and how visual acuity was assessed (i.e. by VEP or by behavioral methods) and the type of essential FA provided (low SoE). Neurological development: Prenatal or postnatal n-3 FA supplementation had no consistent effect on neurological development (low SoE). Cognitive development: Prenatal DHA supplementation with AA or EPA had no effect on cognitive development (moderate SoE). Supplementing breastfeeding women with DHA plus EPA also had no effect on cognitive development in infants and children (low SoE). Supplementing or fortifying preterm infants' formula with DHA plus AA had a positive effect on infant cognition at some short-term followup times (moderate SoE). Supplementing or fortifying infant formula for term infants with any n-3 FA had no effect on cognitive development (low SoE). Evidence is insufficient to support any effect of n-3 FA infant supplementation on long-term cognitive outcomes. Autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and learning disorders: Maternal or infant n-3 FA supplementation had no effect on risk for autism spectrum disorders or ADHD (low SoE). No studies on other learning disorders were identified. Atopic dermatitis (AD), allergies, and respiratory disorders: Pre- and postnatal (maternal and infant) n-3 FA supplementation had no consistent effect on the risk for AD/eczema, allergies, asthma, and other respiratory illnesses (moderate SoE). Biomarkers and intakes had no consistent association with the risk for AD, allergies, and respiratory disorders (low SoE). Adverse events: Prenatal and infant supplementation with n-3 FA or fortification of foods with n-3 FA did not result in any serious or nonserious adverse events (moderate SoE); with the exception of an increased risk for mild gastrointestinal symptoms. CONCLUSIONS: Most studies in this report examined the effects of fish oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus AA. As with the original report, with the exception of small increases in birth weight and length of gestation, n-3 FA supplementation or fortification has no consistent evidence of effects on peripartum maternal or infant health outcomes. No effects of n-3 FA were seen on gestational hypertension, peripartum depression, or postnatal growth. Apparent effects of n-3 FA supplementation were inconsistent across assessment methods and followup times for outcomes related to infant visual acuity, cognitive development and prevention of allergy and asthma. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

[35] Jun S, Datta S, Wang L et al. **The impact of lipids, lipid oxidation, and inflammation on AMD, and the potential role of miRNAs on lipid metabolism in the RPE.** Experimental eye research 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30292489>

ABSTRACT

Literature update week 41 (2018)

The accumulation of lipids within drusen, the epidemiologic link of a high fat diet, and the identification of polymorphisms in genes involved in lipid metabolism that are associated with disease risk, have prompted interest in the role of lipid abnormalities in AMD. Despite intensive investigation, our understanding of how lipid abnormalities contribute to AMD development remains unclear. Lipid metabolism is tightly regulated, and its dysregulation can trigger excess lipid accumulation within the RPE and Bruch's membrane. The high oxidative stress environment of the macula can promote lipid oxidation, impairing their original function as well as producing oxidation-specific epitopes (OSE), which unless neutralized, can induce unwanted inflammation that additionally contributes to AMD progression. Considering the multiple layers of lipid metabolism and inflammation, and the ability to simultaneously target multiple pathways, microRNA (miRNAs) have emerged as important regulators of many age-related diseases including atherosclerosis and Alzheimer's disease. These diseases have similar etiologic characteristics such as lipid-rich deposits, oxidative stress, and inflammation with AMD, which suggests that miRNAs might influence lipid metabolism in AMD. In this review, we discuss the contribution of lipids to AMD pathobiology and introduce how miRNAs might affect lipid metabolism during lesion development. Establishing how miRNAs contribute to lipid accumulation in AMD will help to define the role of lipids in AMD, and open new treatment avenues for this enigmatic disease.

[36] *Iughetti L, Predieri B, Bruzzi P. Novel insights on the treatment of hypercholesterolemia. Expert review of endocrinology & metabolism* 2015; 10:269-271.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30298770>

ABSTRACT

The diagnosis of dyslipidemia is increasing both in adulthood and in childhood because of not only the steadily increasing prevalence of obesity but also a rise of medical attention in detecting unfavorable genetic conditions in patients of all ages. Attempts in lifestyle changes are frequently failing and thus the pharmacological treatment of dyslipidemia is spreading in medical practice to reduce cardiovascular risk. In childhood, statins are authorized by 8 years of age. Nevertheless, data on their long-term safety and efficacy are still lacking, especially in ones with high cardiovascular risk and/or primary dyslipidemia such as homozygous familial hypercholesterolemia, considerable as a mainly exclusively pediatric disease. Thus, new pharmacological approaches are needed and have to be evaluated in all categories of patients. In this context, the update and the critical revision of new medications have become a new duty for scientists and clinicians.

[37] *Boyle AK, Rinaldi SF, Rossi AG et al. Repurposing simvastatin as a therapy for preterm labor: evidence from preclinical models. FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 2018:fj201801104R.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30312114>

ABSTRACT

Preterm birth (PTB), the leading cause of neonatal morbidity and mortality, urgently requires novel therapeutic agents. Spontaneous PTB, resulting from preterm labor, is commonly caused by intrauterine infection/inflammation. Statins are well-established, cholesterol-lowering drugs that can reduce inflammation and inhibit vascular smooth muscle contraction. We show that

Literature update week 41 (2018)

simvastatin reduced the incidence of PTB in a validated intrauterine LPS-induced PTB mouse model, decreased uterine proinflammatory mRNA concentrations (IL-6, Cxcl1, and Ccl2), and reduced serum IL-6 concentration. In human myometrial cells, simvastatin reduced proinflammatory mediator mRNA and protein expression (IL-6 and IL-8) and increased anti-inflammatory cytokine mRNA expression (IL-10 and IL-13). Critically, simvastatin inhibited myometrial cell contraction, basally and during inflammation, and reduced phosphorylated myosin light chain concentration. Supplementation with mevalonate and geranylgeranyl pyrophosphate, but not farnesyl pyrophosphate, abolished these anticontractile effects, indicating that the Rho/Rho-associated protein kinase pathway is critically involved. Thus, simvastatin reduces PTB incidence in mice, inhibits myometrial contractions, and exhibits key anti-inflammatory effects, providing a rationale for investigation into the repurposing of statins to treat preterm labor in women.-Boyle, A. K., Rinaldi, S. F., Rossi, A. G., Saunders, P. T. K., Norman, J. E. Repurposing simvastatin as a therapy for preterm labor: evidence from preclinical models.

[38] *Braga Filho JAF, Abreu AG, Rios CEP et al. Prophylactic Treatment With Simvastatin Modulates the Immune Response and Increases Animal Survival Following Lethal Sepsis Infection. Frontiers in immunology* 2018; 9:2137.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30298072>

ABSTRACT

Chronic use of statins may have anti-inflammatory action, promoting immunomodulation and survival in patients with sepsis. This study aimed to analyze the effects of pretreatment with simvastatin in lethal sepsis induced by cecal ligation and puncture (CLP). Male Swiss mice received prophylactic treatment with simvastatin or pyrogen-free water orally in a single daily dose for 30 days. After this period, the CLP was performed. Naive and Sham groups were performed as non-infected controls. Animal survival was monitored for 60 h after the CLP. Half of mice were euthanized after 12 h to analyze colony-forming units (CFUs); hematological parameters; production of IL-10, IL-12, IL-6, TNF-alpha, IFN-gamma, and MCP-1; cell counts on peritoneum, bronchoalveolar lavage (BAL), bone marrow, spleen, and mesenteric lymph node; immunophenotyping of T cells and antigen presenting cells and production of hydrogen peroxide (H₂O₂). Simvastatin induced an increase in survival and a decrease in the CFU count on peritoneum and on BAL cells number, especially lymphocytes. There was an increase in the platelets and lymphocytes number in the Simvastatin group when compared to the CLP group. Simvastatin induced a greater activation and proliferation of CD4⁺ T cells, as well as an increase in IL-6 and MCP-1 production, in chemotaxis to the peritoneum and in H₂O₂ secretion at this site. These data suggest that simvastatin has an impact on the survival of animals, as well as immunomodulatory effects in sepsis induced by CLP in mice.

[39] *Anez-Bustillos L, Dao DT, Potemkin AK et al. An Intravenous Fish Oil Based Lipid Emulsion successfully treats intractable pruritus and cholestasis in a patient with MVID. Hepatology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30311684>

ABSTRACT

Literature update week 41 (2018)

A PN-dependent 3-year-old male with MVID presented with a history of worsening jaundice and severe pruritus. He was managed at an outside institution with low dose soybean oil-based lipid emulsion (SOLE) Intralipid((R)) (Fresenius-Kabi, Uppsala, Sweden) at 0.2 g/kg/day as a strategy to prevent PN-associated liver disease (PNALD). At 11 months of age he complained of significant pruritus without dermatologic findings. Ursodiol and diphenhydramine were administered with partial resolution. This article is protected by copyright. All rights reserved.

[40] *Barkate H, Patel P, Shah D, Vyas F. Comparison of Efficacy and Safety of Fixed Dose Combination of Rosuvastatin and Choline Fenofibrate to Fixed Dose Combination of Rosuvastatin and Fenofibrate in Patients of Mixed Dyslipidemia: A Randomized, Open-label, Multicentre Clinical Trial in Indian Population. Indian journal of endocrinology and metabolism 2018; 22:627-631.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30294571>

ABSTRACT

Introduction: This study was conducted to evaluate the safety and efficacy of fixed-dose combination (FDC) of rosuvastatin and choline fenofibrate in comparison to rosuvastatin and fenofibrate FDC among Indian patients of mixed dyslipidemia. This would be a first study evaluating FDC of rosuvastatin and choline fenofibrate in Indian population. **Methods:** A multicenter, open-label, randomized, active controlled, comparative, parallel-design study was conducted at 12 centers spread all across India. Mixed dyslipidemic patients aged 18-70 years were randomized to FDC of rosuvastatin 10 mg and choline fenofibrate 135 mg (RCF group) and FDC of rosuvastatin 10 mg and fenofibrate 160 mg (RF group) once daily for approximately 180 days. The primary endpoint of study was percentage change in serum triglyceride level at the end of study from baseline. **Results:** Of 290 patients screened, 240 patients were enrolled in this study (120 patients in each group). At the end of 180 days, there was a significant reduction in triglyceride level in both the groups (-37.7% in RCF group and -37.8% reduction in RF group; $P < 0.0001$ for both); however, the difference between both the groups was not statistically significant ($P = 0.94$). Similarly, there was significant increase ($P < 0.0001$ for both) in high-density lipoprotein cholesterol (HDL-C) in both groups (+17.8% in RCF group and +14.9% in rosuvastatin fenofibrate RF group). Low-density lipoprotein cholesterol (LDL-C), very low-LDL (VLDL-C), and total cholesterol were also reduced significantly in both groups ($P < 0.0001$). However, the difference between two groups for increase in HDL-C and decrease in LDL-C, VLDL-C, and total cholesterol was not significant. Both the treatments were safe and well tolerated. **Conclusion:** Overall, FDC of rosuvastatin and choline fenofibrate is as safe and effective as rosuvastatin and fenofibrate combination in Indian patients with mixed dyslipidemia with added advantage improved patient compliance as it can be taken irrespective of intake of food.

[41] *Devi SB, Chanu KJ, Jeetenkumar T et al. Epicardial Adipose Tissue Thickness and its Corelation with Metabolic Risk Parameters in People Living with HIV: A RIMS Study. Indian journal of endocrinology and metabolism 2018; 22:641-644.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30294574>

ABSTRACT

Literature update week 41 (2018)

Context: Epicardial fat envelopes the coronary vessel adventitia without fascial separation, thus pathologic inflammation in the fat may promote the growth of atherosclerotic plaque in coronary arteries in an 'outside-in' fashion. Epicardial fat is quantitatively increased in HIV compared to un-infected people. Aims: 1. To assess Epicardial Adipose tissue (EAT) by Computed tomography (CT) in PLHIV receiving first line ART (antiretroviral therapy) 2. To correlate EAT with metabolic risk parameters. Material and Methods: 215 HIV-infected patients aged >18 years on first line ART were included in the cross sectional study. EAT thickness were measured by CT scan. Metabolic parameters were measured based on metabolic syndrome criteria. Statistical Analysis Used: Data analysis was done using IBM SPSS version ver. 21. Probability value of less than 0.5 was taken as significant. Ethical Issues: The study was carried out after obtaining approval from the Institutional Ethical Committee (IEC), Regional Institute of Medical Sciences, Imphal. Results: Half of the patients were found to have EAT thickness of 8.1-9 mm and 12.6% of cases had EAT of >9 mm. Mean epicardial thickness was 8.3 mm +/- 0.7 mm for whole population. Triglyceride and high density lipoprotein (HDL) were also found to have positive correlation with EAT thickness (rp= 0.364, P = 0.04 and rp= 0.343, P = 0.05 respectively). Conclusion: Epicardial adipose tissue thickness is increased in PLHIV receiving highly active anti retroviral therapy (HAART) and positively co-related with parameters of metabolic syndrome such as waist circumference, HDL cholesterol and triglyceride level.

[42] *Liu Z, Shi S, Zhu H et al. Novel ASK1 Inhibitor AGI-1067 Attenuates AGE-Induced Fibrotic Response by Suppressing the MKKs/p38 MAPK Pathway in Human Coronary Arterial Smooth Muscle Cells. Int Heart J* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30305582>

ABSTRACT

The phenotype shifting of vascular smooth muscle cells (VSMCs) was indicated to play a role during the initial stage of atherosclerotic plaque formation by facilitating extracellular matrix deposition. This study was aimed at investigating the involvement of the apoptosis signal-regulating kinase 1 (ASK1)/mitogen-activated protein kinase (MAPK) kinases (MKKs)/p38 MAPK pathway in the advanced glycation end product (AGE)-induced fibrotic response of VSMCs. The effect of the novel ASK1 inhibitor AGI-1067 was also studied. Cultured human coronary smooth muscle cells (HCSMCs) were exposed to AGEs. AGI-1067 and siRNAs silencing mkk3, mkk6, and p38 mapk were used to treat the cells. The activation of MKK3, MKK6, and p38 MAPK was assessed by immunoblotting. Fibrotic response was assessed by the fluorescence immunohistochemistry staining of collagen I and collagen VIII. Activation of immunoprecipitation determined the association of ASK1 and its inhibitor thioredoxin. A kinase assay was used to determine ASK1 activity. AGE incubation significantly activated ASK1, MKK3, and MKK6, which led to activation of p38 MAPK, resulting in upregulated fibrotic response in HCSMCs. However, siRNAs knocking down mkk3, mkk6, and p38 mapk impaired this fibrotic response. AGI-1067 administration not only dramatically inhibited the activation of ASK1/MKKs/p38 MAPK but also suppressed the expression of the downstream proteins, including transforming growth factor-beta1, connective tissue growth factor, collagen I, and collagen VIII in HCSMCs exposed to AGEs. The ASK1/MKKs/p38 MAPK pathway was activated by AGEs, leading to the fibrotic response in VSMCs. AGI-1067 reversed this process by maintaining the inactive state of ASK1.

Literature update week 41 (2018)

[43] *Mols RE, Norgaard BL, Vedsted P et al. General practice preventive health care in non-obstructive coronary artery disease determined by coronary computed tomography angiography. International journal of cardiology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30309680>

ABSTRACT

BACKGROUND: The aim of this study was to compare changes in health service utilization, preventive medical management, and cholesterol levels in patients without coronary artery disease (CAD) or with non-obstructive CAD as determined by coronary computed tomography angiography (CTA). METHODS: Single-center five-year observational registry-based cohort study of consecutive patients with chest pain undergoing coronary CTA with subsequent 12 months follow-up in general practice. RESULTS: We included 3032 patients with a normal test result (n=2179) or a diagnosis of non-obstructive CAD (n=853) by coronary CTA. Median age was 55 (interquartile range: 47-63) years and 44% were males. After coronary CTA, the probability of a decrease in consultations with general practitioner was higher in patients with no CAD compared to patients with non-obstructive CAD (adjusted OR=0.81 [95% CI: 0.68-0.96], P=0.016). Accordingly, patients with non-obstructive CAD more frequently received prescriptions on lipid-lowering medical therapy (adjusted OR=4.50 [95% CI: 3.31-6.12], P<0.001) than patients with no CAD after coronary CTA. In patients with non-obstructive CAD, mean total-cholesterol reduction was 0.51 (P<0.001) compared to 0.13mmol/L (P<0.001) in patients without non-obstructive CAD. The relative reduction in low-density lipoprotein was 14% higher (P<0.001) in patients with compared to patients without non-obstructive CAD after coronary CTA. CONCLUSIONS: Coronary CTA with subsequent follow-up in general practice has the potential to align health service utilization that prioritizes high-risk patients and facilitate optimized preventive management.

[44] *Inouye M, Abraham G, Nelson CP et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. Journal of the American College of Cardiology 2018; 72:1883-1893.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30309464>

ABSTRACT

BACKGROUND: Coronary artery disease (CAD) has substantial heritability and a polygenic architecture. However, the potential of genomic risk scores to help predict CAD outcomes has not been evaluated comprehensively, because available studies have involved limited genomic scope and limited sample sizes. OBJECTIVES: This study sought to construct a genomic risk score for CAD and to estimate its potential as a screening tool for primary prevention. METHODS: Using a meta-analytic approach to combine large-scale, genome-wide, and targeted genetic association data, we developed a new genomic risk score for CAD (metaGRS) consisting of 1.7 million genetic variants. We externally tested metaGRS, both by itself and in combination with available data on conventional risk factors, in 22,242 CAD cases and 460,387 noncases from the UK Biobank. RESULTS: The hazard ratio (HR) for CAD was 1.71 (95% confidence interval [CI]: 1.68 to 1.73) per SD increase in metaGRS, an association larger than any other externally tested genetic risk score previously published. The metaGRS stratified individuals into significantly different life course trajectories of CAD risk, with those in the top 20% of metaGRS distribution

Literature update week 41 (2018)

having an HR of 4.17 (95% CI: 3.97 to 4.38) compared with those in the bottom 20%. The corresponding HR was 2.83 (95% CI: 2.61 to 3.07) among individuals on lipid-lowering or antihypertensive medications. The metaGRS had a higher C-index (C = 0.623; 95% CI: 0.615 to 0.631) for incident CAD than any of 6 conventional factors (smoking, diabetes, hypertension, body mass index, self-reported high cholesterol, and family history). For men in the top 20% of metaGRS with >2 conventional factors, 10% cumulative risk of CAD was reached by 48 years of age. CONCLUSIONS: The genomic score developed and evaluated here substantially advances the concept of using genomic information to stratify individuals with different trajectories of CAD risk and highlights the potential for genomic screening in early life to complement conventional risk prediction.

[45] *Stacey RB, Zgibor J, Leaverton PE et al. Abnormal Fasting Glucose Increases Risk of Unrecognized Myocardial Infarctions in an Elderly Cohort. J Am Geriatr Soc* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30298627>

ABSTRACT

OBJECTIVES: To investigate glucose levels as a risk factor for unrecognized myocardial infarctions (UMIs). DESIGN: Cohort SETTING: Cardiovascular Health Study. PARTICIPANTS: Individuals aged 65 and older with fasting glucose measurements (N=4,355; normal fasting glucose (NFG), n = 2,041; impaired fasting glucose (IFG), n = 1,706; DM: n = 608; 40% male, 84% white, mean age 72.4 +/- 5.6). MEASUREMENTS: The relationship between glucose levels and UMI was examined. Participants with prior coronary heart disease (CHD) or UMI on initial electrocardiography were excluded. Using Minnesota codes, UMI was identified according to the presence of pathological Q-waves or minor Q-waves with ST-T abnormalities. Crude and adjusted hazard ratios (HRs) were calculated. Analyses were adjusted for age, sex, body mass index (BMI), hypertension, antihypertensive and lipid-lowering medication use, total cholesterol, high-density lipoprotein cholesterol, and smoking status. RESULTS: Over a mean follow-up of 6 years, there were 459 incident UMIs (NFG, n=202; IFG, n=183; DM, n=74). Participants with IFG were slightly more likely than those with NFG to experience a UMI (hazard ratio (HR)=1.11, 95% confidence interval (CI)=0.91-1.36, p = .30), and those with DM were more likely than those with NFG to experience a UMI (HR=1.65, 95% CI=1.25-2.13, p < .001). After adjustment HR for UMI in IFG those with IFG were no more likely than those with NFG to experience a UMI (HR=1.01, 95% CI=0.82-1.24, p = .93), whereas those with DM were more likely than those with NFG to experience a UMI (HR=1.37, 95% CI=1.02-1.81, p = .03). The 2-hour oral glucose tolerance test was not statistically significantly associated with UMI. CONCLUSION: Fasting glucose status, particularly in the diabetic range, forecasted UMI during 6 years of follow-up in elderly adults. Further studies are needed to clarify the level of glucose at which risk is greater.

[46] *Deng LJ, Wu YL, He XH et al. Simvastatin delivery on PEEK for bioactivity and osteogenesis enhancements. Journal of biomaterials science. Polymer edition* 2018:1-30.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307376>

ABSTRACT

The strategy of a functional biomimetic system built to obtain the positive cellular response remains a field of topical interest. In this study, a hydrogel covered simvastatin-loaded

Literature update week 41 (2018)

polyetheretherketone (PEEK) bio-composites was constructed with the purpose of bone tissue regeneration therapy. Briefly, a three-dimensional (3D) porous structure was fabricated on PEEK surface; then the substrate was functionalized with the poly(L-lactic acid)/simvastatin porous film and hyaluronic acid hydrogel subsequently. In vitro cell attachment, proliferation, and cytoskeletal observation experiments reveal that our scaffolds show better bio-affinity due to the layer of hyaluronic acid hydrogel compared with control. Furthermore, the alkaline phosphatase activity, calcium mineral deposition evaluation, and gene expression for osteogenic potential all exhibit that the superior osteogenic differentiation of MC3T3-E1 pre-osteoblasts on our scaffolds. Therefore, our PEEK samples loaded with simvastatin and covered with hyaluronic acid hydrogel hold great potential in clinical applications for bone repair.

[47] *Penson PE, Mancini GBJ, Toth PP et al. Introducing the 'Drucebo' effect in statin therapy: a systematic review of studies comparing reported rates of statin-associated muscle symptoms, under blinded and open-label conditions. Journal of cachexia, sarcopenia and muscle 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30311434>

ABSTRACT

BACKGROUND: The 'placebo effect' and 'nocebo effect' are phenomena whereby beneficial (placebo) or adverse (nocebo) effects result from the expectation that an inert substance will relieve or cause a particular symptom. These terms are often inappropriately applied to effects experienced on drug therapy. Quantifying the magnitude of placebo and nocebo effects in clinical trials is problematic because it requires a 'no treatment' arm. To overcome the difficulties associated with measuring the nocebo effect, and the fact that its definition refers to inert compounds, rather than drugs, we introduce the concept of 'drucebo' (a combination of DRUG and plaCEBO or noCEBO) to relate to beneficial or adverse effects of a drug, which result from expectation and are not pharmacologically caused by the drug. As an initial application of the concept, we have estimated the contribution of the drucebo effect to statin discontinuation and statin-induced muscle symptoms by performing a systematic review of randomized controlled trial of statin therapy. **METHODS:** This preferred reporting items for systematic reviews and meta-analysis-compliant systematic review was prospectively registered in PROSPERO (CRD42017082700). We searched PubMed and Cochrane Central from inception until 3 January 2018 using a search strategy designed to detect studies including the concepts (Statins AND Placebo AND muscle pain). We included studies that allowed us to quantify the drucebo effect for adverse muscle symptoms of statins by (i) comparing reported rates of muscle symptoms in blinded and unblinded phases of randomized controlled trials and (ii) comparing rates of muscle symptoms at baseline and during blinded therapy in trials that included patients with objectively confirmed statin intolerance at baseline. Extraction was performed by two researchers with disagreements settled by a third reviewer. **RESULTS:** Five studies allowed the estimation of the drucebo effect. All trials demonstrated an excess of side effects under open-label conditions. The contribution of the drucebo effect to statin-associated muscle pain ranged between 38% and 78%. The heterogeneity of study methods, outcomes, and reporting did not allow for quantitative synthesis (meta-analysis) of the results. **CONCLUSIONS:** The drucebo effect may be useful in evaluating the safety and efficacy of medicines. Diagnosis of the drucebo effect in patients presenting with statin intolerance will allow restoration of life-prolonging lipid-lowering therapy. Our study was limited by

Literature update week 41 (2018)

heterogeneity of included studies and lack of access to individual patient data. Further studies are necessary to better understand risk factors for and clinical management of the drucebo effect.

[48] Carrillo-Ibarra S, Miranda-Diaz AG, Sifuentes-Franco S et al. **Effect of statins on oxidative DNA damage in diabetic polyneuropathy.** Journal of circulating biomarkers 2018; 7:1849454418804099.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30302131>

ABSTRACT

Oxidative stress induces nerve damage in type 2 diabetes mellitus and leads to diabetic polyneuropathy (DPN) and can affect the DNA and antioxidant status. Statins have pleiotropic, protective effects on the peripheral nerves of patients with diabetes. The aim of this study was to determine the effects of ezetimibe/simvastatin and rosuvastatin on DNA damage in patients with DPN. This randomized, double-blind, placebo-controlled, clinical trial comprised outpatients from Guadalajara, Mexico. The inclusion criteria were either gender, age 35-80 years, type 2 diabetes, glycated hemoglobin $\leq 10\%$, diabetic polyneuropathy stage 1/2, and signed informed consent. Patients who were taking antioxidant therapy or statins, had hypersensitivity to drugs, experienced organ failure, were pregnant or breastfeeding, or had other types of neuropathy were excluded. We assigned patients to placebo, ezetimibe/simvastatin 10/20 mg, or rosuvastatin 20 mg, and the primary outcomes were 8-hydroxy-2'-deoxyguanosine (8-OHdG) for DNA damage, 8-oxoguanine-DNA-N-glycosilase (hOGG1) for DNA repair, and superoxide dismutase (SOD). Seventy-four patients were recruited. Nine patients were included as negative controls. There were no differences in 8-OHdG between the healthy subjects (4.68 [3.53-6.38] ng/mL) and the DPN patients (4.51 [1.22-9.84] ng/mL), whereas the hOGG1 level was 0.39 (0.37-0.42) ng/mL in the healthy subjects and 0.41 (0.38-0.54) ng/mL in patients with DPN at baseline ($p = 0.01$). SOD decreased significantly in patients with DPN (5.35 [0.01-17.90] U/mL) compared with the healthy subjects (9.81 [8.66-12.61] U/mL) at baseline ($p < 0.001$). No significant changes in DNA biomarkers were observed in any group between baseline and final levels. We noted a rise in hOGG1 in patients with DPN, without modifications after treatment. There was a slight, albeit insignificant, increase in SOD in patients who were on statins.

[49] Dohlmann TL, Morville T, Kuhlman AB et al. **Statin treatment decreases mitochondrial respiration but muscle coenzyme Q10 levels are unaltered: The LIFESTAT study.** The Journal of clinical endocrinology and metabolism 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30299473>

ABSTRACT

Background: Myalgia is a common side effect to statin therapy, but the underlying mechanism is unknown. Statins may reduce Coenzyme Q10 (CoQ10) which is an essential electron carrier in the mitochondrial electron transport system, thereby impairing mitochondrial respiratory function potential leading to myalgia. Objectives: To investigate whether statin induced myalgia is coupled to reduced intramuscular CoQ10 concentration and impaired mitochondrial respiratory function. Methods: 64 men and women in simvastatin therapy were recruited. 25 who experienced myalgia were allocated to the myalgic group. The remaining 39 statin users

Literature update week 41 (2018)

had no symptoms of myalgia (non-sympt). 20 men and women with untreated high blood cholesterol levels were recruited as control group. Blood and muscle samples were obtained. Intramuscular CoQ10 concentration was measured, and mitochondrial respiratory function and reactive oxygen species (ROS) production were measured. Citrate Synthase (CS) activity was used as a biomarker for mitochondrial content in skeletal muscle. Results: Intramuscular CoQ10 concentration was comparable between groups. Mitochondrial complex II-linked respiration was reduced in the statin myalgic and statin non-symptomatic groups compared to control. When mitochondrial respiration was normalized to CS activity respiration rate was higher in the myalgic group compared to non-symptomatic and control group. Maximal ROS production was similar between groups. Discussion: Our results suggests that statin therapy impairs mitochondrial complex-II linked respiration, but the mitochondrial capacity for complex I+II linked respiration is intact. Myalgia is not coupled to reduced intramuscular CoQ10 levels. Intrinsic mitochondrial respiratory capacity is increased with statin induced myalgia, but not accompanied by increased ROS production.

[50] *Ho CLB, Chowdhury EK, Breslin M et al. Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study. Journal of clinical lipidology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293937>

ABSTRACT

BACKGROUND: There is currently insufficient evidence to support the use of lipid-lowering drug treatment (LLT) for primary prevention of cardiovascular disease (CVD) in the elderly.

OBJECTIVES: We examined the relationship of early initiation of LLT with short- and long-term all-cause and CVD mortality in persons older than 65 years in this post hoc study from the Second Australian National Blood Pressure study (ANBP2). **METHODS:** This was an in- and post-trial observational study. About 4257 hypertensive participants aged 65 to 84 years within Australian family practices were randomized to an angiotensin-converting enzyme inhibitor or a diuretic treatment group. After excluding participants with a prior history of CVD, the cohort was stratified into "LLT" and "no LLT" subgroups based on LLT status at randomization.

RESULTS: At randomization, the participants had a mean age of 72 years, average blood pressure of 168/91 mm Hg and estimated 5-year CVD risk of 18.7 +/- 8.3%. In the overall study population, the association of LLT with long-term (11-years) all-cause and non-CVD mortality was significant (hazard ratio [HR] 0.78 [95% confidence interval {CI} 0.66-0.92, P = .003] and HR 0.70 [95% CI 0.54-0.90, P = .006], respectively). Magnitudes of the association of LLT with long-term mortality and the association with short-term mortality were similar; however, no statistically significant association with short-term mortality was observed. In the subgroup analysis by baseline 5-year CVD risk, LLT participants in the highest risk tertile had a substantially lower relative risk for short-term all-cause mortality (HR 0.31, 95% CI 0.13-0.71, P for interaction .02) compared to those with lower estimated CVD risk. All analyses were adjusted for baseline and in-trial characteristics. **CONCLUSION:** Our study showed a strong association between LLT and reduced long-term all-cause mortality. Thus, our findings support recommendations of the use of LLT in patients over 65 years, particularly those with high CVD risk who were more likely to obtain additional benefits in the short term. The findings also suggested that mortality benefits of LLT for the elderly may take longer to become evident.

Literature update week 41 (2018)

[51] *Martin-Campos JM, Plana N, Figueras R et al. Autosomal dominant hypercholesterolemia in Catalonia: Correspondence between clinical-biochemical and genetic diagnostics in 967 patients studied in a multicenter clinical setting. Journal of clinical lipidology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293936>

ABSTRACT

BACKGROUND: Autosomal dominant hypercholesterolemia (ADH) is associated with mutations in the low-density lipoprotein (LDL) receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin 9 (PCSK9) genes, and it is estimated to be greatly underdiagnosed. The most cost-effective strategy for increasing ADH diagnosis is a cascade screening from mutation-positive probands. OBJECTIVE: The objective of this study was to evaluate the results from 2008 to 2016 of ADH genetic analysis performed in our clinical laboratory, serving most lipid units of Catalonia, a Spanish region with approximately 7.5 million inhabitants. METHODS: After the application of the Dutch Lipid Clinic Network (DLCN) clinical diagnostic score for ADH, this information and blood or saliva from 23 different lipid clinic units were investigated in our laboratory. DNA was screened for mutations in LDLR, APOB, and PCSK9, using the DNA-array LIPOchip, the next-generation sequencing SEQPRO LIPO RS platform, and multiplex ligation-dependent probe amplification (MLPA). The Simon Broome Register Group (SBRG) criteria was calculated and analyzed for comparative purposes. RESULTS: A total of 967 unrelated samples were analyzed. From this, 158 pathogenic variants were detected in 356 patients. The main components of the DLCN criteria associated with the presence of mutation were plasma LDL cholesterol (LDLc), age, and the presence of tendinous xanthomata. The contribution of family history to the diagnosis was lower than in other studies. DLCN and SBRG were similarly useful for predicting the presence of mutation. CONCLUSION: In a real clinical practice, multicenter setting in Catalonia, the percentage of positive genetic diagnosis in patients potentially affected by ADH was 38.6%. The DLCN showed a relatively low capacity to predict mutation detection but a higher one for ruling out mutation.

[52] *Nandakumar R, Matveyenko A, Thomas T et al. Effects of Mipomersen, an apoB100 antisense, on Lp(a) metabolism in healthy subjects. Journal of lipid research* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293969>

ABSTRACT

Elevated lipoprotein(a) [Lp(a)] increases risk for cardiovascular disease. Novel treatments that decrease LDL-C also produce reductions in Lp(a) levels. Mipomersen, an antisense oligonucleotide (ASO) that inhibits apolipoprotein B (apoB), is approved for the treatment of homozygous familial hypercholesterolemia. It decreases low density lipoprotein (LDL) cholesterol (C) levels by 25-39% and lowers levels of Lp(a) by 21-39%. We examined the mechanisms regulating Lp(a) lowering after mipomersen treatment. METHODS: Fourteen healthy-volunteers received weekly placebo injections for three weeks, followed by weekly injections of mipomersen for 7 weeks. Stable isotope studies were performed, using D-leucine, at the end of the placebo and mipomersen treatment. The fractional catabolic rate (FCR) of Lp(a) was determined from the leu-enrichment of a peptide specific to apo(a) by LCMS. The production rate (PR) of Lp(a) was calculated from the product of Lp(a) FCR and Lp(a) concentration. RESULTS: Mipomersen reduced plasma Lp(a) levels by 21%. Mipomersen

Literature update week 41 (2018)

treatment resulted in a 27% increase in the FCR of Lp(a) with no significant change in PR. However, there was heterogeneity in response to mipomersen therapy. **CONCLUSION:** Mipomersen treatment decreases Lp(a) levels mainly by increasing FCR of Lp(a), although changes in Lp(a) PR were significant predictors of reductions in Lp(a) levels in some subjects.

[53] *Barnett S, Ogunbenro K, Menochet K et al. Comprehensive evaluation of the utility of 20 endogenous molecules as biomarkers of OATP1B inhibition compared to rosuvastatin and coproporphyrin I. The Journal of pharmacology and experimental therapeutics* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30314992>

ABSTRACT

Endogenous biomarkers can be clinically relevant tools for the assessment of transporter function in vivo and corresponding drug-drug interactions (DDIs). The aim of this study was to perform systematic evaluation of plasma data obtained for 20 endogenous molecules in the same healthy subjects (n=8-12) in the absence and presence of OATP inhibitor rifampicin (600mg s.d.). The extent of rifampicin DDI magnitude (AUCR), estimated fraction transported (fT) and baseline variability were compared across the biomarkers and relative to rosuvastatin and coproporphyrin I (CPI). Out of 20 biomarkers investigated TDA, HDA, GCA GDCA, TDCA and CPIII showed high AUCRs (2.1-8.5) and fT (0.5-0.76), indicative of substantial OATP1B-mediated transport. A significant positive correlation was observed between the individual GDCA and TDCA AUCR and the magnitude of rosuvastatin-rifampicin interaction. CPI and CPIII AUCR were significantly correlated, but no clear trend was established with rosuvastatin AUCR. Moderate inter-individual variability (15-62%) in baseline exposure and AUCR were observed for TDA, HDA and CPIII. In contrast, bile acids demonstrated high inter-individual variability (69-113%) and significant decreases in baseline plasma concentrations during the first 4 hours. This comprehensive analysis in the same individuals confirms that none of the biomarkers supersede CPI in the evaluation of OATP1B-mediated DDI risk. Based on current dataset, combined monitoring of CPI and CPIII or CPI and fatty acids AUCR did not recover extent of rosuvastatin DDI. Monitoring of CPI and GDCA/TDCA may be beneficial for dual OATP1B-NTCP inhibitors with consideration of challenges associated with large inter- and intra-individual variability observed for bile acids.

[54] *Belov YV, Sinyavin GV, Barinov EV, Grabuzdov AM. [Contrast-enhanced ultrasonography as the most perspective diagnostic method for unstable atherosclerotic plaque of carotid artery]. Khirurgiia* 2018:52-56.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307422>

ABSTRACT

Problem of internal carotid artery disease diagnosis appears to be crucial today. Complications of this pathology are strokes and transient ischemic attacks. There is no technology for their prediction or at least stratifying risks. Some recent researches are devoted to a new diagnostic method. This new technology is called Contrast Enhanced Ultrasonography (CEUS) and followed by outstanding results in studying the morphological peculiarities of internal carotid artery plaques and predicting the probability of complications. CEUS is a new way for atherosclerotic process analysis because it is able to detect intraplaque neovascularization and vascular wall inflammation.

Literature update week 41 (2018)

[55] *Popova LV, Aksenova MB, Khlevchuk TV. [Antiplatelet therapy in cardiology]. Klinicheskaia meditsina 2016; 94:729-736.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30299016>

ABSTRACT

Platelets are important components of hemostasis and play a key role in the formation of atherothrombosis. Rupture or erosion of atherosclerotic plaque gives rise to a thrombus with the involvement of platelets. Antiplatelet agents are instrumental in preventing the development of atherothrombosis of different localization, including coronary arteries.

[56] *El Sayed I, Helmy MW, El-Abhar HS. Inhibition of SRC/FAK cue: A novel pathway for the synergistic effect of rosuvastatin on the anti-cancer effect of dasatinib in hepatocellular carcinoma. Life sciences 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30292831>

ABSTRACT

PURPOSE: Statins extended their hypocholesteremic effect to show a promising anticancer activity. Hepatocellular carcinoma (HCC), the third common cause of cancer-related death, responded positively to statins. Some in-vitro studies reveal the rosuvastatin antitumor effect, but barely in-vivo studies. Hence, we evaluated the antitumor potential of rosuvastatin in a HCC model, the possible signaling cues involved, and whether it augments the dasatinib anticancer effect. **METHOD:** For the in-vitro study, the IC50 and the combination (CI)/dose reduction (DRI) indices were determined for HCC cell line (HepG2) treated with dasatinib and/or rosuvastatin. For the in-vivo study, mice with diethylnitrosamine-induced HCC were treated for 21 days with dasatinib and/or rosuvastatin (10 and 20 mg/kg, respectively). The p-focal adhesion kinase/p-pyruvate kinase sarcoma oncogene cellular homolog (p-FAK/p-Src) cascade and its downstream molecules were assessed. **RESULTS:** The in-vitro study confirmed the synergistic effect of rosuvastatin with dasatinib, which entailed the in-vivo results. The two drugs decreased the p-FAK/p-Src cue along with p-Ras/c-Raf, p-STAT-3, and p-Akt levels to enhance apoptosis by an increase in caspase-3 level and a decline in survivin level. Additionally, they inhibited HGF, VEGF, and the MMP-9. Moreover, the different treatments downregulated the expression of proliferative cell nuclear antigen (PCNA) and Ki-67. The best effect was mediated by the combination regimen that surpassed the effect of either drug alone. **CONCLUSION:** Our results highlighted some of the signals involved in rosuvastatin antitumor effect and nominate it as an add-on therapy with dasatinib to yield a better effect in HCC through inhibiting the FAK/Src cascade.

[57] *Jorat MV, Tabrizi R, Mirhosseini N et al. The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Lipids in health and disease 2018; 17:230.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30296936>

ABSTRACT

BACKGROUND: Chronic inflammation and increased oxidative stress significantly contribute to developing coronary artery disease (CAD). Hence, antioxidant supplementation might be an appropriate approach to decrease the incidence of CAD. This systematic review and meta-analysis was aimed to determine the effects of coenzyme Q10 (CoQ10) supplementation on

Literature update week 41 (2018)

lipid profile, as one of the major triggers for CAD, among patients diagnosed with coronary artery disease. METHODS: EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science were searched for studies prior to May 20th, 2018. Cochrane Collaboration risk of bias tool was applied to assess the methodological quality of included trials. I-square and Q-tests were used to measure the existing heterogeneity across included studies. Considering heterogeneity among studies, fixed- or random-effect models were applied to pool standardized mean differences (SMD) as overall effect size. RESULTS: A total of eight trials (267 participants in the intervention group and 259 in placebo group) were included in the current meta-analysis. The findings showed that taking CoQ10 by patients with CAD significantly decreased total-cholesterol (SMD -1.07; 95% CI, - 1.94, - 0.21, P = 0.01) and increased HDL-cholesterol levels (SMD 1.30; 95% CI, 0.20, 2.41, P = 0.02). We found no significant effects of CoQ10 supplementation on LDL-cholesterol (SMD -0.37; 95% CI, - 0.87, 0.13, P = 0.14), lipoprotein (a) [Lp(a)] levels (SMD -1.12; 95% CI, - 2.84, 0.61, P = 0.20) and triglycerides levels (SMD 0.01; 95% CI, - 0.22, 0.24, P = 0.94). CONCLUSIONS: This meta-analysis demonstrated the promising effects of CoQ10 supplementation on lowering lipid levels among patients with CAD, though it did not affect triglycerides, LDL-cholesterol and Lp(a) levels.

[58] Lovett RW. **Absolute cardiovascular disease risk and lipid-lowering therapy among Aboriginal and Torres Strait Islander Australians.** The Medical journal of Australia 2018; 209:368-370.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30309310>

ABSTRACT

[59] Schultz R. **Absolute cardiovascular disease risk and lipid-lowering therapy among Aboriginal and Torres Strait Islander Australians.** The Medical journal of Australia 2018; 209:369.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30309309>

ABSTRACT

[60] Barbar SD, Clere-Jehl R, Bourredjem A et al. **Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis.** The New England journal of medicine 2018; 379:1431-1442.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30304656>

ABSTRACT

BACKGROUND: Acute kidney injury is the most frequent complication in patients with septic shock and is an independent risk factor for death. Although renal-replacement therapy is the standard of care for severe acute kidney injury, the ideal time for initiation remains controversial. METHODS: In a multicenter, randomized, controlled trial, we assigned patients with early-stage septic shock who had severe acute kidney injury at the failure stage of the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification system but without life-threatening complications related to acute kidney injury to receive renal-replacement therapy either within 12 hours after documentation of failure-stage acute kidney injury (early strategy) or after a delay of 48 hours if renal recovery had not occurred (delayed strategy). The failure stage of the RIFLE classification system is characterized by a serum creatinine level 3 times the

Literature update week 41 (2018)

baseline level (or ≥ 4 mg per deciliter with a rapid increase of ≥ 0.5 mg per deciliter), urine output less than 0.3 ml per kilogram of body weight per hour for 24 hours or longer, or anuria for at least 12 hours. The primary outcome was death at 90 days. RESULTS: The trial was stopped early for futility after the second planned interim analysis. A total of 488 patients underwent randomization; there were no significant between-group differences in the characteristics at baseline. Among the 477 patients for whom follow-up data at 90 days were available, 58% of the patients in the early-strategy group (138 of 239 patients) and 54% in the delayed-strategy group (128 of 238 patients) had died ($P=0.38$). In the delayed-strategy group, 38% (93 patients) did not receive renal-replacement therapy. Criteria for emergency renal-replacement therapy were met in 17% of the patients in the delayed-strategy group (41 patients). CONCLUSIONS: Among patients with septic shock who had severe acute kidney injury, there was no significant difference in overall mortality at 90 days between patients who were assigned to an early strategy for the initiation of renal-replacement therapy and those who were assigned to a delayed strategy. (Funded by the French Ministry of Health; IDEAL-ICU ClinicalTrials.gov number, NCT01682590 .).

[61] *Rossidis AC, Stratigis JD, Chadwick AC et al. In utero CRISPR-mediated therapeutic editing of metabolic genes. Nat Med 2018; 24:1513-1518.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30297903>

ABSTRACT

In utero gene editing has the potential to prenatally treat genetic diseases that result in significant morbidity and mortality before or shortly after birth. We assessed the viral vector-mediated delivery of CRISPR-Cas9 or base editor 3 in utero, seeking therapeutic modification of Pcsk9 or Hpd in wild-type mice or the murine model of hereditary tyrosinemia type 1, respectively. We observed long-term postnatal persistence of edited cells in both models, with reduction of plasma PCSK9 and cholesterol levels following in utero Pcsk9 targeting and rescue of the lethal phenotype of hereditary tyrosinemia type 1 following in utero Hpd targeting. The results of this proof-of-concept work demonstrate the possibility of efficiently performing gene editing before birth, pointing to a potential new therapeutic approach for selected congenital genetic disorders.

[62] *Gardiner SL, Harder AVE, Campman YJM et al. Repeat length variations in ATXN1 and AR modify disease expression in Alzheimer's disease. Neurobiology of aging 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30314815>

ABSTRACT

Genomewide association studies (GWASs) have contributed greatly to unraveling the genetic basis of Alzheimer's disease (AD). However, a large amount of "missing heritability" remains. In this exploratory study, we investigated the effect of cytosine-adenine-guanine (CAG) repeats in polyglutamine disease-associated genes (PDAGs) on the risk of AD and its expression. In a cohort of 959 patients diagnosed with AD (Amsterdam Dementia cohort) and 4106 cognitively healthy participants (Leiden 85-plus Study and the Prospective Study of Pravastatin in the Elderly at Risk), we determined the CAG repeat sequences in ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP, HTT, ATN1, and AR. We did not find a significant association between the risk of AD and variations in CAG repeat numbers of PDAGs. However, we found that differences in CAG

Literature update week 41 (2018)

repeat numbers in ATXN1, ATXN2, and AR were significantly associated with several clinical and imaging features in AD patients. Specifically, the association between memory performance in patients with AD and the CAG repeat size in the longer ATXN1 allele, and the association between atrophy in the medial temporal lobes and the CAG repeat number in the longer AR allele remained significant after correction for multiple testing. Our findings suggest that repeat polymorphisms in ATXN1 and AR can act as important genetic modifiers of AD, warranting further scrutiny of their role in its missing heritability and pathogenesis.

[63] *Ruiz-Iruela C, Padro-Miquel A, Pinto-Sala X et al. KIF6 gene as a pharmacogenetic marker for lipid-lowering effect in statin treatment. PLoS one 2018; 13:e0205430.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30304062>

ABSTRACT

INTRODUCTION: The therapeutic response to statins has a high interindividual variability with respect to reductions in plasma LDL-cholesterol (c-LDL) and increases in HDL cholesterol (c-HDL). Many studies suggest that there is a relationship between the rs20455 KIF6 gene variant (c.2155T> C, Trp719Arg) and a lower risk of cardiovascular disease in patients being treated with statins. **AIM:** The aim of this study was to investigate whether or not the c.2155T> C KIF6 gene variant modulates the hypercholesteremic effects of treatment with simvastatin, atorvastatin, or rosuvastatin. **MATERIALS AND METHODS:** This was a prospective, observational and multicenter study. Three hundred and forty-four patients who had not undergone prior lipid-lowering treatment were recruited. Simvastatin, atorvastatin or rosuvastatin were administered. Lipid profiles and multiple clinical and biochemical variables were assessed before and after treatment. **RESULTS:** The c.2155T> C variant of the KIF6 gene was shown to influence physiological responses to treatment with simvastatin and atorvastatin. Patients who were homozygous for the c.2155T> C variant (CC genotype, ArgArg) had a 7.0% smaller reduction of LDL cholesterol levels ($p = 0.015$) in response to hypolipidemic treatment compared to patients with the TT (TrpTrp) or CT (TrpArg) genotype. After pharmacological treatment with rosuvastatin, patients carrying the genetic variant had an increase in c-HDL that was 21.9% lower compared to patients who did not carry the variant ($p = 0.008$). **CONCLUSION:** Being a carrier of the c.2155T> C variant of the KIF6 gene negatively impacts patient responses to simvastatin, atorvastatin or rosuvastatin in terms of lipid lowering effect. Increasing the intensity of hypolipidemic therapy may be advisable for patients who are positive for the c.2155T> C variant.

[64] *Seifert R, Kuhlmann MT, Eligehausen S et al. Molecular imaging of MMP activity discriminates unstable from stable plaque phenotypes in shear-stress induced murine atherosclerosis. PLoS one 2018; 13:e0204305.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30304051>

ABSTRACT

PURPOSE: As atherosclerotic plaque ruptures are the primary cause of ischaemic events, their preventive identification by imaging remains a clinical challenge. Matrix metalloproteinases (MMP) are involved in plaque progression and destabilisation and are therefore promising targets to characterize rupture-prone unstable plaques. This study aims at evaluating MMP imaging to discriminate unstable from stable plaque phenotypes. **METHODS:** ApoE deficient

Literature update week 41 (2018)

mice (ApoE^{-/-}) on a high cholesterol diet underwent implantation of a tapered cuff around the right common carotid artery (CCA) inducing a highly inflamed atherosclerotic plaque upstream (US) and a more stable plaque phenotype downstream (DS) of the cuff. 8 weeks after surgery, the MMP inhibitor-based photoprobe Cy5.5-AF443 was administered i.v. 3h prior to in situ and ex vivo fluorescence reflectance imaging of the CCAs. Thereafter, CCAs were analysed regarding plaque size, presence of macrophages, and MMP-2 and MMP-9 concentrations by immunohistochemistry and ELISA. RESULTS: We found a significantly higher uptake of Cy5.5-AF443 in US as compared to DS plaques in situ (1.29 vs. 1.06 plaque-to-background ratio; $p < 0.001$), which was confirmed by ex vivo measurements. Immunohistochemistry revealed a higher presence of macrophages, MMP-2 and MMP-9 in US compared to DS plaques. Accordingly, MMP-2 concentrations were significantly higher in US plaques (47.2 \pm 7.6 vs. 29.6 \pm 4.6 ng/mg; $p < 0.05$). CONCLUSIONS: In the ApoE^{-/-} cuff model MMP-2 and MMP-9 activities are significantly higher in upstream low shear stress-induced unstable atherosclerotic plaques as compared to downstream more stable plaque phenotypes. MMP inhibitor-based fluorescence molecular imaging allows visualization of these differences in shear stress-induced atherosclerosis.

[65] *Qian H, Luo Z, Xiao C et al. Red cell distribution width in coronary heart disease: prediction of restenosis and its relationship with inflammatory markers and lipids.*

Postgraduate medical journal 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30301834>

ABSTRACT

BACKGROUND: Red cell distribution width (RDW) is associated with a poor prognosis and adverse events in cardiovascular diseases. The aims of this study were to investigate the relationship between serum RDW levels and outcomes after percutaneous coronary intervention and to identify potential novel laboratory markers for evaluating the risk of in-stent restenosis (ISR) with stable angina pectoris. METHODS: A total of 261 patients with coronary heart disease from Dongfeng General Hospital implanted with a coronary drug-eluting stent (DES) were enrolled in the study. We retrospectively analysed the role and prognosis values of serum parameters that were measured before angiography at the first admission. According to the results of the second angiogram, the patients were divided into two groups as follows: the non-ISR group (n=143) and the ISR group (n=118). The clinical characteristics and all laboratory data were considered for univariate and multivariate logistic regression analyses. RESULTS: The white cell count, RDW, neutrophil count, C-reactive protein (CRP), total cholesterol, low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen and uric acid levels were higher in the ISR group than in the non-ISR group. There were no differences in the rates of hypertension, fasting plasma glucose, red cell count, neutrophil to lymphocyte ratio, platelet count, triglyceride, high-density lipoprotein cholesterol and creatinine levels. In the univariate regression analysis, age, diabetes, white cell count, neutrophil count, RDW, CRP, total cholesterol, LDL-C, blood urea nitrogen, Gensini score and number of stents were predictors of ISR. According to the multiple logistic regression analysis, age, RDW and number of stents were independent predictors of ISR. CONCLUSIONS: Preprocedural blood parameters can independently predict ISR. Our study results demonstrated that a high preprocedural RDW is an independent predictor of DES restenosis.

Literature update week 41 (2018)

[66] Akerele OA, Cheema SK. **A diet enriched in longer chain omega-3 fatty acids reduced placental inflammatory cytokines and improved fetal sustainability of C57BL/6 mice.**

Prostaglandins, leukotrienes, and essential fatty acids 2018; 137:43-51.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293596>

ABSTRACT

Omega (n)-3 polyunsaturated fatty acids (PUFA) are important regulators of inflammatory response that may impact pregnancy outcome. The effects of breeding chow diets containing n-3 PUFA from either fish oil (FO) or soybean oil (SO) were investigated on tissue fatty acid composition, inflammatory cytokines and pregnancy outcome. Female C57BL/6 mice (7 weeks old) were fed FO or SO diets for 2 weeks before mating and throughout pregnancy. Animals were sacrificed before and during pregnancy at day 6.5, 12.5 and 18.5. The FO diet increased the incorporation of n-3 PUFA in placenta, with a concomitant decrease in the concentration of pro-inflammatory cytokines. The FO diet increased the mRNA expression of placental specific PUFA transporter, which coincided with accretion of n-3 PUFA in fetal brain. Sites of fetal resorption were noticeable in the SO group but not in the FO group. N-3 PUFA may improve fetal sustainability via altering cytokine levels.

[67] Peres A, Dorneles GP, Boeira MCR et al. **Acute fish oil supplementation modulates the inflammatory response after strenuous exercise in obese men: A cross-over study.**

Prostaglandins, leukotrienes, and essential fatty acids 2018; 137:5-11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293597>

ABSTRACT

AIM: To evaluate the effects of acute fish oil supplementation (FOS) in DNA damage, lymphocyte phenotype and cytokines production after strenuous exercise in obese individuals. METHODS: Sixteen sedentary obese (BMI >30.0 to <35.0kg/m²) men performed two sessions of exhaustive exercise and consumed 2000mg of either placebo or fish oil one hour before the exercise session; trials were separated by 14 days. Peripheral blood mononuclear cells were collected pre, immediately after and 1h after both exercise sessions and stimulated in vitro with 2% phytohemagglutinin for cytokines secretion (IL-6, IL-8, TNF-alpha). Analysis of DNA damage index on total lymphocytes and the peripheral frequency of T helper CD4+ cells, T cytotoxic CD8+ cells, and CD19+ B cells were also performed. RESULTS: FOS prevented the increase in serum cortisol levels and the production of TNF-alpha and IL-8 after strenuous exercise. The DNA damage index decreased 1h after exercise in FOS trial. Moreover, a lymphocytosis, i.e. increases in the frequency of CD4+ and CD8+ T cells was observed immediately after exercise bout in both trials. Moreover, FOS prevented the decrease in CD8+ T cells below to baseline value 1h after strenuous exercise. CONCLUSION: Acute supplementation with fish oil attenuates the proinflammatory cytokine response and diminished the DNA damage after strenuous exercise in obese individuals, suggesting a possible protective effect against the exacerbation of systemic damage induced by exhaustive exercise in obese individuals.

[68] Boozalis T, Devaraj S, Okusaga OO. **Correlations between Body Mass Index, Plasma High-Sensitivity C-Reactive Protein and Lipids in Patients with Schizophrenia.** The Psychiatric quarterly 2018.

Literature update week 41 (2018)

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30315442>

ABSTRACT

High prevalence of obesity in individuals with schizophrenia, associated with metabolic syndrome, leads to high rate of premature deaths from cardiovascular disease (CVD) in this population. Body mass index (BMI) and C-reactive protein (CRP) are correlated in the general population but this relationship has not been fully elucidated in patients with schizophrenia. We aimed to evaluate the correlation between BMI and CRP while relating both variables to plasma lipids in patients with schizophrenia. BMI, fasting high sensitivity CRP (hs-CRP), cotinine, and lipids were measured in 106 patients with schizophrenia (diagnosis confirmed with MINI). Pearson's and partial correlations (adjusting for age, sex, race, education and cotinine) between BMI, hs-CRP and lipids were calculated. Based on BMI, the patients were divided into normal-weight vs. overweight/obese and t-tests and linear regression were done to compare hs-CRP and lipids in the 2 groups. BMI positively correlated with hs-CRP ($r = 0.29$, $p = 0.004$). BMI and hs-CRP negatively correlated with HDL in the total sample ($r = -0.29$, $p = 0.004$; $r = -0.37$, $p < 0.001$ respectively). Furthermore, hs-CRP negatively correlated with HDL in overweight/obese patients ($r = -0.41$, $p = 0.003$), but not in normal-weight patients. hs-CRP and triglycerides were higher (1.62 ± 0.09 mg/L vs. 0.56 ± 0.08 mg/L, $p < 0.001$; 121.77 ± 8.96 mg/dL vs. 91.23 ± 6.52 mg/dL, $p = 0.008$ respectively) and HDL lower (39.55 ± 1.48 mg/dL vs. 50.68 ± 2.24 mg/dL, $p < 0.001$) in overweight/obese patients. Being overweight/obese is associated with increased inflammation and dyslipidemia in patients with schizophrenia. Effective interventions to prevent weight gain in schizophrenia are urgently needed.

[69] *Bello-Chavolla OY, Kuri-Garcia A, Rios-Rios M et al. FAMILIAL COMBINED HYPERLIPIDEMIA: CURRENT KNOWLEDGE, PERSPECTIVES, AND CONTROVERSIES. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion 2018; 70:224-236.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307446>

ABSTRACT

Familial combined hyperlipidemia (FCHL) is the most prevalent primary dyslipidemia; however, it frequently remains undiagnosed and its precise definition is a subject of controversy. FCHL is characterized by fluctuations in serum lipid concentrations and may present as mixed hyperlipidemia, isolated hypercholesterolemia, hypertriglyceridemia, or as a normal serum lipid profile in combination with abnormally elevated levels of apolipoprotein B. FCHL is an oligogenic primary lipid disorder, which can occur due to the interaction of several contributing variants and mutations along with environmental triggers. Controversies surrounding the relevance of identifying FCHL as a cause of isolated hypertriglyceridemia and a differential diagnosis of familial hypertriglyceridemia are offset by the description of associations with USF1 and other genetic traits that are unique for FCHL and that are shared with other conditions with similar pathophysiological mechanisms. Patients with FCHL are at an increased risk of cardiovascular disease and mortality and have a high frequency of comorbidity with other metabolic conditions such as type 2 diabetes, non-alcoholic fatty liver disease, steatohepatitis, and the metabolic syndrome. Management usually requires lipid-lowering therapy directed toward reducing cholesterol and triglyceride concentrations along with cardiovascular risk protection. In recent years, the number of research studies on FCHL has been decreasing, mainly due to a lack of recognition of its impact on disease burden and comorbidity and the

Literature update week 41 (2018)

complexity in identifying probands for studies. This creates areas of opportunity to develop research for FCHL in epidemiology, genetics, pathophysiology, therapeutics, and cardiovascular risk management, which are discussed in depth in this review. (REV INVEST CLIN. 2018;70:224-36).

[70] *Parhofer KG. CONTROVERSIAL ISSUES IN THE TREATMENT OF DYSLIPIDEMIAS IN PATIENTS WITH DIABETES MELLITUS. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion* 2018; 70:237-243.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307445>

ABSTRACT

Patients with diabetes mellitus have an elevated cardiovascular risk. Lipid-lowering therapy is a successful strategy to prevent atherosclerotic events in these patients. Therefore, almost all professional societies recommend statin therapy for patients with diabetes under certain conditions. Despite this broad consensus, a number of controversial issues remain. Thus, it remains unclear in which patients the lipid parameters should be determined in the fasting state and in which postprandial values are sufficient. It is also an open issue whether all patients with diabetes should receive statin therapy and which goals should be achieved. While the benefit of statin-ezetimibe and statin-PCSK9-inhibition combinations has been shown in large outcome trials, results of outcome trials involving statins with triglyceride lowering drugs have been ambiguous. Thus, it is currently unclear which patients benefit from such combinations. Finally, the best strategy to address severe hypertriglyceridemia in patients with diabetes is unclear. This article discusses these issues and aims to provide help and information to practicing physicians taking care of patients with diabetes mellitus. (REV INVEST CLIN. 2018;70:237-43).

[71] *Rivas-Gomez B, Almeda-Valdes P, Tussie-Luna MT, Aguilar-Salinas CA. DYSLIPIDEMIA IN MEXICO, A CALL FOR ACTION. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion* 2018; 70:211-216.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30307444>

ABSTRACT

The purpose of this manuscript is to highlight the peculiarities of the Mexican population regarding the clinical expression, genetics, and treatment of lipid disorders. Furthermore, it is a call for action to address the existing gaps in care and research of dyslipidemias. The Mexican Mestizos are highly susceptible to metabolic disorders (i.e., low high-density lipoprotein cholesterol concentrations, hypertriglyceridemia, abdominal obesity, and type 2 diabetes); these conditions are associated with ethnic-specific genetic variants. On the other hand, despite the high prevalence of dyslipidemia in Mexican adults, there is a lack of awareness of these conditions. The public is not informed about the need for screening and the potential benefit of the lipid-lowering treatments. Underdiagnosis and undertreatment are two of the main challenges to be solved. Dyslipidemias are not among the priorities of the health systems for the prevention of cardiovascular disease; access to laboratory resources and medications is insufficient in primary care units despite the proven cost-benefit of the treatment of lipid disorders. Evidence-based public policies are needed to change the practice and allocation of assets to be capable of preventing cardiovascular diseases. Treatment of dyslipidemia should

Literature update week 41 (2018)

have a prominent role in any effort to decrease the number of preventable deaths caused by non-communicable diseases.

[72] Hemadou A, Laroche-Traineau J, Antoine S et al. **An innovative flow cytometry method to screen human scFv-phages selected by in vivo phage-display in an animal model of atherosclerosis.** *Scientific reports* 2018; 8:15016.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30302027>

ABSTRACT

Atherosclerosis is a chronic, progressive inflammatory disease that may develop into vulnerable lesions leading to thrombosis. This pathology is characterized by the deposition of lipids within the arterial wall and infiltration of immune cells leading to amplification of inflammation. Nowadays there is a rising interest to assess directly the molecular and cellular components that underlie the clinical condition of stroke and myocardial infarction. Single chain fragment variable (scFv)-phages issuing from a human combinatorial library were selected on the lesions induced in a rabbit model of atherosclerosis after three rounds of in vivo phage display. We further implemented a high-throughput flow cytometry method on rabbit protein extracts to individually test one thousand of scFv-phages. Two hundred and nine clones were retrieved on the basis of their specificity for atherosclerotic proteins. Immunohistochemistry assays confirmed the robustness of the designed cytometry protocol. Sequencing of candidates demonstrated their high diversity in VH and VL germline usage. The large number of candidates and their diversity open the way in the discovery of new biomarkers. Here, we successfully showed the capacity of combining in vivo phage display and high-throughput cytometry strategies to give new insights in in vivo targetable up-regulated biomarkers in atherosclerosis.

[73] Mury P, Chirico EN, Mura M et al. **Oxidative Stress and Inflammation, Key Targets of Atherosclerotic Plaque Progression and Vulnerability: Potential Impact of Physical Activity.** *Sports medicine (Auckland, N.Z.)* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30302720>

ABSTRACT

Atherosclerosis, a complex cardiovascular disease, is a leading cause of mortality and morbidity worldwide. Oxidative stress and inflammation are both involved in the development of atherosclerotic plaque as they increase the biological processes associated with this pathology, such as endothelial dysfunction and macrophage recruitment and adhesion. Atherosclerotic plaque rupture leading to major ischemic events is the result of vulnerable plaque progression, which is a result of the detrimental effect of oxidative stress and inflammation on risk factors for atherosclerotic plaque rupture, such as intraplaque hemorrhage, neovascularization, and fibrous cap thickness. Thus, both are key targets for primary and secondary interventions. It is well recognized that chronic physical activity attenuates oxidative stress in healthy subjects via the improvement of antioxidant enzyme capacities and inflammation via the enhancement of anti-inflammatory molecules. Moreover, it was recently shown that chronic physical activity could decrease oxidative stress and inflammation in atherosclerotic patients. The aim of this review is to summarize the role of oxidative stress and inflammation in atherosclerosis and the results of therapeutic interventions targeting them in both preclinical and clinical studies. The

Literature update week 41 (2018)

effects of chronic physical activity on these two key processes are then reviewed in vulnerable atherosclerotic plaques in both coronary and carotid arteries.

[74] *Ibrahim JG, Kim S, Chen MH et al. Bayesian multivariate skew meta-regression models for individual patient data. Statistical methods in medical research 2018:962280218801147.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30309294>

ABSTRACT

We examine a class of multivariate meta-regression models in the presence of individual patient data. The methodology is well motivated from several studies of cholesterol-lowering drugs where the goal is to jointly analyze the multivariate outcomes, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides. These three continuous outcome measures are correlated and shed much light on a subject's lipid status. One of the main goals in lipid research is the joint analysis of these three outcome measures in a meta-regression setting. Since these outcome measures are not typically multivariate normal, one must consider classes of distributions that allow for skewness in one or more of the outcomes. In this paper, we consider a new general class of multivariate skew distributions for multivariate meta-regression and examine their theoretical properties. Using these distributions, we construct a Bayesian model for the meta-data and develop an efficient Markov chain Monte Carlo computational scheme for carrying out the computations. In addition, we develop a multivariate L measure for model comparison, Bayesian residuals for model assessment, and a Bayesian procedure for detecting outlying trials. The proposed multivariate L measure, Bayesian residuals, and Bayesian outlying trial detection procedure are particularly suitable and computationally attractive in the multivariate meta-regression setting. A detailed case study demonstrating the usefulness of the proposed methodology is carried out in an individual patient data multivariate meta-regression setting using 26 pivotal Merck clinical trials that compare statins (cholesterol-lowering drugs) in combination with ezetimibe and statins alone on treatment-naïve patients and those continuing on statins at baseline.

[75] *Sbrana F, Bigazzi F, Dal Pino B et al. Elusive therapeutic effect of PCSK9 inhibitors on lipoprotein(a) levels? Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30311368>

ABSTRACT

Lipoprotein (a) [Lp(a)] is a prevalent genetic risk factor for coronary artery disease [1] and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have demonstrated significant Lp(a)-lowering effects [2, 3]. This article is protected by copyright. All rights reserved.

[76] *Pierantonelli I, Svegliati-Baroni G. Nonalcoholic fatty liver disease: basic pathogenetic mechanisms in the progression from NAFLD to NASH. Transplantation 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30300287>

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) represents a growing cause of chronic liver injury, especially in Western Countries, where it is becoming the most frequent indication for liver

Literature update week 41 (2018)

transplantation (OLTx). NAFLD encompasses a spectrum of diseases that from simple steatosis (pure NAFLD) can progress to Nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC). The pathogenesis of NAFLD and the mechanisms behind its progression to NASH have been extensively studied. However, while the processes that determine fat accumulation are mostly clear, the mechanisms associated with the progression of the disease are not fully characterized. In predisposed patients, lipid accumulation can promote lipotoxicity and mitochondrial dysfunction, thus triggering hepatocyte death, inflammation and fibrosis. The specific role of different lipids has been identified and free fatty acids as well as free cholesterol have been identified as toxic species. To make the picture more complex, the pathogenesis of NAFLD involves pathological connections between several organs, including the adipose tissue and the gut, with the liver. The "inflamed" adipose tissue plays a key role in the release of toxic lipids, while alterations in the gut-liver axis have been associated with the progression from NAFLD to NASH mediated by dysbiosis, alteration of intestinal barrier, and finally bacterial translocation, that can trigger proinflammatory and profibrogenetic pathways, finally leading to cirrhosis development.

[77] *Hu MB, Zhang JW, Gao JB et al. Atorvastatin induces autophagy in MDA-MB-231 breast cancer cells. Ultrastructural pathology 2018:1-7.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30300062>

ABSTRACT

This article explores the effects of atorvastatin on cultured breast cancer cells. Our experiment demonstrated that atorvastatin triggered autophagy and inhibited proliferation in breast cancer cells. A CCK8 assay indicated that atorvastatin can inhibit the activity of MDA-MB-231 breast cancer cells. Western blotting results showed that atorvastatin increased the conversion of light chain 3 (LC3)-I to LC3-phosphatidylethanolamine conjugate (LC3-II). Confocal microscopy was used to reveal the appearance of a punctate structure in the cytoplasm, and electron microscopy was used to reveal the formation of double-membrane autophagosome. In conclusion, our study showed that atorvastatin may affect MDA-MB-231 breast cancer cells by inducing autophagy.

[78] *Peng R, Wang F, Cong XF. [Mechanisms and pathophysiological significance of endothelial injury on superficial erosion of atherosclerotic plaque]. Zhonghua xin xue guan bing za zhi 2018; 46:740-744.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30293384>

ABSTRACT