

Literature update week 19 (2019)

[1] Ben-Omran T, Masana L, Kolovou G et al. **Real-World Outcomes with Lomitapide Use in Paediatric Patients with Homozygous Familial Hypercholesterolaemia.** *Adv Ther* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31102204>

ABSTRACT

INTRODUCTION: Homozygous familial hypercholesterolaemia (HoFH) is a rare, autosomal disease affecting the clearance of low-density lipoprotein cholesterol (LDL-C) from circulation, and leading to early-onset atherosclerotic cardiovascular disease (ASCVD). Treatment consists mainly of statins, lipoprotein apheresis (LA) and, more recently, the microsomal triglyceride transfer protein inhibitor lomitapide. Lomitapide is not licensed for use in children, but has been made available through an expanded access programme or on a named patient basis. **METHODS:** This case series includes 11 HoFH patients in 10 different centres in eight countries, less than 18 years of age (mean 11.6 +/- 1.1 years, 64% male), with signs of ASCVD, and who have received treatment with lomitapide (mean dose 24.5 +/- 4.3 mg/day; mean exposure 20.0 +/- 2.9 months). Background lipid-lowering therapy was given according to local protocols. Lomitapide was commenced with a stepwise dose escalation from 2.5 mg or 5 mg/day; dietary advice and vitamin supplements were provided as per the product label for adults. Laboratory analysis was conducted as part of regular clinical care. **RESULTS:** In the 11 cases, mean baseline LDL-C was 419 +/- 74.6 mg/dL and was markedly reduced by lomitapide to a nadir of 176.7 +/- 46.3 mg/dL (58.4 +/- 6.8% decrease). Six patients achieved recommended target levels for children below 135 mg/dL, five of whom had LA frequency reduced. In one case, LDL-C levels were close to target when lomitapide was started but remained stable despite 75% reduction in LA frequency (from twice weekly to biweekly). Adverse events were mainly gastrointestinal in nature, occurred early in the treatment course and were well managed. Three patients with excursions in liver function tests were managed chiefly without intervention; two patients had decreases in lomitapide dose. **CONCLUSIONS:** Lomitapide demonstrated promising effectiveness in paediatric HoFH patients. Adverse events were manageable, and the clinical profile of the drug is apparently similar to that in adult patients. **FUNDING:** Amryt Pharma.

[2] Button EB, Boyce GK, Wilkinson A et al. **ApoA-I deficiency increases cortical amyloid deposition, cerebral amyloid angiopathy, cortical and hippocampal astroglia, and amyloid-associated astrocyte reactivity in APP/PS1 mice.** *Alzheimer's research & therapy* 2019; 11:44.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31084613>

ABSTRACT

BACKGROUND: Alzheimer's disease (AD) is defined by amyloid beta (Abeta) plaques and neurofibrillary tangles and characterized by neurodegeneration and memory loss. The majority of AD patients also have Abeta deposition in cerebral vessels known as cerebral amyloid angiopathy (CAA), microhemorrhages, and vascular co-morbidities, suggesting that cerebrovascular dysfunction contributes to AD etiology. Promoting cerebrovascular resilience may therefore be a promising therapeutic or preventative strategy for AD. Plasma high-density lipoproteins (HDL) have several vasoprotective functions and are associated with reduced AD risk in some epidemiological studies and with reduced Abeta deposition and Abeta-induced inflammation in 3D engineered human cerebral vessels. In mice, deficiency of apoA-I, the primary protein component of HDL, increases CAA and cognitive dysfunction, whereas overexpression of apoA-I from its native promoter in liver and intestine has the opposite effect

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and lessens neuroinflammation. Similarly, acute peripheral administration of HDL reduces soluble Abeta pools in the brain and some studies have observed reduced CAA as well. Here, we expand upon the known effects of plasma HDL in mouse models and in vitro 3D artery models to investigate the interaction of amyloid, astrocytes, and HDL on the cerebrovasculature in APP/PS1 mice. **METHODS:** APP/PS1 mice deficient or hemizygous for *Apoa1* were aged to 12 months. Plasma lipids, amyloid plaque deposition, Abeta protein levels, protein and mRNA markers of neuroinflammation, and astrogliosis were assessed using ELISA, qRT-PCR, and immunofluorescence. Contextual and cued fear conditioning were used to assess behavior. **RESULTS:** In APP/PS1 mice, complete apoA-I deficiency increased total and vascular Abeta deposition in the cortex but not the hippocampus compared to APP/PS1 littermate controls hemizygous for apoA-I. Markers of both general and vascular neuroinflammation, including *Il1b* mRNA, ICAM-1 protein, PDGFRbeta protein, and GFAP protein, were elevated in apoA-I-deficient APP/PS1 mice. Additionally, apoA-I-deficient APP/PS1 mice had elevated levels of vascular-associated ICAM-1 in the cortex and hippocampus and vascular-associated GFAP in the cortex. A striking observation was that astrocytes associated with cerebral vessels laden with Abeta or associated with Abeta plaques showed increased reactivity in APP/PS1 mice lacking apoA-I. No behavioral changes were observed. **CONCLUSIONS:** ApoA-I-containing HDL can reduce amyloid pathology and astrocyte reactivity to parenchymal and vascular amyloid in APP/PS1 mice.

[3] *Mohamed MFH, Salameh OK, Saeed AAM. Statin-Induced Rhabdomyolysis, Acute Kidney Injury, and Hepatitis Leading to Death. Am J Case Rep 2019; 20:709-712.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31101801>

ABSTRACT

BACKGROUND Statins are effective in reducing cardiovascular morbidity and mortality, and are generally safe, but can rarely result in devastating adverse effects. With the increasing indications and prescriptions of statins, rare adverse effects are more likely to be seen and reported. Unfortunately, there are no accurate predictive tools to estimate the risk of developing these adverse effects. Post-marketing surveillance helps in collecting data on adverse effects and assists in developing better prognostic tools that can help physicians make better therapeutic decisions. **CASE REPORT** A 67-year-old man was admitted to our hospital with generalized body aches, muscle weakness, jaundice, dark urine, and decreased urine output. He was started on atorvastatin 4 months prior to presentation after having an episode of myocardial infarction, and he was diagnosed as having statin-induced hepatitis, rhabdomyolysis, and acute kidney injury. A basic workup excluded other possible causes. The patient, unfortunately, died of unknown causes on day 6 after admission, and an autopsy was not performed. **CONCLUSIONS** Statins are effective and safe but can result in rare and dangerous adverse effects. Physicians should counsel their patients on proper identification and timely reporting of such adverse effects. Physicians also should be encouraged to report any adverse drug reactions and help in promoting post-marketing surveillance studies. The present case is an excellent example of the importance of these studies, especially for commonly-used drugs.

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[4] Zhang LS, Zhang JH, Feng R et al. **Efficacy and Safety of Berberine Alone or Combined with Statins for the Treatment of Hyperlipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials.** The American journal of Chinese medicine 2019:1-17.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31094214>

ABSTRACT

To systematically evaluate the efficacy and safety of berberine for the treatment of hyperlipidemia, six electronic literature databases including SinoMed, CNKI, WanFang Data, PubMed, Embase and The Cochrane Library were searched to collect clinical randomized controlled trials (RCTs) of berberine alone or combined with statins for the treatment of hyperlipidemia from the inception to 8 March 2018. Two reviewers independently screened literature, extracted data and assessed the risk of bias of included RCTs. Then, meta-analysis was performed by using RevMan 5.3 software. A total of 11 RCTs involving 1386 patients were finally included. The results of meta-analysis showed that compared with the placebo group, berberine could significantly reduce the total cholesterol and low-density lipoprotein levels and elevate the high density lipoprotein level ($P < 0.05$). Compared with the simvastatin group, berberine was effective only in reducing the level of triglyceride (MD=-0.37 , 95% CI: - 0.66, - 0.07, $P=0.02$). There, however, was no statistical significance between the BBR group and simvastatin group in the low density lipoprotein and high density lipoprotein levels. Compared with the simvastatin group, berberine plus simvastatin was more effective in reducing the level of triglyceride (MD=-0.33 , 95% CI: - 0.46, - 0.20, $P < 0.00001$) and total cholesterol (MD=-0.36 , 95% CI: - 0.60, - 0.12, $P=0.003$). In terms of adverse reactions, the incidence of adverse reactions including transaminase elevation and muscle aches was lower in the berberine alone or combined with simvastatin group than that in the control group, while the instance of constipation was higher. This study suggests that berberine is effective for hyperlipidemia. The quality and quantity of included studies, however, were dissatisfactory, which might decrease the reliability of the results. Higher quality studies are needed to provide more high quality evidence.

[5] Weghuber D, Barrientos-Perez M, Kovarenko M. **Youth-Onset Type 2 Diabetes Manifestations in other Specialties: Its Many Disguises.** Annals of nutrition & metabolism 2019; 74:339-347.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31096219>

ABSTRACT

BACKGROUND: Youth-onset type 2 diabetes (T2D) is increasing in many countries, creating large personal and societal burdens. While many primary health-care professionals (HCPs) are aware of the classic symptoms of T2D, there are several other manifestations that could indicate its presence. SUMMARY: This narrative review summarizes information on these symptoms and indicators, focusing on those less well known. The classic symptoms and comorbidities include frequent urination, excessive thirst, metabolic syndrome, and obesity. In addition to these, the presence of dermatological (e.g., acanthosis nigricans, granuloma annulare, necrobiosis lipoidica diabetorum, and scleredema), gynecological (e.g., polycystic ovary syndrome, oligomenorrhea, and vulvovaginitis), hepatological (e.g., nonalcoholic fatty liver disease), and psychiatric diseases (e.g., psychosis, depression, and autism) could indicate that a patient has T2D or is at increased risk of T2D. Other less well-known indicators include

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abnormal blood tests (e.g., oxidized lipids, inflammation markers, hepatokines, and adipokines), prescriptions for antipsychotic medications or statins, and disrupted sleep patterns. Key Message: Due to the diversity of T2D manifestations in young people, primary HCPs need to remain alert to its possible presence.

[6] *Ahmed T, Archie SR, Faruk A et al. Evaluation of the anti-inflammatory activities of diclofenac sodium, prednisolone and atorvastatin in combination with ascorbic acid. Anti-inflammatory & anti-allergy agents in medicinal chemistry 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31084596>

ABSTRACT

OBJECTIVES: Inflammation is our body's normal defense mechanism, but in some cases, it may be responsible for causing different kinds of disorders. Several anti-inflammatory drugs are present for the ailment of these disorders; however, the conventional anti-inflammatory drugs give side effects when used in long term and therefore it is better to use them in a low dose for a shorter duration of time. This study was designed to find out whether there is an augmentation of the therapeutic effectiveness of the anti-inflammatory drugs like diclofenac sodium (NSAID), prednisolone (steroid) and atorvastatin (statin) when in combination with ascorbic acid (antioxidant). **METHODS:** Wistar Rats (n=144) were selected and divided into 24 groups of 6 rats in each. Carrageenan and formalin were used to induce local inflammation and neuropsychiatric effects respectively. The inhibitions of such responses were measured after administering a drug alone and in combination with ascorbic acid. **RESULTS:** In case of carrageenan mediated inflammation, the combination of 5 mg/kg diclofenac and 200 mg/kg ascorbic acid gave the highest inhibition of 74.19% compared to other groups of drugs. The combination of 5 mg/kg diclofenac and 200 mg/kg ascorbic acid gave 97.25% inhibition for formalin mediated inflammation group. In both cases, combination therapy showed statistically significant anti-inflammatory activities compared to mono therapy (p values <0.05). **CONCLUSION:** All the data clearly indicate new combinations of drug therapy comprising of diclofenac sodium, prednisolone, atorvastatin with ascorbic acid, which may be more effective against both local edema and neuropsychiatric effect caused due to inflammation.

[7] *Perez de Isla L, Ray KK, Watts GF et al. Potential utility of the SAFEHEART risk equation for rationalising the use of PCSK9 monoclonal antibodies in adults with heterozygous familial hypercholesterolemia. Atherosclerosis 2019; 286:40-45.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31100618>

ABSTRACT

BACKGROUND AND AIMS: Patients with familial hypercholesterolaemia (FH) may require proprotein convertase subtilisin/kexin-type 9 (PCSK9) mAb as add-on therapy to achieve LDL-cholesterol (LDL-C) goals. However, the current cost of these therapies means that choosing suitable patients is based on consensus or clinical judgement rather than a quantitative risk assessment. We used the SAFEHEART Risk Equation (RE) to estimate the number needed to treat (NNT) at different risk thresholds and baseline LDL-C to identify those FH patients more likely to derive the greatest benefit from PCSK9 mAb. **METHODS:** Five-year event rates were calculated using the SAFEHEART-RE for every patient, overall and across LDL-C strata. A 60% reduction of LDL-C after theoretical treatment with PCSK9 mAb was assumed. Individual

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absolute risk simulating the effects of PCSK9 inhibition was calculated using the SAFEHEART-RE and, in a similar way, by using the Cholesterol Treatment Trialists' (CTT) Collaboration criteria. Absolute risk reduction and NNTs were calculated. RESULTS: Of the total SAFEHEART population, 2,153 were FH cases aged 18 years or older, on maximum tolerated lipid lowering treatment. NNTs were dependent of both baseline predicted risk and baseline LDL-C level ranging from 44 to 17 for those with 5-year risk of ≥ 1 to ≥ 5 . The smallest NNT (12) was observed among those with 5-year risk of $\geq 5\%$ and LDL-C ≥ 160 mg/dl. Using the CTT criteria produced similar results. CONCLUSIONS: The SAFEHEART-RE may provide a useful quantitative tool for rationalising the selection of FH patients who might derive greater absolute benefits from PCSK9 mAb.

[8] Matsuo Y, Suematsu Y, Idemoto Y et al. **Changes in the function of angiotensin II type 1 receptor due to cholesterol depletion from cell membrane.** Biochem Biophys Res Commun 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31079923>

ABSTRACT

Blockers of G-protein coupled receptors (GPCRs), angiotensin II (Ang II) type 1 (AT1) receptor and beta1-adrenergic (Ad) receptor, have been shown to improve the prognosis of cardiovascular disease. Cholesterol molecules in the cell membrane are needed to stabilize GPCRs as well as the cell membrane itself. We determined whether the functions of AT1 and beta1-Ad receptors were changed by cholesterol depletion from cardiovascular cell membranes. Ang II-induced inositol phosphate production through AT1 receptor was suppressed by cholesterol depletion from cell membranes using rosuvastatin or methyl-beta-cyclodextrin (MbetaCD), whereas isoproterenol-induced cyclic AMP production through beta1-Ad receptor did not change after cholesterol depletion. In addition, the binding affinities of Ang II and AT1 receptor blocker after cholesterol depletion were significantly lower than those before depletion. Although AT1 receptor expression levels did not change after cholesterol depletion, the expression levels of AT1 receptor that could bind to Ang II significantly decreased after depletion. The changes in the structure of AT1 receptor due to depletion were confirmed by substituted-cysteine accessibility mapping. In conclusion, Ang II-induced activation of AT1 receptor is reduced without affecting the function of beta1-Ad receptor after cholesterol depletion from cardiovascular cell membranes.

[9] Feng YL, Chen H, Chen DQ et al. **Activated NF-kappaB/Nrf2 and Wnt/beta-catenin pathways are associated with lipid metabolism in CKD patients with microalbuminuria and macroalbuminuria.** Biochimica et biophysica acta. Molecular basis of disease 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31102786>

ABSTRACT

Early detection of CKD patients at risk for micro- or macroalbuminuria facilitates prevention and treatment. We aimed to discover plasma lipids that predict the development of micro- or macroalbuminuria. A total of 380 healthy controls and 1156 patients with CKD stages 3 to 5 were stratified by urine albumin-creatinine ratio as microalbuminuria (30-300mg/g) and macroalbuminuria (>300 mg/g). Fasting plasma samples were determined by UPLC-HDMS-lipidomics. Quantitative real-time RT-PCR, Western blot and immunohistochemical analyses

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were used for validating the lipid metabolism-associated pathway. Pathway analysis demonstrated that these lipids are associated with PPARgamma, inflammatory mediator regulation of TRP channels and RAS signaling, which consistent with activated NF-kappaB and Nrf2 pathways. Pathway validation demonstrated that macroalbuminuria patients showed activation of NF-kappaB and up-regulation of inflammatory and oxidant mRNA and protein expression and down-regulation of Nrf2-associated anti-oxidant gene mRNA and protein expression, accompanied by activated Wnt/beta-catenin signaling pathway compared to microalbuminuria patients. Four lipids DTA, 5,8-TDA, GGD3 and DHA is selected by logistic regression analysis and they robustly distinguished microalbuminuria patients from healthy controls with high sensitivity and specificity. Six lipid species CDCA, glucosylceramide, GGD2, TTA, DHA and EDA is selected by logistic lasso regression and they discriminate between CKD patients with microalbuminuria and macroalbuminuria. Gangliosides are first identified and they might be considered as therapeutic targets for CKD patients with the different degree of albuminuria. This study first demonstrates the association of plasma inflammation, oxidative stress, Wnt/beta-catenin and lipid metabolism in CKD patients with microalbuminuria and macroalbuminuria.

[10] *Montgomery MK. Mitochondrial Dysfunction and Diabetes: Is Mitochondrial Transfer a Friend or Foe? Biology* 2019; 8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31083560>

ABSTRACT

Obesity, insulin resistance and type 2 diabetes are accompanied by a variety of systemic and tissue-specific metabolic defects, including inflammation, oxidative and endoplasmic reticulum stress, lipotoxicity, and mitochondrial dysfunction. Over the past 30 years, association studies and genetic manipulations, as well as lifestyle and pharmacological intervention studies, have reported contrasting findings on the presence or physiological importance of mitochondrial dysfunction in the context of obesity and insulin resistance. It is still unclear if targeting mitochondrial function is a feasible therapeutic approach for the treatment of insulin resistance and glucose homeostasis. Interestingly, recent studies suggest that intact mitochondria, mitochondrial DNA, or other mitochondrial factors (proteins, lipids, miRNA) are found in the circulation, and that metabolic tissues secrete exosomes containing mitochondrial cargo. While this phenomenon has been investigated primarily in the context of cancer and a variety of inflammatory states, little is known about the importance of exosomal mitochondrial transfer in obesity and diabetes. We will discuss recent evidence suggesting that (1) tissues with mitochondrial dysfunction shed their mitochondria within exosomes, and that these exosomes impair the recipient's cell metabolic status, and that on the other hand, (2) physiologically healthy tissues can shed mitochondria to improve the metabolic status of recipient cells. In this context the determination of whether mitochondrial transfer in obesity and diabetes is a friend or foe requires further studies.

[11] *Li YR, Ro V, Steel L et al. Impact of long-term lipid-lowering therapy on clinical outcomes in breast cancer. Breast cancer research and treatment* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31087198>

ABSTRACT

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INTRODUCTION: The use of statins has been associated with improved survival in patients with breast cancer in several studies but results have been mixed. This study evaluates the impact of duration of statin use on breast cancer patient outcomes. **METHODS:** This is a single-institution, retrospective cohort, examining the impact of statin use on the outcomes of 1523 women diagnosed with operable breast cancer between 1995 and 2015. Clinical variables were compared using Student's t test, Fisher's exact and Chi square tests. Overall (OS) and disease-free (DFS) survival were performed using Kaplan-Meier and Cox-Proportional Hazard (Cox-PH) analysis in the statistical software R. **RESULTS:** Patients were grouped by duration of statin use: never-statin user [N] (n = 1092), short (< 3 years) [S] (n = 115), moderate [M] (3-5 years) (n = 109) and long [L] (> 5 years) (n = 207) term. Over a median follow-up of 70.2 months, 138 women died (84 died of breast cancer) and 125 had disease recurrence. On multivariable Cox-PH analysis adjusting for clinical variables including metabolic comorbidities using the Charlson comorbidity index, OS in the [S] and [M] subgroups did not differ [N], while OS was improved in [L] (adjusted hazard ratio (AHR) 0.38, confidence interval (CI) 0.17-0.85, $p < 0.018$). DFS was also significantly improved in the [L] subgroup (adjusted HR 0.15, CI 0.05-0.48, $p < 0.001$). Subanalysis stratified by receptor status showed a trend towards improved DFS in all tumor subtypes including triple-negative breast cancer. **CONCLUSIONS:** Our retrospective analyses suggest that long-term statin use (> 5 years) was associated with improved OS and DFS in women with breast cancer regardless of receptor subtype, even after adjusting for metabolic comorbidities.

[12] *Hougaard M, Hansen HS, Thyssen P et al. Influence of ezetimibe on plaque morphology in patients with ST Elevation Myocardial Infarction assessed by Optical Coherence Tomography: An OCTIVUS sub-study. Cardiovascular revascularization medicine : including molecular interventions* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31097383>

ABSTRACT

AIMS: The aim of the trial was to examine the influence of ezetimibe on plaque morphology in patients with ST-segment Elevation Myocardial Infarction (STEMI) with respect to fibrous cap thickness (FCT) and arcs of lipid plaque, calcific plaque, and macrophages using Optical Coherence Tomography (OCT). **METHODS AND RESULTS:** In 87 statin naive patients with STEMI treated with primary percutaneous intervention, a non-culprit study plaque in a non-infarct related coronary artery was assessed with OCT at baseline and after 12 months. Patients were treated with atorvastatin 80mg and randomized (1:1) to ezetimibe 10mg (n=43) or placebo (n=44). An increase in median FCT (ezetimibe 200 (140-260) μm to 240 (190-305) μm ($p=0.002$) vs. placebo 205 (135-260) μm to 230 (180-270) μm ($p<0.001$), between groups $p=ns$), a reduction in lipid arc (ezetimibe 1728.5 (1022.5-3904.7) degrees to 1164.5 (736.6-2580.1) degrees ($p=0.001$) vs. placebo 1671.6 (978.3-2868.7) degrees to 1373.7 (791.2-2267.3) degrees ($p=0.019$), between groups $p=ns$), and macrophage arc (ezetimibe 1730.3 (965.7-2984.4) degrees to 1324.8 (819.0-2819.7) degrees ($p<0.05$) vs. placebo 1570.5 (794.7-3016.8) degrees to 1418.9 (584.1-2501.1) degrees ($p<0.01$), between groups $p=ns$) were observed. **CONCLUSION:** Aggressive LDL-lowering resulted in changes in OCT assessed plaque composition by increased FCT thickness and a reduction in lipid content and macrophage infiltration.

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Addition of ezetimibe 10mg to atorvastatin 80mg resulted in further LDL reduction, but no additional change in plaque composition was found.

[13] *Nakajima K, Tokita Y, Tanaka A, Takahashi S. The VLDL receptor plays a key role in the metabolism of postprandial remnant lipoproteins. Clinica chimica acta; international journal of clinical chemistry* 2019; 495:382-393.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31078566>

ABSTRACT

A new concept to account for the process of postprandial remnant lipoprotein metabolism is proposed based on the characteristics of lipoprotein particles and their receptors. The characteristics of remnant lipoprotein (RLP) were investigated using an immuno-separation method. The majority of the postprandial lipoproteins increased after fat intake was shown to be VLDL remnants, not chylomicron (CM) remnants, based on the significantly high ratio of apoB100/apoB48 in the RLP and the high degree of similarity in the particle size of the apoB48 and apoB100 carrying lipoproteins, which fluctuate in parallel during a 6h period after fat intake. The VLDL receptor was discovered as a receptor for TG-rich lipoprotein metabolism and is located in peripheral tissues such as skeletal muscle, adipose tissue, etc., but not in the liver. Postprandial VLDL particles are strongly bound and internalized into cells expressing the VLDL receptor. Ligands that bind to VLDL receptor, such as LPL and Lp(a), present in RLP. The presence of various specific ligands in VLDL remnants may enhance the capacity for binding to the VLDL receptor, which play the role primarily for energy delivery to the peripheral tissues, but is also a causal factor in atherogenic diseases when excessively and/or continuously remained in plasma.

[14] *Billington S, Shoner S, Lee S et al. PET Imaging of [(11) C]Rosuvastatin Hepatic Concentrations and Hepatobiliary Transport in Humans in the Absence and Presence of Cyclosporine A. Clinical pharmacology and therapeutics* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31102467>

ABSTRACT

Using positron emission tomography (PET) imaging, we determined the hepatic concentrations and hepatobiliary transport of [(11) C]rosuvastatin (IV injection) in the absence (n=6) and presence (n=4 of 6) of cyclosporine A (CsA, IV infusion) following a therapeutic dose of unlabeled rosuvastatin (RSV) (5 mg, PO) in healthy human volunteers. The sinusoidal uptake, sinusoidal efflux and biliary efflux clearance (mL/min) of [(11) C]rosuvastatin, estimated through compartment modeling were 1205.6+/-384.8, 16.2+/-11.2 and 5.1+/-1.8, respectively (n=6). CsA (blood concentration: 2.77+/-0.24 μ M), an organic-anion-transporting polypeptide (OATP), Na(+)-taurocholate cotransporting polypeptide (NTCP) and breast cancer resistance protein (BCRP) inhibitor increased [(11) C]rosuvastatin systemic blood exposure (45%, p<0.05), reduced its biliary efflux clearance (52%, p<0.05) and hepatic uptake (25%, p>0.05) but didn't affect its distribution into the kidneys. CsA increased plasma concentrations of coproporphyrin I and III and total bilirubin by 297+/-69%, 384+/-102% and 81+/-39%, respectively (p<0.05). These data can be used in the future to verify predictions of hepatic concentrations and hepatobiliary transport of rosuvastatin. This article is protected by copyright. All rights reserved.

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[15] *Otani N, Wakuda H, Imai H et al. No Effect of Digoxin on Rosuvastatin Pharmacokinetics in Healthy Subjects: Utility of Oita Combination for Clinical Drug-Drug Interaction Study.*

Clinical and translational science 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31095880>

ABSTRACT

This study evaluated the utility of combination of digoxin (0.25 mg) and rosuvastatin (5 mg) as a new transporter (P-gp/BCRP/OATP1B1/OATP1B3) probe cocktail (Oita combination) for drug-drug interaction (DDI) studies by demonstrating lack of DDI of digoxin on the pharmacokinetics (PK) of rosuvastatin as it was already known rosuvastatin did not affect digoxin PK. This was an open-label, two-period study in which the primary endpoints were the geometric mean ratio (GMR) of the area under the plasma rosuvastatin concentration-time curve from time zero to last (AUClast) after rosuvastatin administration combined with digoxin to that after rosuvastatin administration alone and its 90% confidence interval (CI). As the GMR of AUClast was 0.974 and its 90% CI was 0.911-1.042, it was judged that digoxin does not affect rosuvastatin PK. Results of this study have rationalized utility of the Oita combination as a transporter probe cocktail for clinical DDI studies. This article is protected by copyright. All rights reserved.

[16] *Juan Jose G, Jorge E, Lujan F et al. Type 2 diabetes: Prescription patterns and treatment outcomes of IDMPS survey in Argentina.* *Diabetes Res Clin Pract* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31102686>

ABSTRACT

AIM: To assess prescription patterns for treatment of type 2 diabetes (T2D) and their outcomes in the IDMPS survey in Argentina. METHODS: Data from 2551 people with T2D recruited from 210 physicians participating in IDMPS surveys in Argentina (2006 to 2012 waves) were recorded, including medical history, medications, glycemic control, blood pressure, and lipid status. RESULTS: Most people were treated with oral glucose-lowering drugs (OGLDs) (65%), followed by combinations of these drugs plus insulin (22%) and only insulin (13%). These percentages varied according to T2D duration, the frequency of OGLDs decreasing while contrastingly and only insulin increasing (under 5 years versus over 10 years of disease duration, respectively). Average systolic blood pressure (SBP), HbA1c and LDL-c were significantly higher in patients treated with insulin either alone or associated with OGLDs. The percentage of people at target values for these parameters was also lower in these two groups. The percentage of people that reached simultaneous goal treatment values for BP, HbA1c and LDL-c levels was markedly low. CONCLUSION: Prescription patterns for treatment of T2D follows a chronological trend and the percentage of people at goal values (HbA1c, BP and LDL-c values) was significantly lower in people receiving insulin. These data must be carefully considered by health and academic authorities in order to implement effective strategies to modify this situation.

[17] *Eliasson B, Ekelund J, Amberntsson R et al. Cardiovascular Disease in Patients with Type 2 Diabetes and in Patients Starting Empagliflozin Treatment: Nationwide Survey.* *Diabetes Ther* 2019.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31089969>

ABSTRACT

INTRODUCTION: Were the participants of the EMPA-REG OUTCOME trial representative of patients receiving empagliflozin in clinical practice? The aim of the present study was to examine the prevalence of cardiovascular disease (CVD) in type 2 diabetes patients starting empagliflozin treatment in routine clinical practice in Sweden. **METHODS:** We used nationwide data from the Swedish National Diabetes Register (NDR), the Swedish Prescribed Drug Register, and the Swedish National Patient Register to provide clinical characteristics and ongoing treatments. **RESULTS:** The total study cohort included 460,558 patients, of whom 130,508 (28.3%) had a history of CVD. The number of patients starting empagliflozin during the study period was 16,985. Among these, 1952 (11.5%) had a history of CVD. The patients starting empagliflozin were younger than the total cohort and were more likely to have retinopathy despite having a similar duration of diabetes to the overall cohort. They also exhibited higher BMI, HbA1c, and eGFR, and were more likely to be treated with insulin and lipid-lowering and blood-pressure-lowering medications. The patients with CVD who were starting empagliflozin were slightly older and had been diabetic for slightly longer than the patients without CVD who were starting empagliflozin, but they also had lower eGFR. Among the patients with CVD who were starting empagliflozin, 87% had coronary heart disease, 8% had suffered a stroke, 13% had peripheral artery disease, 16% had atrial fibrillation, and 20% had congestive heart failure. **CONCLUSION:** The prevalence of CVD in patients with type 2 diabetes in clinical practice in Sweden was 28.3% during the study period, and it was 11.5% in the patients starting empagliflozin treatment. Patients of the latter cohort were, however, younger, more obese, and more likely to have unsatisfactory glycemic control, requiring additional treatment. Overall, a large proportion of type 2 diabetes patients should be considered at high cardiovascular risk. **FUNDING:** Boehringer Ingelheim AB, Sweden.

[18] *Rastelli M, Cani PD, Knauf C. The gut microbiome influences host endocrine functions. Endocrine reviews 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31081896>

ABSTRACT

The gut microbiome is now considered as an organ contributing to the regulation of host metabolism. Since the finding of the existence of a relationship between the gut microbiome and specific diseases, numerous studies have also deciphered molecular mechanisms explaining how gut bacteria dialogue with host cells and eventually shape metabolism. Both metagenomic and metabolomic analyses have contributed to the discovery of bacterial-derived metabolites acting on host cells. In this review, we examine the molecular mechanisms by which bacterial metabolites are acting as paracrine or endocrine factors thereby regulating host metabolism. We highlight the impact of specific short chain fatty acids on the secretion of gut peptides (i.e., GLP-1, PYY) as well as other metabolites produced from different amino acids and regulating inflammation, glucose metabolism or energy homeostasis. We also discuss the role of gut microbes on the regulation of bioactive lipids that belong to the endocannabinoid system as well as specific neurotransmitters (e.g., GABA, serotonin, NO). Finally, we review the role of specific bacterial components (i.e., ClpB, Amuc_1100) also acting as endocrine factors and eventually controlling host metabolism. In conclusion, this review summarizes recent state-of-

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the art aiming at providing evidence that the gut microbiome influences host endocrine functions via several bacterial-derived metabolites.

[19] *Jing Y, Hu T, Lin C et al. Resveratrol downregulates PCSK9 expression and attenuates steatosis through estrogen receptor alpha-mediated pathway in L02cells. European journal of pharmacology* 2019; 855:216-226.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31085239>

ABSTRACT

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a promising target for treating dyslipidemia and atherosclerosis. Circulating PCSK9 levels are closely related to hepatic steatosis severity and endogenous estrogen levels. Resveratrol (RSV) is a phytoestrogens that protects against atherosclerosis and hepatic steatosis. Thus, we sought to determine whether RSV had the activities to inhibit PCSK9 expression and to attenuate lipid accumulation in free fatty acid (FFA)-induced L02cells via ERalpha pathway. In this study, RSV (10, 20muM) were cultured with L02cells in the presence of FFA (oleate:palmitate=2:1). RSV significantly reduced the number of lipid droplets and intracellular TG in steatotic L02cells, and Oil red O staining and Nile red staining had the same results. Western blot analysis showed that RSV significantly reduced apoB secretion and intracellular microsomal triglyceride transporter (MTP) expression under lipid-rich conditions. Treatment with RSV reduced expression of PCSK9 while maintaining LDL receptor (LDLR) expression and LDL uptake. RSV decreased SREBP-1c expression at both mRNA and protein levels. In addition, RSV significantly reduced the expression of liver X receptor alpha (LXRalpha) mRNA in L02cells, but did not affect the expression of liver X receptor beta (LXRbeta) mRNA. The luciferase reporter assays suggested that RSV inhibited SREBP-mediated transcription of PCSK9. Finally, these results could be partly reversed by Estrogen receptor alpha (ERalpha) gene silencing. These results suggest that RSV attenuates steatosis and PCSK9 expression through down-regulation of SREBP-1c expression, at least in part through ERalpha-mediated pathway.

[20] *Ruscica M, Reiner Z, Sirtori CR. Can we further optimize statin therapy to increase tolerability? Expert opinion on drug discovery* 2019:1-5.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31096808>

ABSTRACT

[21] *Strilchuck L, Fogacci F, Cicero AF. Safety and tolerability of injectable lipid-lowering drugs: an update of clinical data. Expert opinion on drug safety* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31100030>

ABSTRACT

INTRODUCTION: Cardiovascular (CV) diseases are the leading cause of death and disability in the developed countries. Lipid-lowering therapy is a cornerstone of the CV risk modification strategy. The first line treatment for hyperlipidemia is statins, which decrease low-density lipoprotein cholesterol (LDL-C) by 30-50% and proportionally reduce the CV events. However, they are not always enough to achieve LDL-C goals in many patients, and some patients are statin intolerant. For this reason, new powerful injectable lipid-lowering drugs have been developed. Areas covered: The aim of this narrative review was to summarize the more recent

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clinical data on safety and tolerability of injectable lipid-lowering drugs. After an attentive literature search, the authors resumed here information on proprotein convertase subtilisin/kexin 9 inhibitors (evolocumab and alirocumab), small interfering RNA molecule inclisiran, antisense oligonucleotides (mipomersen, volanesorsen, ISIS 681257), and drugs targeting angiopoietin-like protein 3 (evinacumab, IONIS-ANGPTL3Rx). Expert opinion: Injectable lipid-lowering therapy for patients at high risk for CV disease complications or with severe inherited hypercholesterolemias can be an important element of the available therapeutic armamentarium. Clinical data prove the favorable risk-benefit profile of evolocumab, alirocumab, and inclisiran. Mipomersen, volanesorsen, ISIS 681257, evinacumab, and IONIS-ANGPTL3Rx safety is currently less extensively studied, especially in patients with comorbidities and polypharmacotherapy.

[22] *Bermudez-Lopez M, Forne C, Amigo N et al. An in-depth analysis shows a hidden atherogenic lipoprotein profile in non-diabetic chronic kidney disease patients. Expert opinion on therapeutic targets 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31100024>

ABSTRACT

BACKGROUND: Chronic kidney disease (CKD) is an independent risk factor for atherosclerotic disease. We hypothesized that CKD promotes a proatherogenic lipid profile modifying lipoprotein composition and particle number. METHODS: Cross-sectional study in 395 non-diabetic individuals (209 CKD patients and 186 controls) without statin therapy. Conventional lipid determinations were combined with advanced lipoprotein profiling by nuclear magnetic resonance, and their discrimination ability was assessed by machine learning. RESULTS: CKD patients showed an increase of very-low-density (VLDL) particles and a reduction of LDL particle size. Cholesterol and triglyceride content of VLDLs and intermediate-density (IDL) particles increased. However, low-density (LDL) and high-density (HDL) lipoproteins gained triglycerides and lost cholesterol. Total-Cholesterol, HDL-Cholesterol, LDL-Cholesterol, non-HDL-Cholesterol and Proprotein convertase subtilisin-kexin type (PCSK9) were negatively associated with CKD stages, whereas triglycerides, lipoprotein(a), remnant cholesterol, and the PCSK9/LDL-Cholesterol ratio were positively associated. PCSK9 was positively associated with total-Cholesterol, LDL-Cholesterol, LDL-triglycerides, LDL particle number, IDL-Cholesterol and remnant cholesterol. Machine learning analysis by random forest revealed that new parameters have a higher discrimination ability to classify patients into the CKD group, compared to traditional parameters alone: area under the curve (95% CI), .789 (.711, .853) vs .687 (.611, .755), respectively. CONCLUSIONS: non-diabetic CKD patients have a hidden proatherogenic lipoprotein profile.

[23] *Kok KS, Gilbert T. Lessons learned from an audit of the use of atorvastatin 80 mg for secondary prevention of cardiovascular disease in a tertiary hospital. Future hospital journal 2016; 3:s10.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31098239>

ABSTRACT

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[24] *Bahlmann E, Cramariuc D, Saeed S et al. Low systemic arterial compliance is associated with increased cardiovascular morbidity and mortality in aortic valve stenosis. Heart* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31092548>

ABSTRACT

OBJECTIVE: Lower systemic arterial compliance (SAC) is associated with increased cardiovascular morbidity and mortality in hypertension, but this has not been assessed in a prospective study in aortic valve stenosis (AS). METHODS: Data from 1641 patients (38% women) with initially asymptomatic mild-moderate AS enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study was used. Median follow-up was 4.3 years. SAC was assessed from Doppler stroke volume index to central pulse pressure ratio and considered low if ≤ 0.64 mL/m², corresponding to the lower tertile in the population. The association of SAC with outcome was assessed in Cox regression analysis and reported as HR and 95% CI. RESULTS: Low SAC at baseline was characterised by older age, female sex, hypertension, obesity, presence of a small aortic root, lower mean aortic gradient and more severe AS by effective aortic valve area (all $p < 0.01$). In Cox regression analysis adjusting for factors, low SAC was associated with higher HRs for cardiovascular death (HR 2.13(95% CI 1.34 to 3.40) and all-cause mortality (HR 1.71(95% CI 1.23 to 2.38)), both $p = 0.001$). The results did not change when systolic or diastolic blood pressure, other measures of AS severity or presence of discordantly graded AS were included in subsequent models. Presence of low SAC did not improve mortality prediction in reclassification analysis. CONCLUSIONS: In patients with AS without diabetes and known cardiovascular disease, but a high prevalence of hypertension, low SAC was associated with higher cardiovascular and all-cause mortality independent of well-known prognosticators. TRIAL REGISTRATION NUMBER: NCT00092677; Post-results.

[25] *Parsamanesh N, Moossavi M, Bahrami A et al. NLRP3 inflammasome as a treatment target in atherosclerosis: A focus on statin therapy. Int Immunopharmacol* 2019; 73:146-155.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31100709>

ABSTRACT

Activation of NOD-like receptor (NLR) family and pyrin domain containing 3 (NLRP3) inflammasome contributes to inflammation and may lead to atherosclerosis. The NLRP3 inflammasome as a molecular platform regulates the activation of ATP signaling, K⁽⁺⁾ efflux, cathepsin-B activity, lysosomal function and pro-inflammatory cytokines (i.e. IL-1 β and IL-18). Statins has been widely prescribed for the treatment of hyperlipidemia and cardiovascular diseases. In addition to lipid-lowering effect, statins have immunomodulatory, anti-inflammatory, antioxidant and antiapoptotic functions. An increasing number of studies indicated NLRP3 inflammasome and their downstream mediators as important targets for statin drugs in inflammatory diseases. In this review, we discussed different aspect of the NLRP3 inflammasome signaling pathways and focused on the effect of statin drugs on NLRP3 inflammasomes in association to atherosclerosis in order to elucidate possible targets for future research and clinical settings.

[26] *Ntaios G, Milionis H. Low-density lipoprotein cholesterol lowering for the prevention of cardiovascular outcomes in patients with ischemic stroke. Int J Stroke*

2019;1747493019851283.

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PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31092149>

ABSTRACT

BACKGROUND: Low-density lipoprotein (LDL) cholesterol has been long associated with the risk for ischemic stroke, myocardial infarction, and cardiovascular death. For more than a decade, the main pharmacological option to prevent stroke and myocardial infarction through LDL-cholesterol lowering was the use of statins. During the recent years, two novel classes of drugs have proven their efficacy and safety to reduce LDL-cholesterol and prevent cardiovascular events in large, well-conducted randomized controlled trials: ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. **AIMS:** The present review summarizes the evidence arising from the latest trials of lipid-lowering treatment for cardiovascular outcomes prevention and discusses their implications for secondary prevention strategies in patients with ischemic stroke. **SUMMARY OF REVIEW:** There is strong evidence which confirms the hypothesis that the lower the LDL-cholesterol, the less frequent the cardiovascular events are and underlines the importance of treating our ischemic stroke patients with intensive statin treatment aiming at low LDL-cholesterol levels. The very low levels of LDL cholesterol seem to be safe, even in the mid/long term but longer follow-up data are needed. Currently there are no tools to reliably predict cardiovascular outcomes in the specific population of ischemic stroke patients. **CONCLUSIONS:** Stroke physicians should aim for low LDL-cholesterol levels by intensive statin treatment in all ischemic stroke patients. For those patients who are at the highest risk for recurrent stroke or another cardiovascular event and have unacceptable LDL-cholesterol levels despite intensive statin treatment, PCSK9 inhibitors should be considered.

[27] *Hovingh GK, Reeskamp LF, Ray KK. Hypercholesterolemia Among Premature Infarcts: Time to Start the Clock of Familial Hypercholesterolemia Assessment. Journal of the American College of Cardiology* 2019; 73:2451-2453.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31097166>

ABSTRACT

[28] *Singh A, Gupta A, Collins BL et al. Familial Hypercholesterolemia Among Young Adults With Myocardial Infarction. Journal of the American College of Cardiology* 2019; 73:2439-2450.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31097165>

ABSTRACT

BACKGROUND: There are limited data on the prevalence and treatment of familial hypercholesterolemia (FH) among U.S. adults who experience a myocardial infarction (MI) at a young age. **OBJECTIVES:** This study aimed to evaluate the prevalence of clinically defined FH and examine the rates of statin utilization and low-density lipoprotein cholesterol (LDL-C) achieved 1-year post MI. **METHODS:** The YOUNG-MI registry is a retrospective cohort study that includes patients who experience an MI at or below age 50 years between 2000 and 2016 at 2 academic centers. Probable or definite FH was defined by the Dutch Lipid Clinic criteria. Outcomes included the proportion of patients classified as probable or definite FH, use of lipid-lowering therapy, and LDL-C achieved 1-year post MI. **RESULTS:** The cohort consisted of 1,996 adults with a median age of 45 years; 19% were women, and 54% had ST-segment elevation MI. Probable/definite FH was present in 180 (9%) of whom 42.8% were not on statins prior to their MI. Of the 1,966 patients surviving until hospital discharge, 89.4% of FH patients and 89.9% of

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non-FH patients were discharged on statin therapy ($p = 0.82$). Among FH patients, 63.3% were discharged on high-intensity statin compared with 48.4% for non-FH patients ($p < 0.001$). At 1-year follow-up, the percent reduction in LDL-C among FH patients was -44.4% compared with -34.5% ($p = 0.006$) in non-FH patients. The proportion of patients with LDL-C ≥ 70 mg/dl was higher among FH patients (82.2%) compared with non-FH patients (64.5%; $p < 0.001$).

CONCLUSIONS: Clinically defined FH was present in nearly 1 of 10 patients with MI at a young age. Only two-thirds of FH patients were discharged on high-intensity statin therapy, and the vast majority had elevated LDL-C at 1 year. These findings reinforce the need for more aggressive lipid-lowering therapy in young FH and non-FH patients post-MI.

[29] *Vlachopoulos C, Kosteria I, Sakka S et al. PCSK9 and Lp(a) levels of children born after assisted reproduction technologies. Journal of assisted reproduction and genetics* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31079266>

ABSTRACT

PURPOSE: Proprotein convertase subtilisin/kexin type 9 (PCSK9) and lipoprotein (a) (Lp[a]) levels are associated with cardiovascular risk. To investigate PCSK9 and Lp(a) levels of children born after assisted reproduction technologies (ART) compared with naturally conceived (NC) controls. **METHODS:** In this exposure-matched cohort study, 73 racial-, sex-, and age-matched children (mean age 98 +/- 35 months) of ART (intracytoplasmic sperm injection [ICSI] $n = 33$, classic in vitro fertilization [IVF] $n = 40$) and 73 NC children were assessed. Blood lipid profile, including PCSK9 and Lp(a) levels, was measured. Children were grouped according to age (< 8 years, 8-10 years, ≥ 10 years). **RESULTS:** In the overall population, PCSK9 levels were related to total cholesterol, low-density lipoprotein, and systolic blood pressure, while Lp(a) levels were related to age, apolipoprotein-B, birth weight, height, waist-to-hip ratio, insulin resistance, insulin, and high-sensitivity C-reactive protein. No significant differences were observed regarding lipid biomarkers between ART and NC children. However, a significant interaction was found between age groups and conception method ($p < 0.001$) showing that PCSK9 levels increase with age in ART children, while they decline with age in NC offspring. IVF children showed higher levels of adjusted mean Lp(a) than ICSI (13.5 vs. 6.8 mg/dl, $p = 0.010$) and NC children (12.3 vs. 8.3 mg/dl, $p = 0.048$). **CONCLUSIONS:** We show that PCSK9 levels increase with age in ART children, indicating a gradual deterioration of lipidemic profile that could lead to increased cardiovascular risk. Moreover, our results indicate that ART method may be of importance given that classic IVF is associated with higher levels of Lp(a).

[30] *Tsujita M, Akita N, Yokota T et al. Selective Correction of Genotype Yield by Probucol in HDL-Deficient Mice Propagation. Journal of atherosclerosis and thrombosis* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31092744>

ABSTRACT

AIM: Probucol is a controversial drug to inhibit ATP-binding cassette transporter A1 (ABCA1) and to exhibit some positive clinical effects such as regression of xanthomas. It reportedly rescues female infertility in scavenger receptor BI-deficient mice. Here, we investigated the effect of probucol on propagation in HDL-deficient mice as alternative models for impaired HDL-mediated cholesterol delivery. **METHODS:** Propagation of ABCA1-deficient (Abca1 $^{-/-}$) mice and lecithin: cholesterol acyltransferase (LCAT)-deficient (Lcat $^{-/-}$) mice were quantitatively

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observed under the probucol treatment. RESULTS: *Abca1*^{-/-} and *Lcat*^{-/-} mice appear with negligible plasma HDL concentration. Upon backcrossing *Abc1*^{+/-} with the *Abc1*^{-/-} mice and cross-breeding between *Abc1*^{+/-} mice, the numbers of *Abc1*^{-/-} weaned pups were reduced to 54.7% and to 57.1% from those expected by Mendelian genetics, respectively. Similarly, *Lcat*^{-/-} weaned pups decreased to 67.7% and to 35.9% but only in the male. Probucol severely reduced plasma HDL-cholesterol to 5% in the wild-type mice, but showed no effects on their propagation. Probucol corrected the deflections of the genotype distribution in the weaned pups recovery in the LCAT-deficient mice propagation but not in the ABCA1-deficient mice while plasma HDL was kept negligible. Probucol had no effect on cholesterol content in the steroidogenic organs of the HDL-deficient mice, while it somewhat increased plasma corticosterone and expression of adrenal cortex HMG-CoA reductase, StAR, cytochrome P450_{sc}, and VKORC1 indicating increase in the synthesis of cholesterol and steroid hormones and in vitamin K turn-over. However, no evident mechanistic background was indicated. CONCLUSIONS: Probucol corrected deflection of genotype distribution in propagation of the LCAT-deficient mice but not the ABCA1-deficient mice at the weaning stage, apparently not through normalization of hypoalphalipoproteinemia.

[31] *Jaskiewicz A, Pajak B, Labieniec-Watala M et al. Diverse Action of Selected Statins on Skeletal Muscle Cells-An Attempt to Explain the Protective Effect of Geranylgeraniol (GGOH) in Statin-Associated Myopathy (SAM). Journal of clinical medicine* 2019; 8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31100888>

ABSTRACT

The present study is centered on molecular mechanisms of the cytoprotective effect of geranylgeraniol (GGOH) in skeletal muscle harmed by statin-associated myopathy (SAM). GGOH via autophagy induction was purportedly assumed to prevent skeletal muscle viability impaired by statins, atorvastatin (ATR) or simvastatin (SIM). The C2C12 cell line was used as the 'in vitro' model of muscle cells at different stages of muscle formation, and the effect of ATR or SIM on the cell viability, protein expression and mitochondrial respiration were tested. Autophagy seems to be important for the differentiation of muscle cells; however, it did not participate in the observed GGOH cytoprotective effects. We showed that ATR- and SIM-dependent loss in cell viability was reversed by GGOH co-treatment, although GGOH did not reverse the ATR-induced drop in the cytochrome c oxidase protein expression level. It has been unambiguously revealed that the mitochondria of C2C12 cells are not sensitive to SIM, although ATR effectively inhibits mitochondrial respiration. GGOH restored proper mitochondria functioning. Apoptosis might, to some extent, explain the lower viability of statin-treated myotubes as the pan-caspase inhibitor, N-Benzoyloxycarbonyl-Val-Ala-Asp(O-Me) fluoromethyl ketone (Z-VAD-FMK), partly reversed ATR- or SIM-induced cytotoxic effects; however, it does not do so in conjunction with caspase-3. It appears that the calpain inhibitor, N-Acetyl-L-leucyl-L-leucyl-L-norleucinal (ALLM), restored the viability that was reduced by ATR and SIM ($p < 0.001$). GGOH prevents SAM, in part, as a consequence of a caspase-3 independent pathway, probably by calpain system inactivation.

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[32] *Abdulle A, Inman CK, Saleh A et al. Metabolic dysfunction in Emirati subjects in Abu Dhabi: Relationship to levels of soluble RAGEs. Journal of clinical & translational endocrinology* 2019; 16:100192.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31080742>

ABSTRACT

Background: The United Arab Emirates is experiencing increasing rates of type 2 diabetes (T2D) and its complications. As soluble levels of the receptor for advanced glycation end products, (sRAGE), and endogenous secretory RAGE (esRAGE), the latter an alternatively spliced form of AGER (the gene encoding RAGE), have been reported to be associated with T2D and its complications, we tested for potential relationships between these factors and T2D status in Emirati subjects. Methods: In a case-control study, we recruited Emirati subjects with T2D and controls from the Sheikh Khalifa Medical City in Abu Dhabi. Anthropomorphic characteristics, levels of plasma sRAGE and esRAGE, and routine chemistry variables were measured. Results: Two hundred and sixteen T2D subjects and 215 control subjects (mean age, 57.4+/-12.1 vs. 50.7+/-15.4years; $P < 0.0001$, respectively) were enrolled. Univariate analyses showed that levels of sRAGE were significantly lower in the T2D vs. control subjects (1033.9+/-545.3 vs. 1169.2+/-664.1pg/ml, respectively; $P = 0.02$). Multivariate analyses adjusting for age, sex, systolic blood pressure, pulse, body mass index, Waist/Hip circumference ratio, fasting blood glucose, HDL, LDL, insulin, triglycerides, Vitamin D and urea levels revealed that the difference in sRAGE levels between T2D and control subjects remained statistically-significant, $P = 0.03$, but not after including estimated glomerular filtration rate in the model, $P = 0.14$. There were no significant differences in levels of esRAGE. Levels of plasma insulin were significantly higher in the control vs. the T2D subjects (133.6+/-149.9 vs. 107.6+/-93.3pg/L. respectively; $P = 0.01$, after adjustment for age and sex). Conclusion/discussion: Levels of sRAGE, but not esRAGE, were associated with T2D status in Abu Dhabi, but not after correction for eGFR. Elevated levels of plasma insulin in both control and T2D subjects suggests the presence of metabolic dysfunction, even in subjects without diabetes.

[33] *Severino P, D'Amato A, Netti L et al. Myocardial Ischemia and Diabetes Mellitus: Role of Oxidative Stress in the Connection between Cardiac Metabolism and Coronary Blood Flow. Journal of diabetes research* 2019; 2019:9489826.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31089475>

ABSTRACT

Ischemic heart disease (IHD) has several risk factors, among which diabetes mellitus represents one of the most important. In diabetic patients, the pathophysiology of myocardial ischemia remains unclear yet: some have atherosclerotic plaque which obstructs coronary blood flow, others show myocardial ischemia due to coronary microvascular dysfunction in the absence of plaques in epicardial vessels. In the cross-talk between myocardial metabolism and coronary blood flow (CBF), ion channels have a main role, and, in diabetic patients, they are involved in the pathophysiology of IHD. The exposition to the different cardiovascular risk factors and the ischemic condition determine an imbalance of the redox state, defined as oxidative stress, which shows itself with oxidant accumulation and antioxidant deficiency. In particular, several products of myocardial metabolism, belonging to oxidative stress, may influence ion channel function, altering their capacity to modulate CBF, in response to myocardial metabolism, and

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predisposing to myocardial ischemia. For this reason, considering the role of oxidative and ion channels in the pathophysiology of myocardial ischemia, it is allowed to consider new therapeutic perspectives in the treatment of IHD.

[34] *Sheng LT, Jiang YW, Pan XF et al. Association between Dietary Intakes of B Vitamins in Midlife and Cognitive Impairment in Late-Life: the Singapore Chinese Health Study. J Gerontol A Biol Sci Med Sci* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31094422>

ABSTRACT

BACKGROUND: Dietary intakes of B vitamins (e.g., folate) are related to cognitive function according to epidemiologic studies in western countries. But prospective studies in Asian populations are scarce. This study evaluated the relations of dietary intakes of six B vitamins in midlife with cognitive impairment in old age in a Chinese population living in Singapore. **METHODS:** This study included 16,948 participants from the Singapore Chinese Health Study, a population-based prospective cohort. Baseline dietary intakes of B vitamins were assessed using a validated 165-item food frequency questionnaire when the participants were 45-74 years (1993-1998). After an average follow-up of 20 years, cognitive function was examined using a Singapore-modified version of Mini-Mental State Examination (SM-MMSE) scale in 2014-2016, and cognitive impairment was defined using education-specific cut-offs. Logistic regression models were applied to estimate the association between B vitamins and cognitive impairment. All the six B vitamins were mutually adjusted in the final model. **RESULTS:** In the 2014-2016 interview, 2,443 participants were defined as cognitive impairment. Riboflavin and folate were significantly and independently associated with cognitive impairment in a dose-dependent manner: the odds ratio (95% confidence interval) comparing the highest with the lowest quartile was 0.82 (0.69, 0.97) for riboflavin, and 0.83 (0.70, 0.98) for folate (both p-trend <.05). Dietary intakes of thiamine, niacin, vitamin B-6 and B-12 were not significantly associated with risk of cognitive impairment. **CONCLUSIONS:** Higher dietary intakes of riboflavin and folate in midlife were associated with a lower risk of cognitive impairment in late-life in the Chinese population.

[35] *Ramms B, Patel S, Nora C et al. ApoC-III ASO Promotes Tissue LPL Activity in Absence of ApoE-Mediated TRL Clearance. Journal of lipid research* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31092690>

ABSTRACT

Hypertriglyceridemia results from accumulation of triglyceride (TG)-rich lipoproteins (TRLs) in the circulation and is associated with increased cardiovascular disease risk. ApoC-III is an apolipoprotein on TRLs and a prominent negative regulator of TG catabolism. We recently established that in vivo apoC-III predominantly inhibits LDLR and LRP1 mediated hepatic TRL clearance and that apoC-III enriched TRLs are preferentially cleared by syndecan-1 (SDC1). In this study, we determined the impact of apoE, a common ligand for all three receptors, on apoC-III metabolism using apoC-III antisense oligonucleotide (ASO) treatment in mice lacking apoE and functional SDC1 (ApoE^{-/-}Ndst1f/fAlb-Cre⁺). ApoC-III ASO treatment significantly reduced plasma TG levels in ApoE^{-/-}Ndst1f/fAlb-Cre⁺ mice without reducing hepatic VLDL production or improving hepatic TRL clearance. Further analysis revealed that apoC-III ASO

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treatment lowered plasma TGs in Apoe^{-/-}Ndst1f/fAlb-Cre⁺ mice, which was associated with increased LPL activity in white adipose tissue (WAT) in the fed state. Finally, clinical data confirm that ASO-mediated lowering of apoC-III via volanesorsen can reduce plasma TG levels independent of the apoE isoform genotype. Our data indicate that apoE determines the metabolic impact of apoC-III as we establish that apoE is essential to mediate inhibition of TRL clearance by apoC-III and that in the absence of functional apoE apoC-III inhibits tissue LPL activity.

[36] Santos-Marcos JA, Perez-Jimenez F, Camargo A. **The role of diet and intestinal microbiota in the development of metabolic syndrome.** The Journal of nutritional biochemistry 2019; 70:1-27.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31082615>

ABSTRACT

Metabolic syndrome (MetS) is a cluster of metabolic factors that increase the risk of cardiovascular disease and type 2 diabetes mellitus (T2DM), which is in itself a major cardiovascular disease risk factor. The aim of this review is to summarize the data related to the influence of the gut microbiota on the development of obesity and the MetS, highlighting the role of diet in controlling the MetS by modifying the gut microbiota. The main alterations in the gut microbiota of individuals with MetS consist of an increased Firmicutes/Bacteroidetes ratio and a reduced capacity to degrade carbohydrates to short-chain fatty acids, which in turn is related with the metabolic dysfunction of the host organism rather than with obesity itself. In addition to a low-fat, high-carbohydrate diet, with its high fiber intake, a diet with 30% fat content but with a high content in fruit and vegetables, such as the Mediterranean diet, is beneficial and partially restores the dysbiosis found in individuals with MetS. Overall, the shaping of the gut microbiota through the administration of prebiotics or probiotics increases the short-chain fatty acid production and is therefore a valid alternative in MetS treatment.

[37] Cao L, Guo Y, Zhu Z. **Study of the Inflammatory Mechanisms in Hyperhomocysteinemia on Large-Artery Atherosclerosis Based on Hypersensitive C-Reactive Protein-A Study from Southern China.** Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31080137>

ABSTRACT

OBJECTIVE: To study the inflammatory mechanism of hyperhomocysteinemia on large-artery atherosclerosis based on hypersensitive C-reactive protein in patients. METHODS: In all, 153 inpatients and 1357 physical examinees were selected. The levels of homocysteine were compared between the carotid/intracranial artery stenosis group and the nonstenosis group, between the carotid artery unstable plaque group and the nonplaque group, and between the intima-media thickness (IMT) greater than or equal to 1 group and the normal IMT group. The hypersensitive C-reactive protein levels were compared between the lacunar infarction (LI) group and the nonstroke control group and between the unstable plaque group and the nonplaque group. RESULTS: Homocysteine level was significantly higher in the carotid/intracranial artery stenosis group than in the nonstenosis group, in the LI group than in the inpatient nonstroke group, and in the IMT greater than or equal to 1 group than in the

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normal IMT group. The hypersensitive C-reactive protein level was significantly higher in the LI group than in the nonstroke group and in the unstable plaque group than in the nonplaque group. **CONCLUSIONS:** Hyperhomocysteinemia may aggravate the development of IMT, carotid atherosclerotic plaque instability, and carotid/intracranial artery stenosis by increasing inflammation, ultimately leading to the occurrence of LI. Hyperhomocysteinemia-induced inflammation mechanism warrants further study.

[38] *Eynard AR, Repossi G. Role of omega3 polyunsaturated fatty acids in diabetic retinopathy: a morphological and metabolically cross talk among blood retina barriers damage, autoimmunity and chronic inflammation. Lipids in health and disease* 2019; 18:114.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31092270>

ABSTRACT

Vision disorders are one of the most serious complications of diabetes mellitus (DM) affecting the quality of life of patients and eventually cause blindness. The ocular lesions in diabetes mellitus are located mainly in the blood vessels and retina layers. Different retina lesions could be grouped under the umbrella term of diabetic retinopathies (DMRP). We propose that one of the main causes in the etiopathogenesis of the DMRP consists of a progressive loss of the selective permeability of blood retinal barriers (BRB). The loss of selective permeability of blood retinal barriers will cause a progressive autoimmune process. Prolonged autoimmune injures in the retinal territory will triggers and maintains a low-grade chronic inflammation process, microvascular alterations, glial proliferation and subsequent fibrosis and worse, progressive apoptosis of the photoreceptor neurons. Patients with long-standing DM disturbances in retinal BRBs suffer of alterations in the enzymatic pathways of polyunsaturated fatty acids (PUFAs), increase release of free radicals and pro-inflammatory molecules and subsequently incremented levels of vascular endothelial growth factor. These facts can produce retinal edema and photoreceptor apoptosis. Experimental, clinical and epidemiological evidences showing that adequate metabolic and alimentary controls and constant practices of healthy life may avoid, retard or make less severe the appearance of DMRP. Considering the high demand for PUFAs omega3 by photoreceptor complexes of the retina, it seems advisable to take fish oil supplements (2 g per day). The cellular, subcellular and molecular basis of the propositions exposed above is developed in this article. Synthesizer drawings the most relevant findings of the ultrastructural pathology, as well as the main metabolic pathways of the PUFAs involved in balance and disbalanced conditions are provided.

[39] *Angelico F, Baratta F, Pastori D, Del Ben M. Statins and non-alcoholic fatty liver disease. Liver international : official journal of the International Association for the Study of the Liver* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31081583>

ABSTRACT

In April 9 issue, van den Berg EH et al.(1) report interesting results on the indication for lipid-lowering treatment in a large cohort with suspected NAFLD within the population-based Lifelines Cohort Study. FLI \geq 60 was used as a proxy of NAFLD and the NAFLD fibrosis score (NFS) to identify NAFLD patients with suspected advanced fibrosis. CVD risk was established by

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the 2016 ESC/EAS Guidelines for the Management of Dyslipidemias(2) . This article is protected by copyright. All rights reserved.

[40] *Rege SD, Luiz R, Tsai B et al. Brain Trauma Disrupts Hepatic Lipid Metabolism: Blame it on Fructose? Molecular nutrition & food research* 2019:e1801054.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31087499>

ABSTRACT

SCOPE: The action of brain disorders on peripheral metabolism is poorly understood. We studied the impact of traumatic brain injury (TBI) on peripheral organ function, and how TBI effects could be influenced by the metabolic perturbation elicited by fructose ingestion. METHODS AND RESULTS: We found that TBI affected glucose metabolism, and signaling proteins for insulin and growth hormone in the liver; these effects were exacerbated by fructose ingestion. Fructose, principally metabolized in the liver, potentiated the action of TBI on hepatic lipid droplet accumulation. Studies in isolated cultured hepatocytes identified GH and fructose as factors for the synthesis of lipids. The liver has a major role in the synthesis of lipids used for brain function and repair. TBI resulted in differentially expressed genes in the hypothalamus, primarily associated with lipid metabolism, providing cues to understand central control of peripheral alterations. Fructose-fed TBI animals had elevated levels of markers of inflammation, lipid peroxidation, and cell energy metabolism, suggesting the pro-inflammatory impact of TBI and fructose in the liver. CONCLUSION: Results reveal the impact of TBI on systemic metabolism and the aggravating action of fructose. The hypothalamic-pituitary-growth axis seems to play a major role in the regulation of the peripheral TBI pathology. This article is protected by copyright. All rights reserved.

[41] *Telle-Hansen VH, Gaundal L, Myhrstad MCW. Polyunsaturated Fatty Acids and Glycemic Control in Type 2 Diabetes. Nutrients* 2019; 11.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31091649>

ABSTRACT

The impact of dietary fat on the risk of cardiovascular disease (CVD) has been extensively studied in recent decades. Solid evidence indicates that replacing saturated fatty acids (SFAs) with polyunsaturated fatty acids (PUFAs) decreases blood cholesterol levels and prevents CVD and CVD mortality. Studies indicate that fat quality also may affect insulin sensitivity and hence, the risk of type 2 diabetes (T2D). A high intake of SFAs has shown to increase the risk of T2D in prospective studies, while a high intake of PUFAs reduces the risk. Whether PUFAs from marine or vegetable sources affect glycemic regulation differently in T2D remains to be elucidated. The aim of the present review was therefore to summarize research on human randomized, controlled intervention studies investigating the effect of dietary PUFAs on glycemic regulation in T2D. About half of the studies investigating the effect of fish, fish oils, vegetable oils, or nuts found changes related to glycemic control in people with T2D, while the other half found no effects. Even though some of the studies used SFA as controls, the majority of the included studies compared PUFAs of different quality. Considering that both marine and vegetable oils are high in PUFAs and hence both oils may affect glycemic regulation, the lack of effect in several of the included studies may be explained by the use of an inappropriate control group. It is therefore not possible to draw a firm conclusion, and more studies are needed.

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[42] *Ahi S, Amouzegar A, Gharibzadeh S et al. Trend of lipid and thyroid function tests in adults without overt thyroid diseases: A cohort from Tehran thyroid study. PloS one 2019; 14:e0216389.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31095584>

ABSTRACT

CONTEXT: While the role of overt hypothyroidism in lipid disorders is clear, the association between dyslipidemia and subclinical thyroid diseases remains unclarified. **OBJECTIVE:** To examine lipid trends based on thyroid function over a 10-year period. **DESIGN:** This is a prospective population based cohort study. **SETTING:** General community. **PARTICIPANTS:** 2383 euthyroid participants, as well as those with subclinical thyroid diseases, in all residents of district 13 of Tehran were examined. Subjects who were on levothyroxine, anti-hyperthyroid drugs, and glucocorticoids, those with a history of thyroid surgery or RAI and pregnant women were excluded. **MAIN OUTCOME MEASURES:** Lipid trends in Model 1 were adjusted for age and follow up duration, and in Model 2 gender-specific multivariate adjustments were performed for thyroid status, diabetes mellitus, smoking status, education, BMI, lipid lowering medications, age and follow up duration by using generalized estimating equations. **RESULTS:** In every four years of assessments, there were significant decreases in levels of all lipid parameters (all Ps <0.001) except for HDL-C, in which a decrescendo-crescendo trend was observed. The results did not change after adjusting for thyroid status, consumption of lipid lowering drugs during the follow-up period, or other variables. There were significant decreases in the prevalence of hypercholesterolemia and hypertriglyceridemia (all Ps <0.001) during the follow-up period. **CONCLUSION:** During a 10 year follow-up, decrescendo trends were observed in levels of total cholesterol, triglycerides, which were not be accounted for by the consumption of lipid lowering drugs and thyroid status.

[43] *Hao F, Xu Q, Wang J et al. Lipophilic statins inhibit YAP nuclear localization, co-activator activity and colony formation in pancreatic cancer cells and prevent the initial stages of pancreatic ductal adenocarcinoma in KrasG12D mice. PloS one 2019; 14:e0216603.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31100067>

ABSTRACT

We examined the impact of statins on Yes-associated Protein (YAP) localization, phosphorylation and transcriptional activity in human and mouse pancreatic ductal adenocarcinoma (PDAC) cells. Exposure of sparse cultures of PANC-1 and MiaPaCa-2 cells to cerivastatin or simvastatin induced a striking re-localization of YAP from the nucleus to the cytoplasm and inhibited the expression of the YAP/TEAD-regulated genes Connective Tissue Growth Factor (CTGF) and Cysteine-rich angiogenic inducer 61 (CYR61). Statins also prevented YAP nuclear import and expression of CTGF and CYR61 stimulated by the mitogenic combination of insulin and neurotensin in dense culture of these PDAC cells. Cerivastatin, simvastatin, atorvastatin and fluvastatin also inhibited colony formation by PANC-1 and MiaPaCa-2 cells in a dose-dependent manner. In contrast, the hydrophilic statin pravastatin did not exert any inhibitory effect even at a high concentration (10 µM). Mechanistically, cerivastatin did not alter the phosphorylation of YAP at Ser127 in either PANC-1 or MiaPaCa-2 cells incubated without or with neurotensin and insulin but blunted the assembly of actin stress

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fiber in these cells. We extended these findings with human PDAC cells using primary KC and KPC cells, (expressing KrasG12D or both KrasG12D and mutant p53, respectively) isolated from KC or KPC mice. Using cultures of these murine cells, we show that lipophilic statins induced striking YAP translocation from the nucleus to the cytoplasm, inhibited the expression of Ctgf, Cyr61 and Birc5 and profoundly inhibited colony formation of these cells. Administration of simvastatin to KC mice subjected to diet-induced obesity prevented early pancreatic acini depletion and PanIN formation. Collectively, our results show that lipophilic statins restrain YAP activity and proliferation in pancreatic cancer cell models in vitro and attenuates early lesions leading to PDAC in vivo.

[44] *Laukkanen JA, Kunutsor SK. Is Sauna Bathing Protective of Sudden Cardiac Death? A Review of the Evidence. Prog Cardiovasc Dis 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31102597>

ABSTRACT

Sudden cardiac death (SCD) is a global public health burden accounting for 15-20% of all deaths. Though established atherosclerotic risk factors explain a large proportion of the risk of SCD, these factors are often absent in a large proportion of SCD victims and the pathogenesis of SCD is still not fully established. It therefore appears that additional factors may be involved. Sauna bathing is a traditional Finnish activity that is mainly used for the purposes of relaxation and pleasure. Beyond its use for these purposes, sauna bathing has been linked with several health benefits. Emerging evidence suggests that sauna bathing is associated with reduced risk of adverse cardiovascular (CV) disease (CVD) and non-CVD outcomes as well as mortality. A number of reports have linked sauna bathing with reduced or increased risk of SCD, but the evidence is uncertain. This review summarizes available studies linking sauna bathing with SCD, the postulated mechanistic pathways underlying these associations, outlines areas of outstanding uncertainty, and the implications for prevention. We employed a comprehensive search for observational studies, randomized controlled trials (RCTs), and non-RCTs from MEDLINE and Embase since their inception until March 2019. Observational data suggest that regular sauna bathing is associated with a substantial risk reduction in SCD. Furthermore, the data suggest that a combination of regular physical activity and sauna baths confers substantial risk reduction for SCD compared with either modality alone. Few reports have linked sauna baths with SCDs, but these single case incidents have been attributed to the effects of dehydration, hypotension, and cardiac arrhythmias due to a combination of sauna exposure and alcohol consumption. Sauna bathing is generally safe for most healthy people and even among patients with stable CVD, if used sensibly and with caution. Plausible pathways underlying the protective effect of sauna bathing on SCD may be linked to the impact on CV function via reduced arterial stiffness, decreases in inflammation and oxidative stress, stabilization of the autonomic nervous system, beneficial changes in circulating lipid profiles and other CVD risk markers, and lowering of systemic blood pressure. Sauna is a potential novel tool to promote SCD prevention in addition to other known means, being an enjoyable way to take care of general health and well-being.

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[45] *Viana-Huete V, Fuster JJ. Potential therapeutic value of interleukin 1beta-targeted strategies in atherosclerotic cardiovascular disease. Revista espanola de cardiologia (English ed.) 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31078457>

ABSTRACT

Clinical trials have unequivocally shown that cholesterol-lowering drugs decrease the risk of atherosclerotic cardiovascular disease in an exceptionally wide range of individuals. Yet, even when treated optimally according to current standards, many individuals still experience life-threatening ischemic events. Emerging experimental and clinical evidence strongly suggests that persistent inflammation is a major driver of this residual risk, which has opened the door to the application of anti-inflammatory drugs for cardiovascular disease prevention. Here, we review our current knowledge of the biology of interleukin-1beta, a key regulator of inflammation in atherosclerotic plaque and the target of the first clinical trial to demonstrate that an anti-inflammatory drug can effectively reduce cardiovascular risk. We discuss the challenges faced by interleukin-1beta inhibitors and other anti-inflammatory compounds in their translation to the clinical scenario, and identify other potential targets within this signaling pathway that hold promise in the cardiovascular setting.

[46] *Sanvee GM, Bouitbir J, Krahenbuhl S. Insulin prevents and reverts simvastatin-induced toxicity in C2C12 skeletal muscle cells. Scientific reports 2019; 9:7409.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31092879>

ABSTRACT

Simvastatin is an inhibitor of the 3-hydroxy-3-methylglutaryl-CoA reductase used for decreasing low density lipoprotein (LDL)-cholesterol in patients. It is well-tolerated but can cause myopathy. Our aims were to enlarge our knowledge regarding mechanisms and effects of insulin on simvastatin-associated myotoxicity in C2C12 myotubes. Simvastatin (10 microM) reduced membrane integrity and ATP content in myotubes treated for 24 hours, which could be prevented and partially reversed concentration- and time-dependently by insulin. Furthermore, simvastatin impaired the phosphorylation of Akt (Protein Kinase B) mainly at Ser473 and less at Thr308, indicating impaired activity of the mammalian Target of Rapamycin Complex 2 (mTORC2). Impaired activation of Akt increased mRNA expression of the muscle atrophy F-Box (MAFbx), decreased activation of the mammalian Target of Rapamycin Complex 1 (mTORC1) and stimulated apoptosis by impairing the Ser9 phosphorylation of glycogen synthase kinase 3beta. Decreased phosphorylation of Akt at both phosphorylation sites and of downstream substrates as well as apoptosis were prevented concentration-dependently by insulin. In addition, simvastatin caused accumulation of the insulin receptor beta-chain in the endoplasmic reticulum (ER) and increased cleavage of procaspase-12, indicating ER stress. Insulin reduced the expression of the insulin receptor beta-chain but increased procaspase-12 activation in the presence of simvastatin. In conclusion, simvastatin impaired activation of Akt Ser473 most likely as a consequence of reduced activity of mTORC2. Insulin could prevent the effects of simvastatin on the insulin signaling pathway and on apoptosis, but not on the endoplasmic reticulum (ER) stress induction.

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[47] Orsi FA, Cannegieter SC, Lijfering WM. **Statin Therapy to Revert Hypercoagulability and Prevent Venous Thromboembolism: A Narrative Review.** Seminars in thrombosis and hemostasis 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31096309>

ABSTRACT

Venous thromboembolism (VTE) causes a major disease burden worldwide, so that effective preventive measures are warranted. Although oral anticoagulation is effective in preventing VTE episodes, bleeding complications are a major concern that may lead to treatment avoidance. Statin therapy, which is widely used for prevention of arterial cardiovascular disease, is a promising alternative treatment for VTE prophylaxis, as the drug may affect hemostasis without increasing the risk of bleeding. In the past years, clinical studies have suggested that statins can interfere with blood coagulation and, in turn, reduce the risk of VTE. These effects, however, are still regarded with skepticism, as the underlying mechanisms by which statins may affect hemostasis in humans are not clear and data showing that statin therapy reduces VTE risk mostly came from observational studies, while only one randomized trial was conducted to evaluate this issue. In this review, the authors summarize the currently available evidence regarding the effect of statin therapy on coagulation and on VTE prevention. Recent randomized data showed that statin therapy, in particular rosuvastatin, leads to decreased levels of coagulation factors in patients with prior VTE. This evidence provides a reasonable basis for interventional studies necessary to establish the efficacy of statins on reducing the risk of incident and recurrent VTE.

[48] Rix A, Curaj A, Liehn E, Kiessling F. **Ultrasound Microbubbles for Diagnosis and Treatment of Cardiovascular Diseases.** Seminars in thrombosis and hemostasis 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31096311>

ABSTRACT

Ultrasound (US) imaging of heart and major arteries and veins is among the most frequently used diagnostic techniques applied in humans. Conventional cardiovascular US sessions include anatomical B-mode and functional M-, pulsed-wave- and Doppler mode, which have their limitations in both precise cardiac chambers' delineation and small vessel imaging. The introduction of contrast-enhanced US, employing microbubble suspensions as contrast agent, has enabled a better delineation of heart chambers, the visualization of myocardial microvasculature, and the atherosclerotic plaque neovascularization. Moreover, specific disease-related molecular tracers have been developed by modifying the microbubbles with targeting ligands directed to biological markers exposed to the luminal side of the blood vessels. Microbubble functionalization has enabled in vivo molecular US imaging of various stages of atherosclerosis, from plaque initiation to plaque vulnerability, and neointima formation following revascularization procedures. Furthermore, oscillating microbubbles have been used to mechanically dissolve thrombus material and may act as carriers of drugs and nucleic acids that are released locally by US pulses. This review article summarizes recent advances in functional and molecular US images and discusses therapeutic applications of microbubbles. The addressed topics include an overview on microbubble formats, microbubble detection methods, molecular targets of cardiovascular diseases, and the use of microbubbles for thrombolysis and drug delivery.

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[49] Chhetry M, Jialal I. Lipid Lowering Drug Therapy. In: StatPearls. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC.; 2019.

[50] Djadjo S, Bajaj T. Niacin (Nicotinic Acid). In: StatPearls. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC.; 2019.

[51] *Sergienko IV, Ansheles AA, Drapkina capital O CEMC et al. ANICHKOV study: the effect of combined hypotensive and lipid-lowering therapy on cardiovascular complications in patients of high and very high risk. Terapevticheskii arkhiv 2019; 91:90-98.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31094482>

ABSTRACT

AIM: The aim of the study was to assess cardiovascular risk in patients with elevated levels of total cholesterol and LDL-C and concomitant AH, a comparative analysis of adherence, efficacy and safety of various forms of combined therapy in outpatient practice, including promising lisinopril/amlodipine/rosuvastatin FC (Ekvamer(R)). MATERIALS AND METHODS: The ANICHKOV study included 702 patients in Moscow and the Moscow region over 18 years old with a -cholesterol level ≥ 7.5 mmol/l and/or LDL-C ≥ 4.9 mmol/l from March 2017 to December 2018 based on 2 federal centers. According to the results of visit I, patients were prescribed with one of three therapy schemes. In the absence of AH, patients received scheme I -(Mertenil(R) at initial dosage of 10 mg/day). When history of AH existed or AH detected at visit I, patients were randomized to scheme II (Ekvamer(R) 5/10/10 mg/day) or III (Mertenil(R) 10 mg/day + Ekvator(R) 5/10 mg/day). During the observation, the treatment scheme remained unchanged, however, if the target levels of LDL-C and/or BP were not reached, the doses could be increased. The analysis of the main effects of the prescribed therapy were carried out for 12 months, and the frequency of MACE (CVD, ACS, stroke, or hospitalization to perform PCI) was also evaluated. RESULTS: Following the visit I, scheme I was assigned to 390 patients (55.6%), scheme II - 190 (27.1%), scheme III - 122 (17.4%). In 147 patients (20.9%), TG level was > 2.3 mmol/l, which required additional fenofibrate intake in a dose of 145 mg/day. Adherence level was 89.5%, including scheme I - 91.7%, scheme II - 90.5%, scheme III - only 81.8%. In general, among compliant patients (n = 590), the decrease in TCh level was 41.0%, LDL-C - 47.4%. 16.6% of patients reached target levels of LDL-C ≤ 2.5 mmol/l, 5.6% - ≤ 1.8 mmol/l. In the fenofibrate subgroup, TG level decrease was 34.6%. During the follow-up period, 47 cases of side effects were observed in 27 patients (4.6%), that did not require modification of therapy. Systolic BP reduction in compliant patients of schemes II and III was 20 mm. Hg (13.1%), diastolic BP - 12 mm. Hg (13.6%), target BP levels ($\leq 140/90$ mm. Hg) reached 83.7% and 80.8% of patients, respectively, target levels of BP and LDL-C ≤ 2.5 mmol/l reached 14.5% and 13.1% of patients, respectively, ≤ 1.8 mmol/l - 5.8% and 5.1%, respectively. During the observation period no deaths were recorded, other components of MACE were observed in 38 patients (5.8%), including 27 among compliant patients (4.6%) and 11 among non-compliant (15.9%, $p < 0.01$). In 19 out of 38 patients (50%), hospitalization for routine PCI was the end point, ACS - in 12 (31.6%), and stroke - in 7 (18.4%). CONCLUSION: The results of the study demonstrated a sufficient hypolipidemic effect and high safety of Mertenil(R) and Ekvamer(R). A higher adherence to the combined preparation than to two monodrugs was noted. Achieving

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target levels of BP and LDL-C is problematic, which dictates the expediency of using fixed combinations of drugs, especially in primary prevention.

[52] *Orringer CE. Icosapent ethyl: Where will it fit into guideline-based medical therapy for high risk atherosclerotic cardiovascular disease? Trends in cardiovascular medicine* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31101399>

ABSTRACT

Patients who are at high or very high risk for atherosclerotic cardiovascular disease (ASCVD) events derive the greatest benefit when clinicians prescribe evidence-based preventive therapies. The writing process used in the creation of the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol employed a thorough evaluation of the highest quality evidence, and synthesis of this evidence into actionable recommendations for ASCVD risk reduction. Clinical trials supporting the addition of ezetimibe, PCSK9 inhibitors, or both to evidence-based statins provide the basis for the updated recommendations for the preventive care of these patients. The publication in late 2018 of a randomized controlled trial supporting the net ASCVD risk reduction benefit of adding icosapent ethyl to statins in selected hypertriglyceridemic patients with clinical ASCVD and/or type 2 diabetes with multiple additional risk markers provides the rationale for incorporation of icosapent ethyl therapy into future ASCVD preventive care regimens.

[53] *Roth L, der Donckt CV, Veseli BE et al. Nitric oxide donor molsidomine favors features of atherosclerotic plaque stability and reduces myocardial infarction in mice. Vascular pharmacology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31085310>

ABSTRACT

Nitric oxide (NO) donors are commonly used for the prevention and treatment of ischemic heart disease. Besides their effects on the heart, NO donors may also prevent hypoxic brain damage and exert beneficial effects on atherosclerosis by favoring features of plaque stability. We recently described that apolipoprotein E (ApoE) deficient mice with a mutation in the fibrillin-1 (Fbn1) gene (ApoE(-/-)Fbn1(C1039G+/-)) develop accelerated atherosclerosis, plaque rupture, myocardial infarction, cerebral hypoxia and sudden death. In the present study, we evaluated the effects of chronic treatment with the NO donor molsidomine on atherosclerotic plaque stability, cardiac function, neurological symptoms and survival in the ApoE(-/-)Fbn1(C1039G+/-) mouse model. Female ApoE(-/-)Fbn1(C1039G+/-) mice were fed a Western diet (WD). After 8 weeks of WD, the mice were divided into two groups receiving either molsidomine via the drinking water (1mg/kg/day; n=34) or tap water (control; n=36) until 25 weeks of WD. Survival tended to increase after molsidomine treatment (68% vs. 58% in controls). Importantly, atherosclerotic plaques of molsidomine-treated mice had a thicker fibrous cap (11.1±1.2 vs. 8.1±0.7µm) and showed an increased occurrence of plaque macrocalcifications (30% vs. 0%), indicative of a more stable phenotype. Molsidomine also improved cardiac function, as fractional shortening was increased (40±2% vs. 27±2%) combined with a decreased end diastolic (3.1±0.2 vs. 3.9±0.2mm) and end systolic diameter (1.9±0.1 vs. 2.9±0.2mm). Furthermore, perivascular fibrosis (23±2 vs. 30±2%) and the

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occurrence of myocardial infarctions (12% vs. 36%) was significantly reduced. Track width, a measure of the animal's hind limb base of support and representative of hypoxic brain damage, was also normalized as a result of molsidomine treatment (2.54±0.04 vs. 2.91±0.09cm in controls). These findings demonstrate that the NO donor molsidomine improves cardiac function, reduces neurological symptoms and enhances atherosclerotic plaque stability.

[54] *Schroner Z, Uliciansky V. The role of GLP-1 receptor agonists and their fixed combination with insulin in the treatment of type 2 diabetes mellitus. Vnitr Lek 2019; 65:284-288.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31091948>

ABSTRACT

Therapy with GLP1 receptors agonists shows various multiorgans benefits. Possible reasons of preference of this treatment are: efficacy, decrease of weight, CV protectivity, slow down the progression of nephropathy, protection of function of B-cells, safety (low risk of hypoglycemia, small incidence of serious adverse events), decrease of blood pressure, lipids, biomarkers of CV risk, markers of chronic subclinical inflammation. In context of individual approach, therapy with GLP1 receptors agonists should be preferably used in early stages of type 2 diabetes mellitus, as second choice treatment after metformin, mainly in more obese patients with subclinical or clinical manifestations of atherosclerosis, but without symptoms of heart failure.

[55] *Feng BL, Yu HH, Shen W. [Ursodeoxycholic acid combined with bezafibrate in the treatment of refractory primary biliary cholangitis: a meta-analysis]. Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese journal of hepatology 2019; 27:304-311.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=31082343>

ABSTRACT

Objective: To evaluate the efficacy, safety and remission rates of pruritus of bezafibrate and UDCA combination therapy in the treatment of refractory PBC. **Methods:** PubMed, Embase, The Cochrane Library databases, Science direct, Web of Science, CBM, WangFang Data, CNKI, VIP databases were searched to collect randomized controlled trials, crossover trials and self-control clinical trials of combination therapy of UDCA and bezafibrate with UDCA monotherapy for PBC up to June, 2018. RevMan 5.3 software was used for meta-analysis. Two evaluators independently screened the literature, extracted the data, and evaluated the risk of bias of relevant study. **Results:** Eleven studies, including 465 patients were included. Ursodeoxycholic acid combined with bezafibrate had greatly improved liver biochemical indicators ($P < 0.01$) and pruritus scores in patients with refractory primary biliary cholangitis (MD = -2.97, 95% CI: -4.34~-1.60, $P < 0.01$). However, there was no statistically significant differences in adverse events (RR = 1.28, 95% CI: 0.96 to 1.70, $P = 0.09$), and mortality rate (RR = 2.58, 95% CI: 0.57 to 11.73, $P = 0.22$) between the two groups. **Conclusion:** Ursodeoxycholic acid combined with bezafibrate may improve the biochemical response and pruritus score of refractory PBC, but has no significant effect on adverse events and mortality rate.