Literature update week 28 (2019)

[1] *Vanwonterghem Y, Shadid S*. **Simvastatin-induced erythromelalgia: less is more**. Acta clinica Belgica 2019:1-2.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31291834
ABSTRACT
We describe a case of a woman with uncomplicated Type 2 diabetes mellitus, presenting with severe burning pains and intense redness of the legs, for which only cooling could provide relief. Although the description was classic of erythromelalgia, the lack of familiarity of the disorder caused considerable doctor's delay as well as the erroneous advice to start pain killers and amitriptyline. However, empirical discontinuation of simvastatin made all symptoms disappear. Erthyromelalgia is a rare but debilitating disease which is diagnosed by exclusion only. It usually occurs as a secondary feature to (hematologic) malignant disorders, autoimmune diseases or, infections or, most notoriously, to pharmacological agents. One of the latter might be simvastatin, and possibly all HMG CoA Reductase inhibitors.

[2] *Sanfelice R, da Silva SS, Bosqui LR et al.* **Pravastatin and Simvastatin Pretreatment in Combination with Pyrimethamine and Sulfadiazine Reduces Infection Process of Toxoplasma gondii Tachyzoites (RH Strain) in HeLa Cells**. Acta parasitologica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31286354
ABSTRACT
PURPOSE: Toxoplasma gondii is a protozoan from phylum Apicomplexa, which causes the toxoplasmosis infection; this one exhibits an apicoplast organelle which assists in the metabolism of isoprenoids and other pivotal mediators for the parasite survival. Statins are drugs that inhibit cholesterol synthesis, blocking the conversion of the substrate HMG-CoA to mevalonate, thus preventing the initial processes of the biosynthesis of these precursors, both in humans and parasite. Our goal was to verify whether the Toxoplasma gondii (RH strain) tachyzoites form pretreated with pravastatin and simvastatin in association with pyrimethamine and sulfadiazine at low concentrations could affect the infection processes, suggesting direct action on protozoa intracellular proliferation through the inhibition of isoprenoids in the parasite's apicoplast. METHODS: To have the adhesion, infection, and parasite proliferation during experimental infection investigated, HeLa cells (10(5)) were subjected to a 24-hour infection by T. gondii tachyzoites forms of RH strain (5 x 10(5)) pretreated for 30 min with pravastatin and/or simvastatin combined or not with pyrimethamine and sulfadiazine. RESULTS: Combined with conventional drugs at low concentrations pravastatin and simvastatin inhibit the adhesion, invasion, and intracellular proliferation of T. gondii in HeLa cells which are similar to the positive control. CONCLUSION: Pravastatin and simvastatin in association with pyrimethamine and sulfadiazine at low concentrations can be regarded as a promising, effective alternative to toxoplasmosis treatment with reduced side effects.

[3] *Wong ND, Amsterdam EA, Ballantyne C et al.* **Spotlight from the American Society for Preventive Cardiology on Key Features of the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidelines on the Management of Blood Cholesterol**. American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31286451

ABSTRACT

The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol retains focus on recommendations for statin treatment in the original four statin-eligible groups [those with atherosclerotic cardiovascular disease (ASCVD), diabetes, low-density lipoprotein cholesterol (LDL-C) >/= 190 mg/dL, and higher risk primary prevention] without the use of treatment initiation or target LDL-C levels from the earlier 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline, but has several new features. First, patients with primary prevention are divided into those who are at low (< 5%), borderline (5% to < 7.5%), intermediate (7.5% to < 20%), and high (>/= 20%) risk based on the ASCVD risk estimator. Moreover, the new guideline goes further to consider a wider range of factors [now called "risk enhancers"-premature family history of ASCVD, persistently high LDL-C, chronic kidney disease (CKD), metabolic syndrome, conditions specific to women, inflammatory diseases, and high-risk ethnicities] that can be used to better inform the treatment decision. Moreover, more detailed recommendations on how the results of coronary calcium scanning can be used to inform the treatment decision are provided, including how it may be used to "de-risk" certain patients for delaying or avoiding the use of statin therapy. There are also specific sections for cholesterol management in other patient subgroups including women, children, certain ethnic groups, those with CKD, chronic inflammatory disorders and HIV, as well as discussion on the management of hypertriglyceridemia. Importantly, for persons with known ASCVD, a distinction is made for those who are at "very high risk" based on having had two major ASCVD events or one major event and two or more other high risk conditions, such as diabetes or other major risk factors, or bypass surgery or percutaneous intervention. Finally, the concept of a threshold LDL-C for initiating a non-statin therapy (after considering highest tolerated statin dosage) is provided, with ezetimibe recommended as the key non-statin to be added if the LDL-C still remains >/= 70 mg/dL for all ASCVD patients, and in those who are at "very high risk", further consideration for using a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. While the new guideline does have greater detail (and arguably, complexity), the refinements provide a strategy for guiding the clinician to target both statin and non-statin therapy to those most likely to derive benefit.

[4] *Prasad C, Davis KE, Imrhan V et al.* **Advanced Glycation End Products and Risks for Chronic Diseases: Intervening Through Lifestyle Modification**. American journal of lifestyle medicine 2019; 13:384-404.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31285723

ABSTRACT

Advanced glycation end products (AGEs) are a family of compounds of diverse chemical nature that are the products of nonenzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids. AGEs bind to one or more of their multiple receptors (RAGE) found on a variety of cell types and elicit an array of biologic responses. In this review, we have summarized the data on the nature of AGEs and issues associated with their measurements, their receptors, and changes in their expression under different physiologic and disease states. Last, we have used this information to prescribe lifestyle choices to modulate AGE-RAGE cycle for better health.

[5] *Salvatore T, Morganti R, Marchioli R, De Caterina R*. **Cholesterol lowering and stroke: no longer room for pleiotropic effects of statins - confirmation from PCSK9 inhibitor studies**. The American journal of medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31301293
ABSTRACT
BACKGROUND: The relationship between cholesterol levels and stroke has been much less clear than between cholesterol levels and coronary heart disease. This is likely mostly due to the inadequate power of older studies and the low intensity of cholesterol-lowering interventions at that time available. Because a reduction in stroke has been, conversely, clearly observed in trials with statins, for long "pleiotropic" effects of such drugs, unrelated to cholesterol lowering, have been invoked. In a previous analysis of all randomized trials of cholesterol-lowering treatments reporting on stroke we had, however, reached the conclusion that any cholesterol lowering is related to a significant reduction of stroke, in a relationship that appeared to exist for both statin and non-statin cholesterol-lowering interventions. Outcome results of the FOURIER trial with evolocumab, SPIRE-1 and -2 with bococizumab, and ODISSEY OUTCOMES trial with alirocumab now offer the opportunity of clearly confirming or confuting this concept. METHODS: We here report on an updated meta-regression of the relationship of total cholesterol changes occurred with various drugs or treatments and changes in the risk of stroke compared with control. RESULTS: Figures of the RR here found in FOURIER, SPIRE-1/2 and ODISSEY OUTCOMES (0.79, 0.60 and 0.79) are extremely close to the RR of 0.79, 0.79 and 0.84 predicted by our new meta-regression, respectively. CONCLUSIONS: These findings offer a definitive proof that the pure total (and low-density lipoprotein) cholesterol lowering, with any available lipid-lowering intervention, reduce stroke risk proportional to the extent of cholesterol reduction, without the need of invoking "pleiotropic" effects of any such treatment.

[6] *Moss ME, Lu Q, Iyer SL et al.* **Endothelial Mineralocorticoid Receptors Contribute to Vascular Inflammation in Atherosclerosis in a Sex-Specific Manner**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha119312954.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31294624
ABSTRACT
OBJECTIVE: MR (mineralocorticoid receptor) activation is associated with cardiovascular ischemia in humans. This study explores the role of the MR in atherosclerotic mice of both sexes and identifies a sex-specific role for endothelial cell (EC)-MR in vascular inflammation. Approach and Results: In the AAV-PCSK9 (adeno-associated virus-proprotein convertase subtilisin/kexin type 9) mouse atherosclerosis model, MR inhibition attenuated vascular inflammation in males but not females. Further studies comparing male and female littermates with intact MR or EC-MR deletion revealed that although EC-MR deletion did not affect plaque size in either sex, it reduced aortic arch inflammation specifically in male mice as measured by flow cytometry. Moreover, MR-intact females had larger plaques but were protected from vascular inflammation compared with males. Intravital microscopy of the mesenteric vasculature demonstrated that EC-MR deletion attenuated TNFalpha (tumor necrosis factor alpha)-induced leukocyte slow rolling and adhesion in males, while females exhibited fewer leukocyte-endothelial interactions with no additional effect of EC-MR deletion. These effects

corresponded with decreased TNFalpha-induced expression of the endothelial adhesion molecules ICAM-1 (intercellular adhesion molecule-1) and E-selectin in males with EC-MR deletion compared with MR-intact males and females of both genotypes. These observations were also consistent with MR and estrogen regulation of ICAM-1 transcription and E-selectin expression in primary cultured mouse ECs and human umbilical vein ECs. CONCLUSIONS: In male mice, EC-MR deletion attenuates leukocyte-endothelial interactions, plaque inflammation, and expression of E-selectin and ICAM-1, providing a potential mechanism by which the MR promotes vascular inflammation. In females, plaque inflammation and leukocyte-endothelial interactions are decreased relative to males and EC-MR deletion is not protective.

[7] *Wisloff T, Mundal LJ, Retterstol K et al.* **Economic evaluation of lipid lowering with PCSK9 inhibitors in patients with familial hypercholesterolemia: Methodological aspects**. Atherosclerosis 2019; 287:140-146.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31280039
ABSTRACT
BACKGROUND AND AIMS: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have proved to reduce low density lipoprotein cholesterol levels in numerous clinical trials. In two large clinical trials, PCSK9 inhibitor treatment reduced the risk of cardiovascular disease. Our aim was to explore the impact of varying assumptions about clinical effectiveness on health and economic outcomes for patients with familial hypercholesterolemia. METHODS: We used a previously published and validated Norwegian model for cardiovascular disease. The model was updated with recent data from the world's second largest registry of patients with genetically confirmed familial hypercholesterolemia. We performed analyses for 24 different subgroups of patients based on age, gender, statin tolerance and previous history of cardiovascular disease. RESULTS: In 1 out of 24 subgroups, PCSK9 inhibitors were cost-effective when effectiveness was modelled using direct relative efficacy as reported in the FOURIER trial. When using assumptions, as suggested in a recent consensus statement from the European Atherosclerosis Society, 14 subgroups were cost-effective. CONCLUSIONS: Cost-effectiveness of PCSK9 inhibitors depends highly on assumptions regarding effectiveness. Basing assumptions only on randomised controlled trials, and not taking into account varying effects based on baseline cholesterol level, results in much fewer groups being cost-effective.

[8] *Bahrami A, Barreto GE, Lombardi G et al.* **Emerging roles for high-density lipoproteins in neurodegenerative disorders**. Biofactors 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31301192
ABSTRACT
Lipoproteins are the complexes of different lipids and proteins, which are devoted to the transport and clearance of lipids or lipid-related molecules in the circulation. Lipoproteins have been found to play a crucial role in brain function and may influence myelination process. Among lipoproteins, high-density lipoproteins (HDLs) and their major protein component, apoA-I, are directly involved in cholesterol efflux in the brain. It has been suggested that inadequate or dysfunctional brain HDLs may contribute to cerebrovascular dysfunctions, neurodegeneration, or neurovascular instability. HDL deficiency could also promote cognitive decline through impacting on atherosclerotic risk. The focus of this review is to discuss

knowledge on HDL dysregulation in neurological disorders. A better understanding on how changes in cellular HDL and apolipoprotein homeostasis affect central nervous system function may provide promising novel avenues for the treatment of specific HDL-related neurological disorders.

[9] *Demoz GT, Wahdey S, Kasahun GG et al.* **Prescribing pattern of statins for primary prevention of cardiovascular diseases in patients with type 2 diabetes: insights from Ethiopia**. BMC research notes 2019; 12:386.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31288848
ABSTRACT
OBJECTIVE: Although most clinical practice guidelines endorsed statin use in type 2 diabetes (T2D) patients for reducing cardiovascular diseases (CVD), little is known about statin utilization in case of Ethiopia. Hence, this study was aimed to evaluate prescribing pattern of statins for primary prevention of CVD in T2D patients. A retrospective study conducted in T2D patients with the age group of 40-75 years. Prescriptions were audited for details of statin use and dose intensity. Descriptive analysis was performed using SPSS version 22.0. RESULTS: We included a total of 323 study subjects. Of those, 55.7% study subjects were found to be received statin for their primary prevention of CVD. Commonly prescribed type of statins was simvastatin (37.2%), atorvastatin (32.8%) and rosuvastatin (15.6%). Low, moderate and high intensive dose of statins were prescribed in 27.8%, 46.1%, and 26.1%, respectively. Of those subjects received statin, 60.6% had on target cholesterol level. Overall, a significant percentage of subjects did not receive their recommended statin for primary prevention of CVD which is below the guidelines' recommendation. Therefore, adherence to guidelines may help to promote the use of statins for primary prevention of CVD in T2D and advance interventions to improve statin prescribing should be considered.

[10] *Mazidi M, Katsiki N, Mikhailidis DP, Banach M*. **Dietary Choline is Positively Related to Overall and Cause-Specific Mortality: Results from Individuals of the National Health and Nutrition Examination Survey and Pooling Prospective Data**. The British journal of nutrition 2019:1-22.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31288869
ABSTRACT
Little is known about the association between dietary choline intake and mortality. We evaluated the link between choline consumption and overall as well as cause-specific mortality by using both individual data and pooling prospective studies by meta-analysis and systematic review. Furthermore, adjusted means of cardiometabolic risk factors across choline intake quartiles were calculated. Data from the National Health and Nutrition Examination Survey (1999-2010) were collected. Adjusted Cox regression was performed to determine the risk ratio (RR) and 95 % CI (95 % CI), as well as random-effects models and generic inverse variance methods to synthesise quantitative and pooling data, followed by a leave-one-out method for sensitivity analysis. After adjustments, we found that individuals consuming more choline had worse lipid profile and glucose homeostasis, but lower CRP levels (p < 0.001 for all comparisons) with no significant differences in anthropometric parameters and blood pressure. Multivariable Cox regression models revealed that individuals in the highest quartile (Q4) of

choline consumption had a greater risk of total (23 %), cardiovascular disease (CVD) (33 %) and stroke (30 %) mortality compared with the first quartile (Q1) (p < 0.001 for all comparison). These results were confirmed in a meta-analysis, showing that choline intake was positively and significantly associated with overall (RR: 1.12, 95 % CI: 1.08-1.17, I2: 2.9) and CVD (RR: 1.28, 95 % CI: 1.17-1.39, I2: 9.6) mortality risk. In contrast, the positive association between choline consumption and stroke mortality became non-significant (RR: 1.18, 95 % CI: 0.97-1.43, p = 0.092, I2: 1.1). Our findings shed light on the potential adverse effects of choline intake on selected cardiometabolic risk factors and mortality risk.

[11] *Ostbye TK, Berge GM, Nilsson A et al.* **The long chain monounsaturated cetoleic acid improves the efficiency of the omega-3 fatty acid metabolic pathway in Atlantic salmon and human HepG2 cells**. The British journal of nutrition 2019:1-29.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31288871
ABSTRACT
This study aimed to determine if the long chain monounsaturated fatty acid cetoleic acid (22:1n-11) can improve the capacity to synthesize the health promoting omega-3 fatty acids EPA and DHA in human and fish models.Human hepatocytes (HepG2) and salmon primary hepatocytes were first enriched with cetoleic acid,and thereafter their capacities to convert radiolabeled 18:3n-3 (alpha-linolenic acid, ALA) to EPA and DHA were measured. Increased endogenous levels of cetoleic acid led to increasedproduction of radiolabeled EPA+DHAin HepG2 by 40% and EPA in salmon hepatocytes by 12%. In order to verify if dietary intake of a fish oil rich in cetoleic acid would have the same beneficial effects on the omega-3 fatty acid metabolic pathway in vivo as found in vitro, Atlantic salmon were fedfour dietssupplemented with either sardine oil low in cetoleic acid or herring oil high in cetoleic acid at two inclusion levels (Low or High). The diets were balanced for EPA+DHA content within the Low and within the High groups.The salmon were fed these diets from 110g to 242g. The level of EPA+DHA in liverand whole-body retention ofDPA and EPA+DHA relative to what was eaten,increasedwith increased dietary cetoleic acid levels. Thus, it is concluded that cetoleic acid stimulated the synthesis of EPA and DHA from ALAin human HepG2 and of EPA in salmon hepatocytes in vitro and increasedwhole body retention of EPA+DHA in salmon by 15% points after dietary intake of cetoleic acid.

[12] *Chen G, Farris MS, Cowling T et al.* **Treatment and Low-Density Lipoprotein Cholesterol Management in Patients Diagnosed With Clinical Atherosclerotic Cardiovascular Disease in Alberta**. The Canadian journal of cardiology 2019; 35:884-891.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31292087
ABSTRACT
BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) is an important indicator in the development and management of atherosclerotic cardiovascular disease (ASCVD). Herein, we describe the management of LDL-C with lipid-lowering therapy, among patients diagnosed with clinical ASCVD in Alberta, Canada. METHODS: A retrospective study was conducted by linking multiple health system databases to examine clinical characteristics, treatments, and LDL-C assessments. Patients with ASCVD were identified using a specific case definition on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification/International

Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada codes between 2011 and 2015. LDL-C was assessed at the first measurement (index test) and second measurement (follow-up test) during the study period. LDL-C levels were evaluated on the basis of the 2016 Canadian Cardiovascular Society guideline recommendations for achieving < 2.0 mmol/L or a 50% reduction. Statin therapies were categorized as low-, moderate-, and high-intensity. RESULTS: Among the 281,665 individuals identified with ASCVD during the study period, 219,488 (77.9%) had an index LDL-C test, whereas 120,906 (55.1%) and 144,607 (65.9%) were prescribed lipid-lowering therapy before and after their index test, respectively. Most patients who received any lipid-lowering therapy were receiving moderate-/high-intensity statins (n = 133,029; 60.6%). Among the study cohort who had 2 LDL-C tests (n = 91,841; 32.6%), 48.5% of patients who received any lipid-lowering therapy did not achieve LDL-C levels < 2.0 at index date, whereas 36.6% did not achieve LDL-C levels < 2.0 or a 50% reduction at the follow-up test. CONCLUSIONS: The current study revealed that only two-thirds of patients with ASCVD were receiving pharmacotherapy and of those, a significant proportion did not reach recommended LDL-C levels. A remarkable treatment gap was identified for at-risk ASCVD patients. Further implementation strategies are required to address this undermanagement.

[13] *Umeda T, Hayashi A, Fujimoto G et al.* **Medication Adherence/Persistence and Demographics of Japanese Dyslipidemia Patients on Statin-Ezetimibe as a Separate Pill Combination Lipid-Lowering Therapy- An Observational Pharmacy Claims Database Study**. Circulation journal : official journal of the Japanese Circulation Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31281135

ABSTRACT

BACKGROUND: This study aimed to identify potential predictors of medication adherence and persistence with statin-ezetimibe combinational lipid-lowering therapy (LLT) as a separate pill combination in a real-world setting in Japan.Methods and Results:Patients newly switched to statin-ezetimibe combinational LLT from statin monotherapy were identified within a Japanese national pharmacy claims database during January 2015 to April 2018. Adherence and persistence were measured by the proportion of days covered (PDC), time to treatment discontinuation and persistence rate at 1 year. A stepwise multivariate logistic regression model and Cox proportional hazards regression model were used to explore potential predictors associated with adherence and persistence, respectively. Among 6,921 patients, 71.9% were adherent (PDC >/=80%), and 83.6% were persistent at 1 year after initiation. Patients aged </=54 years and >/=75 years were prone to be more non-adherent. Secondary prevention was associated with better adherence and longer persistence. Concomitant use of medications for depression/anxiety was associated with shorter persistence, whereas use of antihypertensive drugs was associated with better adherence and persistence. CONCLUSIONS: Age, concomitant use of certain classes of medications (or the existence of these diseases) and secondary prevention were associated with adherence and persistence of statin-ezetimibe combinational LLT. Given that dyslipidemia is a chronic disease requiring life-long control, active interventions are required for patients with poor adherence and persistence.

Literature update week 28 (2019)

[14] *Masson W, Epstein T, Huerin M et al.* **Association between non-HDL-C/HDL-C ratio and carotid atherosclerosis in postmenopausal middle-aged women**. Climacteric : the journal of the International Menopause Society 2019:1-5.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31287342
ABSTRACT
Background: A novel lipid relation, the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol (non-HDL-C/HDL-C) ratio gathers information on all atherogenic and antiatherogenic particles on a single date. The relationship between this lipid marker and the presence of carotid atherosclerotic plaque (CAP) in postmenopausal women is unknown. Methods: Postmenopausal women in primary prevention up to 70 years of age were recruited. Association between the non-HDL-C/HDL-C ratio and presence of CAP, assessed by ultrasonography, was analyzed. Receiver operating characteristic (ROC) curve analysis was performed. Results: A total of 440 females with a mean age of 58.1 +/- 5.3 years were recruited. The mean non-HDL-C/HDL ratio was 3.1 +/- 1.2 and 28.2% of woman had CAP. A positive relationship was seen between quintiles of the non-HDL-C/HDL-C ratio and prevalence of CAP ($p < 0.001$). Regardless of other risk factors, women with higher non-HDL-C/HDL-C ratios had a greater chance of having CAP (odds ratio 1.30, 95% confidence interval: 1.07-1.58, $p = 0.009$). In the ROC curve analysis, the area under the curve of the non-HDL-C/HDL ratio for detecting CAP was 0.703 (95% confidence interval: 0.640-0.765) and the optimal cut-off point was 3.0 (Youden index 0.395). Conclusion: The present study suggests that the non-HDL-C/HDL-C ratio might be a strong marker for predicting the risk of CAP in postmenopausal women.

[15] *Tsujikawa LM, Fu L, Das S et al.* **Apabetalone (RVX-208) reduces vascular inflammation in vitro and in CVD patients by a BET-dependent epigenetic mechanism**. Clinical epigenetics 2019; 11:102.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31300040
ABSTRACT
BACKGROUND: Apabetalone (RVX-208) is a bromodomain and extraterminal protein inhibitor (BETi) that in phase II trials reduced the relative risk (RR) of major adverse cardiac events (MACE) in patients with cardiovascular disease (CVD) by 44% and in diabetic CVD patients by 57% on top of statins. A phase III trial, BETonMACE, is currently assessing apabetalone's ability to reduce MACE in statin-treated post-acute coronary syndrome type 2 diabetic CVD patients with low high-density lipoprotein C. The leading cause of MACE is atherosclerosis, driven by dysfunctional lipid metabolism and chronic vascular inflammation (VI). In vitro studies have implicated the BET protein BRD4 as an epigenetic driver of inflammation and atherogenesis, suggesting that BETi may be clinically effective in combating VI. Here, we assessed apabetalone's ability to regulate inflammation-driven gene expression and cell adhesion in vitro and investigated the mechanism by which apabetalone suppresses expression. The clinical impact of apabetalone on mediators of VI was assessed with proteomic analysis of phase II CVD patient plasma. RESULTS: In vitro, apabetalone prevented inflammatory (TNFalpha, LPS, or IL-1beta) induction of key factors that drive endothelial activation, monocyte recruitment, adhesion, and plaque destabilization. BRD4 abundance on inflammatory and adhesion gene promoters and enhancers was reduced by apabetalone. BRD2-4 degradation by MZ-1 also prevented TNFalpha-induced transcription of monocyte and endothelial cell adhesion

molecules and inflammatory mediators, confirming BET-dependent regulation. Transcriptional regulation by apabetalone translated into a reduction in monocyte adhesion to an endothelial monolayer. In a phase II trial, apabetalone treatment reduced the abundance of multiple VI mediators in the plasma of CVD patients (SOMAscan(R) 1.3 k). These proteins correlate with CVD risk and include adhesion molecules, cytokines, and metalloproteinases. Ingenuity(R) Pathway Analysis (IPA(R)) predicted that apabetalone inhibits pro-atherogenic regulators and pathways and prevents disease states arising from leukocyte recruitment. CONCLUSIONS: Apabetalone suppressed gene expression of VI mediators in monocytes and endothelial cells by inhibiting BET-dependent transcription induced by multiple inflammatory stimuli. In CVD patients, apabetalone treatment reduced circulating levels of VI mediators, an outcome conducive with atherosclerotic plaque stabilization and MACE reduction. Inhibition of inflammatory and adhesion molecule gene expression by apabetalone is predicted to contribute to MACE reduction in the phase III BETonMACE trial.

[16] *Tugnait M, Gupta N, Hanley MJ et al.* **Effects of Strong CYP2C8 or CYP3A Inhibition and CYP3A Induction on the Pharmacokinetics of Brigatinib, an Oral Anaplastic Lymphoma Kinase Inhibitor, in Healthy Volunteers**. Clinical pharmacology in drug development 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31287236
ABSTRACT
In vitro data support involvement of cytochrome P450 (CYP)2C8 and CYP3A4 in the metabolism of the anaplastic lymphoma kinase inhibitor brigatinib. A 3-arm, open-label, randomized, single-dose, fixed-sequence crossover study was conducted to characterize the effects of the strong inhibitors gemfibrozil (of CYP2C8) and itraconazole (of CYP3A) and the strong inducer rifampin (of CYP3A) on the single-dose pharmacokinetics of brigatinib. Healthy subjects (n = 20 per arm) were administered a single dose of brigatinib (90 mg, arms 1 and 2; 180 mg, arm 3) alone in treatment period 1 and coadministered with multiple doses of gemfibrozil 600 mg twice daily (BID; arm 1), itraconazole 200 mg BID (arm 2), or rifampin 600 mg daily (QD; arm 3) in period 2. Compared with brigatinib alone, coadministration of gemfibrozil with brigatinib did not meaningfully affect brigatinib area under the plasma concentration-time curve (AUC0-inf ; geometric least-squares mean [LSM] ratio [90%CI], 0.88 [0.83-0.94]). Coadministration of itraconazole with brigatinib increased AUC0-inf (geometric LSM ratio [90%CI], 2.01 [1.84-2.20]). Coadministration of rifampin with brigatinib substantially reduced AUC0-inf (geometric LSM ratio [90%CI], 0.20 [0.18-0.21]) compared with brigatinib alone. The treatments were generally tolerated. Based on these results, strong CYP3A inhibitors and inducers should be avoided during brigatinib treatment. If concomitant use of a strong CYP3A inhibitor is unavoidable, the results of this study support a dose reduction of brigatinib by approximately 50%. Furthermore, CYP2C8 is not a meaningful determinant of brigatinib clearance, and no dose modifications are needed during coadministration of brigatinib with CYP2C8 inhibitors.

[17] *Liu XZ, Xu X, Zhu JQ, Zhao DB*. **Association between three non-insulin-based indexes of insulin resistance and hyperuricemia**. Clinical rheumatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31300980
ABSTRACT

OBJECTIVE: The association between hyperuricemia and insulin resistance (IR) has been demonstrated by many studies, but the traditional IR indexes are too impractical to be used in clinical practice for the recognition of the IR state in individuals with hyperuricemia. Therefore, we aimed to further investigate the association between hyperuricemia and three non-insulin-based IR indexes in this large-scale cross-sectional study. METHODS: A total of 174,695 adults without self-reported use of antihyperuricemic agents, hypoglycemic agents, or lipid-lowering drugs were included in the current analysis. The triglyceride to high-density lipoprotein cholesterol ratio (TG/HDLc), the product of fasting triglycerides and glucose (TyG), and metabolic score for IR (METS-IR) were calculated. Then, logistic regression analyses were applied to explore their association with hyperuricemia. RESULTS: The TG/HDLc, TyG, and METS-IR all had positive correlations with uric acid level. However, only TG/HDLc and TyG were significantly associated with hyperuricemia in both sexes and body mass index (BMI) classification (the ORs of the highest quartile for each were 6.751 and 1.505 in females and 6.487 and 1.646 in males, respectively). The AUC values of TG/HDLc and TyG to discriminate hyperuricemia were also statistically significant in both sexes and BMI classification (all greater than 0.7). CONCLUSIONS: TG/HDLc and TyG are strongly associated with hyperuricemia regardless of BMI classification. These two obtainable and cost-effective non-insulin-based IR indexes could be potential monitors during the management of hyperuricemia and prevention of its IR-driven comorbidities. Key Points * In this large-scale study, we identified TG/HDLc and TyG as indicators for identification of IR in patients with hyperuricemia. * These simple and practical IR indicators are of substantial clinical importance for implementing preventive strategies against IR-driven comorbidities of hyperuricemia.

[18] *Khalid SA, Inayat F, Tahir MK et al.* **Nicotinic Acid as a Phosphate-lowering Agent in Patients with End-stage Renal Disease on Maintenance Hemodialysis: A Single-center Prospective Study**. Cureus 2019; 11:e4566.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31281749
ABSTRACT
Background Hyperphosphatemia increases the risk of mortality and morbidity in patients with end-stage renal disease (ESRD). In addition to dietary restriction and renal replacement therapy, phosphorus-binding agents are the mainstay of treatment. While the use of calcium-containing binders has certain limitations, non-calcium-based binders are expensive and not readily available in developing countries. Previous studies on nicotinic acid as a phosphorus-lowering agent have limited data. In this study, we evaluated the efficacy of nicotinic acid in patients with ESRD on hemodialysis (HD) in Pakistan. Methods Forty-five patients with ESRD on maintenance HD having serum phosphorus levels >5.5 mg/dL were recruited. Nicotinic acid 250 mg was administered with food for four weeks. All patients with serum phosphorus levels <8 mg/dL were placed on a twice-daily regimen while the rest received it three times a day with meals. Patients were assessed at the beginning and end of the study with serum phosphorus levels. Results Mean age of the sample population was 44.6 +/- 13.9 years and 57.8% of participants were male. Serum phosphorus level before treatment ranged from 5.6 to 10.8 mg/dL (mean, 6.91 +/- 1.33). After nicotinic acid therapy, it ranged from 2.60 to 8.70 mg/dL (mean, 5.82 +/- 1.40). Mean decrease in serum phosphorus levels with nicotinic acid after one month of treatment was 1.08 +/- 1.16 mg/dL (p-value <0.001). Conclusion Nicotinic acid is

effective in lowering serum phosphorus levels in patients with ESRD who are under renal replacement therapy with maintenance HD.

[19] *Menini S, Iacobini C, Fantauzzi CB, Pugliese G*. **L-carnosine and its Derivatives as New Therapeutic Agents for the Prevention and Treatment of Vascular Complications of Diabetes**. Curr Med Chem 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31296153
ABSTRACT
Vascular complications are among the most serious manifestations of diabetes. Atherosclerosis is the main cause of reduced life quality and expectancy in diabetics, whereas diabetic nephropathy and retinopathy are the most common causes of end-stage renal disease and blindness. An effective therapeutic approach to prevent vascular complications should counteract the mechanisms of injury. Among them, the toxic effects of advanced glycation (AGEs) and lipoxidation (ALEs) end-products are well-recognized contributors to these sequelae. L-carnosine (beta-alanyl-L-histidine) acts as a quencher of the AGE/ALE precursors reactive carbonyl species (RCS), which are highly reactive aldehydes derived from oxidative and non-oxidative modifications of sugars and lipids. Consistently, L-carnosine was found to be effective in several disease models in which glyco/lipoxidation plays a central pathogenic role. Unfortunately, L-carnosine is rapidly inactivated by serum carnosinase in humans. Therefore, the search for carnosinase-resistant derivatives of L-carnosine represents a suitable strategy against carbonyl stress-dependent disorders, particularly diabetic vascular complications. In this review, we present and discuss available data on the efficacy of L-carnosine and its derivatives in preventing vascular complications in rodent models of diabetes and metabolic syndrome. We also discuss genetic findings providing evidence for the involvement of the carnosinase/L-carnosine system in the risk of developing diabetic nephropathy and for preferring the use of carnosinase-resistant compounds in human disease. The availability of therapeutic strategies capable to prevent both long-term glucose toxicity, resulting from insufficient glucose-lowering therapy, and lipotoxicity may help to reduce the clinical and economic burden of vascular complications of diabetes and related metabolic disorders.

[20] *Ctoi AF, Vodnar DC, Corina A et al.* **Gut Microbiota, Obesity and Bariatric Surgery: Current Knowledge and Future Perspectives**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31298152
ABSTRACT
BACKGROUND: There is an urgent need for a better understanding and management of obesity and obesity-associated diseases. It is known that obesity is associated with structural and functional changes in the microbiome. METHODS: The purpose of this review is to present current evidence from animal and human studies, demonstrating the effects and the potential efficacy of microbiota modulation in improving obesity and associated metabolic dysfunctions. RESULTS: This review discusses possible mechanisms linking gut microbiota dysbiosis and obesity, since there is a dual interaction between the two of them. Furthermore, comments on bariatric surgery, as a favourable model to understand the underlying metabolic and inflammatory effects, as well as its association with changes in the composition of the gut microbiota, are included. Also, a possible impact of anti-obesity drugs and the novel

antidiabetic drugs on the gut microbiota has been briefly discussed. CONCLUSION: More research is needed to better understand here discussed association between microbiota modulation and obesity. It is expecting that research in this field, in the following years, will lead to a personalized therapeutic approach considering the patient's microbiome, and also give rise to the discovery of new drugs and/or the combination therapies for the management of obesity and obesity-related co-morbidities.

[21] *Sunderic M, Robajac D, Gligorijevic N et al.* **Is There Something Fishy About Fish Oil?** Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31298156
ABSTRACT
BACKGROUND: Fish is consumed as a food worldwide and is considered as a rich source of essential nutrients required for healthy life of humans. Supplementation with fish oil has been adopted as a solution to prevent or cure many pathophysiological states and diseases by both the professionals and the civil population. The beneficial effects are, however, being questioned, as some controversial results were obtained in clinical and population studies. METHOD: Critical evaluation of studies regarding known effects of fish oil, both in favour of its consumption and related controversies. RESULTS: From the literature review, contradictory allegations about the positive action of the fish oil on human health emerged, so that a clear line about its beneficial effect cannot be withdrawn. CONCLUSION: Scientific results on the application of fish oil should be taken with caution as there is still no standardised approach in testing its effects and there are significantly different baselines in respect to nutritional and other lifestyle habits of different populations.

[22] *Zhang L, Lv H, Zhang Q et al.* **Association of SLCO1B1 and ABCB1 Genetic Variants with Atorvastatin-induced Myopathy in Patients with Acute Ischemic Stroke**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31298164
ABSTRACT
BACKGROUND: Certain patients experience muscle-related adverse effects after taking atorvastatin. Genetic factors play an important role in the occurrence of statin-induced myopathy. AIM: We aimed to identify genetic variants associated with statin-induced myotoxicity. METHODS: We prospectively enrolled 1,102 acute ischemic stroke patients who underwent atorvastatin treatment for the first time after admission. Patients were separated into case and control groups after a follow-up of 3 months. We used a biochemical definition of myopathy consisting of serum creatine kinase values more than ten times the upper limit of normal for the reference laboratory (150 U/L). Fifty single nucleotide polymorphisms (SNPs) from seven genes of ABCB1, CoQ2, HTR3B, RYR2, CYP3A5, HTR7 and SLCO1B1 were selected and genotyped. The effects of genetic polymorphisms on myopathy were observed. RESULTS: 61 cases and 110 controls were recruited in the study. Compared with the controls, the cases had a significant higher mutant frequency of the allele A (ABCB1, rs2373588) (OR = 2.01, 95%CI = 1.10-3.67, P = 0.001) and a significant lower mutant frequency of the allele A (SLCO1B1, rs976754) (OR = 1.85, 95%CI = 1.12-3.03, P = 0.042). Genotypes or alleles of the other SNPs had no significant difference between the two groups (P > 0.05). CONCLUSION: Our findings reveal

that SLCO1B1 and ABCB1 genetic variants are associated with statin-induced myopathy. These are valuable biomarkers for the evaluation of atorvastatin safety.

[23] *Alkhalil M*. **Mechanistic Insights to Target Atherosclerosis Residual Risk**. Current problems in cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31285037
ABSTRACT
Current pharmacological and mechanical therapies have reduced future cardiovascular risk. Nonetheless, a significant proportion of patients remained at high risk of recurrent events despite achieving guideline-directed therapeutic targets. This residual risk poses challenges despite tackling 'traditional' risk factors. Targeting the residual risk has been the focus of numerous pharmacotherapies which were associated with variable success. Incomplete understanding of the mechanistic nature combined with the lack of tools to precisely quantify the residual risk contributed to the relatively high residual risk after 'optimal' medical therapy. The development of atherosclerotic plaque is derived from lipid retention within arterial intima that triggers an inflammatory cascade accelerating atherosclerosis progression and rendering plaque more prone to rupture. The exposed subendothelial space with activated platelets causes arterial occlusion leading to potential fatality. Therefore, a distinctive approach to characterize these features may offer the opportunity to tailor novel antiatherosclerotic to reduce the residual risk. The traditional approach of measuring risk factors is beneficial at population-level but maybe less informative upon quantifying risk at an individual-basis. This review will discuss lipid accumulation, thrombosis, and inflammation as therapeutic targets of atherosclerosis. Additionally, we will summarize previous challenges of antiatherosclerosis therapies and the future role to tackle the residual risk.

[24] *Wu Z, Zhang Z, Lei Z, Lei P*. **CD14: Biology and role in the pathogenesis of disease**. Cytokine & growth factor reviews 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31296363
ABSTRACT
Human monocyte differentiation antigen CD14 is a pattern recognition receptor (PRR) that enhances innate immune responses. CD14 was first identified as a marker of monocytes to signal intracellular responses upon bacterial encounters. Given the absence of an intracellular tail, CD14 was doubted to have the signaling capacities. Later CD14 was confirmed as the TLR co-receptor for the detection of pathogen-associated molecular patterns. However, CD14 has been revealed as a multi-talented receptor. In last decade, CD14 was identified to activate NFAT to regulate the life cycle of myeloid cells in a TLR4-independent manner and to transport inflammatory lipids to induce phagocyte hyperactivation. And its influences on multiple related diseases have been further considered. In this review, we summarize advancements in the basic biology of the CD14 including its structure, binding ligands, signaling pathways, and its roles in the pathogenesis of inflammation, atherosclerosis, tumor and metabolic diseases. We also discuss the therapeutic potential of targeting the CD14 in related diseases.

[25] *Parhofer KG, von Stritzky B, Pietschmann N et al.* **PEARL: A Non-interventional Study of Real-World Alirocumab Use in German Clinical Practice**. Drugs - real world outcomes 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31280466

ABSTRACT

BACKGROUND: Several lipid guidelines recommend that proprotein convertase subtilisin/kexin type 9 inhibitors should be considered for patients with atherosclerotic cardiovascular disease who are inadequately treated with maximally tolerated lipid-lowering treatment. OBJECTIVES: The PEARL study assessed the efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in patients with hypercholesterolemia in a real-world setting. METHODS: PEARL was an open, prospective, multicenter, non-interventional study conducted in Germany. Patients (n = 619) for whom treating physicians decided to use alirocumab 75 or 150 mg every 2 weeks according to German guidelines (low-density lipoprotein cholesterol > 1.8/2.6 mmol/L [> 70/100 mg/dL], depending on cardiovascular risk, despite maximally tolerated statin therapy with/without other non-alirocumab lipid-lowering therapy) were enrolled and followed for 24 weeks. Physicians could adjust the alirocumab dose based on their clinical judgment. The primary efficacy endpoint was low-density lipoprotein cholesterol reduction from baseline (prior to alirocumab therapy) to week 24. RESULTS: Overall, 72.8% of patients reported complete or partial statin intolerance. Mean low-density lipoprotein cholesterol was 4.7 mmol/L (180.5 mg/dL) and 2.3 mmol/L (89.8 mg/dL) at baseline and week 24, respectively. Least-squares mean percentage change from baseline to week 24 in low-density lipoprotein cholesterol was - 48.6%. Initial alirocumab dose was 75 mg in 72.9% of patients and 150 mg in 24.5% of patients; 19.6% of patients received an alirocumab dose increase (75 to 150 mg) and 1.6% of patients received a dose decrease. Adverse events were reported in 10.3% of patients, with myalgia being the most common. CONCLUSIONS: In a real-world setting in Germany, alirocumab was used in patients who had high baseline low-density lipoprotein cholesterol levels with/without statin intolerance. Efficacy and safety were consistent with findings observed in the ODYSSEY Phase III program.

[26] *Nogueira-Recalde U, Lorenzo-Gomez I, Blanco FJ et al.* **Fibrates as drugs with senolytic and autophagic activity for osteoarthritis therapy**. EBioMedicine 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31285188

ABSTRACT

BACKGROUND: Ageing-related failure of homeostasis mechanisms contributes to articular cartilage degeneration and osteoarthritis (OA), for which disease-modifying treatments are not available. Our objective was to identify molecules to prevent OA by regulating chondrocyte senescence and autophagy. METHODS: Human chondrocytes with IL-6 induced senescence and autophagy suppression and SA-beta-gal as a reporter of senescence and LC3 as reporter of autophagic flux were used to screen the Prestwick Chemical Library of approved drugs. Preclinical cellular, tissue and blood from OA and blood from OA and ageing models were used to test the efficacy and relevance of activating PPARalpha related to cartilage degeneration. FINDINGS: Senotherapeutic molecules with pro-autophagic activity were identified. Fenofibrate (FN), a PPARalpha agonist used for dyslipidaemias in humans, reduced the number of senescent cells via apoptosis, increased autophagic flux, and protected against cartilage degradation. FN reduced both senescence and inflammation and increased autophagy in both ageing human and OA chondrocytes whereas PPARalpha knockdown conferred the opposite effect. Moreover, PPARalpha expression was reduced through both ageing and OA in mice and also in blood and

cartilage from knees of OA patients. Remarkably, in a retrospective study, fibrate treatment improved OA clinical conditions in human patients from the Osteoarthritis Initiative (OAI) Cohort. INTERPRETATION: These results demonstrate that FDA-approved fibrate drugs targeting lipid metabolism protect against cartilage degeneration seen with ageing and OA. Thus, these drugs could have immediate clinically utility for age-related cartilage degeneration and OA treatment. FUND: This study was supported by Instituto de Salud Carlos III- Ministerio de Ciencia, Innovacion y Universidades, Spain, Plan Estatal 2013-2016 and Fondo Europeo de Desarrollo Regional (FEDER), "Una manera de hacer Europa", PI14/01324 and PI17/02059, by Innopharma Pharmacogenomics platform applied to the validation of targets and discovery of drugs candidates to preclinical phases, Ministerio de Economia y Competitividad, by grants of the National Instiutes of Health to PDR (P01 AG043376 and U19 AG056278). We thank FOREUM Foundation for Research in Rheumatology for their support.

[27] *Szychlinska MA, Ravalli S, Musumeci G*. **Pleiotropic effect of fibrates on senescence and autophagy in osteoarthritis**. EBioMedicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31300346
ABSTRACT

[28] *Wang Q, Wang Y, Lehto K et al.* **Genetically-predicted life-long lowering of low-density lipoprotein cholesterol is associated with decreased frailty: A Mendelian randomization study in UK biobank**. EBioMedicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31300347
ABSTRACT
BACKGROUND: High circulating low-density lipoprotein cholesterol (LDL-C) is a major risk factor for atherosclerosis and age-associated cardiovascular events. Long-term dyslipidaemia could contribute to the development of frailty in older individuals through its role in determining cardiovascular health and potentially other physiological pathways. METHODS: We conducted Mendelian randomization (MR) analyses using genetic variants to estimate the effects of long-term LDL-C modification on frailty in UK Biobank (n=378,161). Frailty was derived from health questionnaire and interview responses at baseline when participants were aged 40 to 69years, and calculated using an accumulation-of-deficits approach, i.e. the frailty index (FI). Several aggregated instrumental variables (IVs) using 50 and 274 genetic variants were constructed from independent single-nucleotide polymorphisms (SNPs) to instrument circulating LDL-C concentrations. Specific sets of variants in or near genes that encode six lipid-lowering drug targets (HMGCR, PCSK9, NPC1L1, APOB, APOC3, and LDLR) were used to index effects of exposure to related drug classes on frailty. SNP-LDL-C effects were available from previously published studies. SNP-FI effects were obtained using adjusted linear regression models. Two-sample MR analyses were performed with the IVs as instruments using inverse-variance weighted, MR-Egger, weighted median, and weighted mode methods. To address the stability of the findings, MR analyses were also performed using i) a modified FI excluding the cardiometabolic deficit items and ii) data from comparatively older individuals (aged >/=60years) only. Several sensitivity analyses were also conducted. FINDINGS: On average 0.14% to 0.23% and 0.16% to 0.31% decrements in frailty were observed per standard deviation reduction in LDL-C exposure, instrumented by the general IVs consisting of 50 and 274 variants,

respectively. Consistent, though less precise, associations were observed in the HMGCR-, APOC3-, NPC1L1-, and LDLR-specific IV analyses. In contrast, results for PCSK9 were in the same direction but more modest, and null for APOB. All sensitivity analyses produced similar findings. INTERPRETATION: A genetically-predicted life-long lowering of LDL-C is associated with decreased frailty in midlife and older age, representing supportive evidence for LDL-C's role in multiple health- and age-related pathways. The use of lipid-lowering therapeutics with varying mechanisms of action may differ by the extent to which they provide overall health benefits.

[29] *Fujiwara Y, Eguchi S, Murayama H et al.* **Relationship between diet/exercise and pharmacotherapy to enhance the GLP-1 levels in type 2 diabetes**. Endocrinology, diabetes & metabolism 2019; 2:e00068.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31294084
ABSTRACT
The rapid rise in the prevalence of type 2 diabetes mellitus (T2DM) poses a huge healthcare burden across the world. Although there are several antihyperglycaemic agents (AHAs) available including addition of new drug classes to the treatment algorithm, more than 50% of patients with T2DM do not achieve glycaemic targets, suggesting an urgent need for treatment strategies focusing on prevention and progression of T2DM and its long-term complications. Lifestyle changes including implementation of healthy diet and physical activity are cornerstones for the management of T2DM. The positive effects of diet and exercise on incretin hormones such as glucagon-like peptide-1 (GLP-1) have been reported. We hypothesize an IDEP concept (Interaction between Diet/Exercise and Pharmacotherapy) aimed at modifying the diet and lifestyle, along with pharmacotherapy to enhance the GLP-1 levels, would result in good glycaemic control in patients with T2DM. Consuming protein-rich food, avoiding saturated fatty acids and making small changes in eating habits such as eating slowly with longer mastication time can have a positive impact on the GLP-1 secretion and insulin levels. Further the type of physical activity (aerobic/resistance training), intensity of exercise, duration, time and frequency of exercise have shown to improve GLP-1 levels. Apart from AHAs, a few antihypertensive drugs and lipid-lowering drugs have also shown to increase endogenous GLP-1 levels, however, due to quick degradation of GLP-1 by dipeptidyl peptidase-4 (DPP-4) enzyme, treatment with DPP-4 inhibitors would protect GLP-1 from degradation and prolong its activity. Thus, IDEP concept can be a promising treatment strategy, which positively influences the GLP-1 levels and provide additive benefits in terms of improving metabolic parameters in patients with T2DM and slowing the progression of T2DM and its associated complications.

[30] *Degano IR, Ramos R, Garcia-Gil M et al.* **Three-year events and mortality in cardiovascular disease patients without lipid-lowering treatment**. European journal of preventive cardiology 2019:2047487319862103.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31288537
ABSTRACT

[31] *Yan L, Zhu T*. **Effects of rosuvastatin on neuronal apoptosis in cerebral ischemic stroke rats via Sirt1/NF-kappa B signaling pathway**. European review for medical and pharmacological sciences 2019; 23:5449-5455.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31298398

ABSTRACT

OBJECTIVE: To investigate the effects of rosuvastatin on nerve cell apoptosis in rats with cerebral ischemic stroke through Sirt1/NF-kappaB pathway. MATERIALS AND METHODS: 30 model rats were divided into three groups: normal group, stroke group (rats with cerebral ischemic stroke) and stroke+RVT group (cerebral ischemic stroke rats treated with rosuvastatin). The expression of Sirt1/NF-kappaB, areas of stroke infarction, cell cycles, as well as apoptosis situation in different groups were detected by Western Blot, immunohistochemistry, histomorphological observation, triphenyl tetrazolium chloride (TTC) staining and flow cytometry as well as immunofluorescent staining. RESULTS: Optical microscope observation showed cells in normal group presented complete and clear cellular hierarchical structure, regular cell arrangement, bluish violet cell nucleus and pink cytoplasm. No damage or necrosis was observed under normal condition. In stroke group, the boundary line between cytoplasm and nucleus was blurry and some apoptosis bodies were also observed. However, after rosuvastatin treatment, necrosis disappeared in stroke+RVT group. Western Blot analysis showed that the expression of SIRT1 decreased and NF-kappaB elevated in stroke group compared with those in normal group ($p<0.05$). However, rosuvastatin could reverse the effects of stroke on SIRT1 and NF-kappaB ($p<0.05$). The results of immunohistochemistry and immunofluorescent staining also confirmed our findings in SIRT1 and NF-kappaB expression after stroke. The areas of cerebral infarction increased significantly in stroke group and this effect could also be reversed by rosuvastatin treatment ($p<0.05$). Besides, cell cycle detection also showed that rosuvastatin treatment could inhibit the shortening of G1, S as well as G2 periods in cell cycles after stoke ($p<0.05$). CONCLUSIONS: Rosuvastatin may have great effects on improving cerebral infarction condition in rats with cerebral ischemic stroke. The mechanisms may be through Sirt1/ NF-kappaB pathway, thereby reducing the apoptosis rate and improving cell cycle of brain cells.

[32] *Tang X*. **Analysis of interleukin-17 and interleukin-18 levels in animal models of atherosclerosis**. Experimental and therapeutic medicine 2019; 18:517-522.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31281442

ABSTRACT

This study investigated the correlation between the levels of interleukin (IL)-17 and IL-18 and atherosclerotic plaques. A total of 60 Apo E gene (Apo E-/-) mice were fed with high-fat diet in the model group and 20 wild male C57BL/6 mice were fed with the basic diet in the control group. The serum levels of IL-17 and IL-18 were determined by enzyme-linked immunosorbent assay. Carotid artery ultrasonography was performed and divided into stable plaque, unstable plaque and non-plaque groups. The severity of plaque was estimated by semi-quantitative method and divided into grades I, II and III. The expression levels of low-density lipoprotein cholesterol, plasma total cholesterol and blood glucose level in the model group induced by high-fat diet were significantly higher than those in the control group ($P<0.05$). The level in the model group was significantly higher than in the control group at the 16th week ($P<0.05$). The expression of IL-17 and IL-18 in the model group was significantly higher than that in the control group ($t=6.903$, 11.02, $P<0.05$). The concentration of IL-17 and IL-18 in the non-plaque group was significantly lower than that in the stable plaque and unstable plaque groups ($P<0.05$). The

concentration of IL-17 and IL-18 in the stable plaque group was significantly lower than that in the unstable plaque group (P<0.05). Based on the correlation of IL-17 and IL-18 expressions in the model group, the expression of IL-18 increased with the expression of IL-17, indicating that the expression of IL-17 was positively correlated with that of IL-18 (r=0.7195, P<0.001). In conclusion, serum IL-17 and IL-18 played an important role in the formation and development of atherosclerotic plaque, and were related to the stability and severity of plaque. The expression of IL-17 and IL-18 was positively correlated.

[33] *Sathyapalan T, Hobkirk JP, Javed Z et al.* **The Effect of Atorvastatin (and Subsequent Metformin) on Adipose Tissue Acylation-Stimulatory-Protein Concentration and Inflammatory Biomarkers in Overweight/Obese Women With Polycystic Ovary Syndrome**. Frontiers in endocrinology 2019; 10:394.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31293514

ABSTRACT

Background: Atorvastatin has been shown to improve cardiovascular risk (CVR) indices in women with polycystic ovary syndrome (PCOS). Low-grade chronic inflammation of adipose tissue may link PCOS and adverse CVR. In pro-inflammatory states such as PCOS, spontaneous activation of the alternative pathway of complement results in increased generation of acylation stimulating protein (ASP) from adipocytes irrespective of body mass index. Methods: The objective of this study was to determine the effect of atorvastatin on markers of adipose tissue dysfunction and inflammation; acylation-stimulating-protein (ASP), interleukin-6 (IL-6), and monocyte-chemoattractant-protein-1 (MCP-1) in PCOS. This was a randomized, double-blind, placebo-controlled study where 40 medication-naive women with PCOS and biochemical hyperandrogenaemia were randomized to either atorvastatin 20 mg daily or placebo for 12 weeks. Following the 12 week randomization; both group of women with PCOS were subsequently started on metformin 1,500 mg daily for further 12 weeks to assess whether pre-treatment with atorvastatin potentiates the effects of metformin on markers of adipose tissue function We conducted a post-hoc review to detect plasma ASP and the pro-inflammatory cytokines IL6 and MCP-1 before and after 12 and 24 weeks of treatment. Results: There was significant reduction in ASP (156.7 +/- 16.2 vs. 124.4 +/- 14.8 ng/ml p <0.01), IL-6 (1.48 +/- 0.29 vs.0.73 +/- 0.34 pg/ml p = 0.01) and MCP-1 (30.4 +/- 4.2 vs. 23.0 +/- 4.5 pg/ml p = 0.02) after 12 weeks of atorvastatin that was maintained subsequently with 12 weeks treatment with metformin. There was a significant positive correlation between ASP levels with CRP (p < 0.01), testosterone (p < 0.01) and HOMA-IR (p < 0.01); IL-6 levels with CRP (p <0.01) and testosterone (p < 0.01) and MCP-1 with CRP (p < 0.01); testosterone (p < 0.01) and HOMA-IR (p < 0.02). Conclusions: This post-hoc analysis revealed that 12 weeks of atorvastatin treatment significantly decreased the markers of adipose tissue dysfunction and inflammation, namely ASP, IL-6 and MCP-1 in obese women with PCOS. Changes in adipose tissue markers were significantly associative with substantial improvements in HOMA-IR, testosterone and hs-CRP levels. ISRCTN Number: ISRCTN24474824.

[34] *Pinto X, Sarasa I*. **[New perspectives in the treatment of hypercholesterolaemia since the availability of PCSK9 inhibitors]**. Hipertens Riesgo Vasc 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31288990

ABSTRACT
The large clinical trials on cardiovascular prevention have demonstrated that the more atherogenic cholesterol is reduced the greater the preventive benefit, and neither a threshold value below which that effect disappears nor negative effects on health have been observed. Therefore, the objectives of hypercholesterolaemia control in patients at high cardiovascular risk are becoming ever stricter. The fact that most high-risk patients do not achieve these objectives requires, among other measures, rational use of available lipid-lowering drugs, including monoclonal antibodies that inhibit the protein PCSK9 (PCSK9i). The PCSK9i that are currently licensed for clinical use, evolocumab and alirocumab, have shown high potency in lowering LDL-cholesterol, which can exceed 60%, and other favourable effects on lipid profiles, including a very marked reduction of non-HDL cholesterol and apolipoproteinB. Likewise, through large-scale clinical trials, both drugs have demonstrated a preventive effect against cardiovascular diseases, and a high degree of safety. In addition, in the case of alirocumab, a reduction in all-cause mortality has been observed. However, the high cost of the PCSK9i means that prescription is restricted to patients at highest cardiovascular risk who cannot be controlled with high-potency statins and ezetimibe. It is to be hoped that the new guidelines that are to be issued soon by various scientific societies will define in greater detail the patients and the conditions in which we can use PCSK9i, drugs which currently constitute the greatest advance in hypercholesterolaemia of recent decades.

[35] *Kovacs E, Wang X, Strobl R, Grill E*. **Economic evaluation of guideline implementation in primary care: a systematic review**. International journal for quality in health care : journal of the International Society for Quality in Health Care 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31290962

ABSTRACT
PURPOSE: To review the economic evaluation of the guideline implementation in primary care. DATA SOURCES: Medline and Embase. STUDY SELECTION: Electronic search was conducted on April 1, 2019, focusing on studies published in the previous ten years in developed countries about guidelines of non-communicable diseases of adult (>/=18 years) population, the interventions targeting the primary care provider. Data extraction was performed by two independent researchers using a Microsoft Access based form. RESULTS OF DATA SYNTHESIS: Among the 1338 studies assessed by title or abstract, 212 qualified for full text reading. From the final 39 clinically eligible studies, 14 reported economic evaluation. Cost consequences analysis, presented in four studies, provided limited information. Cost-benefit analysis was reported in five studies. Patient mediated intervention, and outreach visit applied in two studies showed no saving. Audit resulted significant savings in lipid lowering medication. Audit plus financial intervention was estimated to reduce referrals into secondary care. Analysis of incremental cost-effectiveness ratios was applied in four studies. Educational meeting evaluated in a simulated practice was cost-effective. Educational meeting extended with motivational interview showed no improvement; likewise two studies of multifaceted intervention. Cost-utility analysis of educational meeting supported with other educational materials showed unfavourable outcome. CONCLUSION: Only a minor proportion of studies reporting clinical effectiveness of guideline implementation interventions included any type of economic evaluation. Rigorous and standardized cost-effectiveness analysis would be required,

supporting decision-making between simple and multifaceted interventions through comparability.

[36] *Takeguchi-Kikuchi S, Hayasaka T, Katayama T et al.* **Anti-signal Recognition Particle Antibody-positive Necrotizing Myopathy with Secondary Cardiomyopathy: The First Myocardial Biopsy- and Multimodal Imaging-proven Case**. Intern Med 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31292376
ABSTRACT
A 69-year-old Japanese woman was admitted to our hospital with progressive muscle weakness and dysphagia. She was taking pitavastatin for dyslipidemia. Her serum creatine kinase was 6,300 U/L. Pitavastatin was stopped, but her symptoms deteriorated, and cardiac congestion appeared. A muscle biopsy showed necrotizing myopathy (NM), and anti-signal recognition particle (SRP) antibody was positive. (18)F-fluorodeoxyglucose-positron emission tomography showed an abnormal uptake, and magnetic resonance imaging showed abnormal gadolinium enhancement in the left ventricular wall. An endomyocardial biopsy revealed inflammatory cardiomyopathy. Steroid, tacrolimus, and intravenous immunoglobulins were effective against the symptoms. This is the first case of biopsy-proven secondary cardiomyopathy due to anti-SRP-positive NM.

[37] *Interator H, Brener A, Hoshen M et al.* **Sex, Ethnicity, and Socioeconomic Status Affect on Israeli Pediatric Lipid Testing Despite Equality in National Healthcare Services**. The Israel Medical Association journal : IMAJ 2019; 21:369-375.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31280503
ABSTRACT
BACKGROUND: In Israel, coronary heart disease mortality rates are significantly higher among the Arab population than the Jewish population. Dyslipidemia prevention should begin in childhood. OBJECTIVES: To identify sociodemographic disparities in the preventive health measurement of lipid profile testing and lipoprotein levels among Israeli children and adolescents. METHODS: A cross-sectional analysis of 1.2 million children and adolescents insured by Clalit Health Services between 2007 and 2011 was conducted using sociodemographic data and serum lipid concentrations. RESULTS: Overall, 10.1% individuals had undergone lipid testing. Those with male sex (odds ratio [OR] = 0.813, 95% confidence interval [95%CI] 0.809-0.816), Arab ethnicity (OR = 0.952, 95%CI 0.941-0.963), and low socioeconomic status (SES) (OR = 0.740, 95%CI 0.728-0.752) were less likely to be tested. By 2010, differences among economic sectors narrowed and Arab children were more likely to be tested (OR = 1.039, 95%CI 1.035-1.044). Girls had higher total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and non-high-density lipoprotein-cholesterol levels compared to boys ($P < 0.001$). Jewish children had higher cholesterol and low-density and high-density lipoprotein-cholesterol, as well as lower triglyceride levels than Arabs ($P < 0.001$). Children with low SES had lower cholesterol, low-density and high-density lipoprotein-cholesterol, and non-high-density lipoprotein-cholesterol levels ($P < 0.001$). CONCLUSIONS: We found that boys, Arab children, and those with low SES were less likely to be tested. Over time there was a gradual reduction in these disparities. Publicly sponsored healthcare services can diminish

disparities in the provision of preventive health among diverse socioeconomic groups that comprise the national population.

[38] *Ashoor IF, Mansfield SA, O'Shaughnessy MM et al.* **Prevalence of Cardiovascular Disease Risk Factors in Childhood Glomerular Diseases**. Journal of the American Heart Association 2019; 8:e012143.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31286821
ABSTRACT
Background Cardiovascular disease is a major cause of morbidity and mortality in children with chronic kidney disease. We sought to determine the prevalence of cardiovascular risk factors in children with glomerular disease and to describe current practice patterns regarding risk factor identification and management. Methods and Results Seven-hundred sixty-one children aged 0 to 17 years with any of 4 biopsy-confirmed primary glomerular diseases (minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy/vasculitis) were enrolled at a median of 16 months from glomerular disease diagnosis in the multicenter prospective Cure Glomerulonephropathy Network study. Prevalence of traditional (hypertension, hypercholesterolemia, and obesity) and novel (proteinuria, prematurity, and passive smoke exposure) cardiovascular risk factors were determined at enrollment and compared across glomerular disease subtypes. Frequency of screening for dyslipidemia and prescribing of lipid-lowering or antihypertensive medications were compared across glomerular disease subtype, steroid exposure, and remission status groups. Compared with the general population, all traditional risk factors were more frequent: among those screened, 21% had hypertension, 51% were overweight or obese, and 71% had dyslipidemia. Children who were not in remission at enrollment were more likely to have hypertension and hypercholesterolemia. Fourteen percent of hypertensive children were not receiving antihypertensives. Only 49% underwent screening for dyslipidemia and only 9% of those with confirmed dyslipidemia received lipid-lowering medications. Conclusions Children with primary glomerular diseases exhibit a high frequency of modifiable cardiovascular risk factors, particularly untreated dyslipidemia. Lipid panels should be routinely measured to better define the burden of dyslipidemia in this population. Current approaches to screening for and treating cardiovascular risk factors are not uniform, highlighting a need for evidence-based, disease-specific guidelines.

[39] *Robinson JG, Jayanna MB, Brown AS et al.* **Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31281070
ABSTRACT
Acquisition costs and cost-effectiveness have limited access and recommendations to use proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibiting monoclonal antibodies (mAbs). Recently, prices were reduced by 60% for alirocumab and evolocumab. This statement systematically reviewed subgroup analyses from statin and PCSK9 mAb trials to identify higher risk groups for which PCSK9 mAbs at the new price could be considered a reasonable (<US$100,000 per quality adjusted life year [QALY]) or high (<US$50,000 per QALY) value. In patients at extremely high risk, with a high burden of atherosclerotic cardiovascular disease

(ASCVD) or ASCVD with multiple poorly controlled or adverse risk factors, PCSK9 mAbs can provide reasonable value when low-density lipoprotein cholesterol (LDL-C) is >/=70 mg/dL. In patients at very high risk (ASCVD without peripheral arterial disease and lower levels of poorly controlled risk factors), PCSK9 mAbs provide a reasonable value when LDL-C levels are >/=100 mg/dL. High-risk patients (less-extensive ASCVD with well-controlled risk factors) may experience reasonable value when LDL-C levels are >/=130 mg/dL. Patients with heterozygous familial hypercholesterolemia or severe hypercholesterolemia with untreated LDL-C levels >/=220 mg/dL also should experience reasonable or high value from PCSK9 mAbs when LDL-C is >/=100 mg/dL for primary prevention and >/=70 mg/dL for secondary prevention.

[40] *Yesiltas B, Torkkeli M, Almasy L et al.* **Interfacial structure of 70% fish oil-in-water emulsions stabilized with combinations of sodium caseinate and phosphatidylcholine**. Journal of colloid and interface science 2019; 554:183-190.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31299546
ABSTRACT
We report on the structural evaluation of high fat fish oil-in-water emulsions emulsified with sodium caseinate (CAS) and phosphatidylcholine (PC). The microemulsions contained 70% (w/w) fish oil with 1.05-1.4% (w/w) CAS and 0.4-1.75% (w/w) PC and were studied by the combination of light scattering together with small-angle X-ray and neutron scattering (SAXS/SANS). Aqueous CAS forms aggregates having a denser core of about 100kDa and less dense shell about 400kDa with the hard sphere diameter of 20.4nm. PC appears as multilayers whose coherence length spans from 40 to 100nm. PC monolayer separates oil and water phases. Moreover, 80% CAS particles are loosely bound to the interface but are not forming continuous coverage. The distance between aggregated CAS particles in microemulsion is increased compared to CAS aggregates in pure CAS-in-water system. PC multilayers become larger in the presence of oil-water interface compared to the pure PC mixtures. Bilayers become larger with increasing PC concentration. This study forms a structural base for the combination of CAS and PC emulsifiers forming a well-defined thin and dense PC layer together with thick but less dense CAS layer, which is assumed to explain its better oxidative stability compared to single emulsifiers.

[41] *Kim HG, Huang M, Xin Y et al.* **The epigenetic regulator SIRT6 protects the liver from alcohol-induced tissue injury by reducing oxidative stress in mice**. Journal of hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31295533
ABSTRACT
BACKGROUND & AIMS: As an NAD(+)-dependent deacetylase and a key epigenetic regulator, sirtuin 6 (SIRT6) has been implicated in the regulation of metabolism, DNA repair, and inflammation. However, the role of SIRT6 in alcoholic liver disease (ALD) remains unclear. The aim of this study was to investigate the function and mechanism of SIRT6 in ALD pathogenesis. METHODS: We developed and characterized Sirt6 knockout (KO) and transgenic (Tg) mouse models that were treated with either control or ethanol diet. Hepatic steatosis, inflammation, and oxidative stress were analyzed using biochemical and histological methods. Gene regulation was analyzed by luciferase reporter and chromatin immunoprecipitation assays. RESULTS: The Sirt6 KO mice developed severe liver injury manifested by a remarkable increase

of oxidative stress and inflammation whereas the Sirt6 Tg mice were protected from ALD via normalization of hepatic lipids, inflammatory response, and oxidative stress. Our molecular analysis has identified a number of novel Sirt6-regulated genes that are involved in anti-oxidative stress, including metallothionein 1 and 2 (Mt1 and Mt2). Mt1/2 genes were down-regulated in the livers of Sirt6 KO mice and alcoholic hepatitis patients. Overexpression of Mt1 in the liver of Sirt6 KO mice improved ALD by reducing hepatic oxidative stress and inflammation. We also identified a critical link between SIRT6 and metal regulatory transcription factor 1 (Mtf1) via a physical interaction and functional coactivation. Mt1/2 promoter reporter assays showed a strong synergistic effect of SIRT6 on the Mtf1 transcriptional activity. CONCLUSIONS: Our data suggest that SIRT6 plays a critical protective role against ALD and it may serve as a potential therapeutic target for ALD. LAY SUMMARY: Liver, the primary organ for ethanol metabolism, can be damaged by the byproducts of ethanol metabolism including reactive oxygen species. In this study, we have identified a key epigenetic regulator SIRT6 that plays a critical role in protecting liver from the oxidative stress-induced liver injury. Thus, our data suggest that SIRT6 may be a potential therapeutic target for alcohol-related liver disease.

[42] *Sokolov V, Helmlinger G, Nilsson C et al.* **Comparative quantitative systems pharmacology modeling of anti-PCSK9 therapeutic modalities in hypercholesterolemia**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31292220
ABSTRACT
Since the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) as an attractive target in the treatment of hypercholesterolemia, multiple anti-PCSK9 therapeutic modalities have been pursued in drug development. The objective of this original research is to set the stage for the quantitative benchmarking of two anti-PCSK9 pharmacological modality classes, monoclonal antibodies (mAbs) and small interfering RNA (siRNA). To this end, we developed an integrative mathematical model of lipoprotein homeostasis describing the dynamic interplay between PCSK9, LDL cholesterol (LDLc), VLDL cholesterol, HDL cholesterol (HDLc), apoliprotein B (ApoB), lipoprotein A (Lp(a)) and triglycerides (TG). We demonstrate that LDLc decreased proportionally to PCSK9 reduction for both mAb and siRNA modalities. At marketed doses, however, treatment with mAbs resulted in an additional ~20% LDLc reduction compared to siRNA. We further used the model as an evaluation tool and determined that no quantitative differences were observed in HDLc, Lp(a), TG or ApoB responses, suggesting that disruption of PCSK9 synthesis would provide no additional effects on lipoprotein-related biomarkers in the patient segment investigated. Predictive model simulations further indicate siRNA therapies may reach reductions in LDLc levels comparable to those achieved with mAbs, if the current threshold of 80% PCSK9 inhibition via siRNA could be overcome.

[43] *Kanda N, Okajima F*. **Atopic Dermatitis-Like Rash During Evolocumab Treatment of Familial Hypercholesterolemia**. Journal of Nippon Medical School = Nippon Ika Daigaku zasshi 2019; 86:187-190.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31292332
ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that targets the low-density lipoprotein (LDL) receptor for lysosomal degradation. PCSK9 impedes the receptor-mediated clearance of LDL-cholesterol, thereby increasing serum LDL-cholesterol levels. Evolocumab, a human monoclonal antibody against PCSK9, effectively reduces serum LDL-cholesterol levels. We report the first known case of a patient who developed an atopic dermatitis (AD)-like rash during evolocumab therapy. A 43-year-old Japanese man with heterozygous familial hypercholesterolemia was treated with subcutaneous injection of 140 mg evolocumab biweekly, for 16 months. The therapy was then changed to subcutaneous injection of 420 mg evolocumab monthly. A few days after the first dose, the patient experienced pruritus and rash on his extremities. The rash worsened, while the pruritus subsided, then relapsed after the second and third doses. He had erythema and excoriation on his legs, lichenification over his popliteal fossa, xerosis on his forearms, an increased serum IgE level, and a family history of AD in his siblings. We made a provisional diagnosis of AD characterized by enhanced type 2 helper T (Th2) activity and treated him with topical corticosteroids and oral anti-histamines. His rash improved and did not relapse after the fifth dose; however, his LDL-cholesterol level increased. PCSK9 or oxidized LDL activates macrophages or dendritic cells, respectively, and enhances their activity to induce Th1 cells antagonizing Th2 cells. We hypothesized that high-dose evolocumab may suppress Th1 activity to antagonize Th2, and unmask Th2 disposition based on the patient's atopic diathesis, triggering the rash mimicking AD. Clinicians should be aware of rash development during evolocumab therapy.

[44] *Jayawardana KS, Mundra PA, Giles C et al.* **Changes in plasma lipids predict pravastatin efficacy in secondary prevention**. JCI insight 2019; 4.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31292301

ABSTRACT

BACKGROUNDStatins have pleiotropic effects on lipid metabolism. The relationship between these effects and future cardiovascular events is unknown. We characterized the changes in lipids upon pravastatin treatment and defined the relationship with risk reduction for future cardiovascular events.METHODSPlasma lipids (n = 342) were measured in baseline and 1-year follow-up samples from a Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study subcohort (n = 4991). The associations of changes in lipids with treatment and cardiovascular outcomes were investigated using linear and Cox regression. The effect of treatment on future cardiovascular outcomes was examined by the relative risk reduction (RRR).RESULTSPravastatin treatment was associated with changes in 206 lipids. Species containing arachidonic acid were positively associated while phosphatidylinositol species were negatively associated with pravastatin treatment. The RRR from pravastatin treatment for cardiovascular events decreased from 23.5% to 16.6% after adjustment for clinical risk factors and change in LDL-cholesterol (LDL-C) and to 3.0% after further adjustment for the change in the lipid ratio PI(36:2)/PC(38:4). Change in PI(36:2)/PC(38:4) mediated 58% of the treatment effect. Stratification of patients into quartiles of change in PI(36:2)/PC(38:4) indicated no benefit of pravastatin in the fourth quartile.CONCLUSIONThe change in PI(36:2)/PC(38:4) predicted benefit from pravastatin, independent of change in LDL-C, demonstrating its potential as a biomarker for monitoring the clinical benefit of statin treatment in secondary prevention.TRIAL REGISTRATIONAustralian New Zealand Clinical Trials Registry identifier

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[45] *Jiang H, Ruan Z, Wang Z et al.* **Simvastatin reduces atherosclerotic plaques and endothelial inflammatory response in atherosclerosis rats through TGF-beta/Smad pathway**. Minerva medica 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31295982
ABSTRACT

[46] *Scheja L, Heeren J*. **The endocrine function of adipose tissues in health and cardiometabolic disease**. Nature reviews. Endocrinology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31296970
ABSTRACT
In addition to their role in glucose and lipid metabolism, adipocytes respond differentially to physiological cues or metabolic stress by releasing endocrine factors that regulate diverse processes, such as energy expenditure, appetite control, glucose homeostasis, insulin sensitivity, inflammation and tissue repair. Both energy-storing white adipocytes and thermogenic brown and beige adipocytes secrete hormones, which can be peptides (adipokines), lipids (lipokines) and exosomal microRNAs. Some of these factors have defined targets; for example, adiponectin and leptin signal through their respective receptors that are expressed in multiple organs. For other adipocyte hormones, receptors are more promiscuous or remain to be identified. Furthermore, many of these hormones are also produced by other organs and tissues, which makes defining the endocrine contribution of adipose tissues a challenge. In this Review, we discuss the functional role of adipose tissue-derived endocrine hormones for metabolic adaptations to the environment and we highlight how these factors contribute to the development of cardiometabolic diseases. We also cover how this knowledge can be translated into human therapies. In addition, we discuss recent findings that emphasize the endocrine role of white versus thermogenic adipocytes in conditions of health and disease.

[47] *Witard OC, Combet E, Gray SR*. **Long-chain n-3 fatty acids as an essential link between musculoskeletal and cardio-metabolic health in older adults**. The Proceedings of the Nutrition Society 2019:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31282319
ABSTRACT
This narrative review aims to critically evaluate scientific evidence exploring the therapeutic role(s) of long-chain n-3 PUFA in the context of ageing, and specifically, sarcopenia. We highlight that beyond impairments in physical function and a lack of independence, the age-related decline in muscle mass has ramifications for cardio-metabolic health. Specifically, skeletal muscle is crucial in regulating blood glucose homeostasis (and by extension reducing type 2 diabetes mellitus risk) and providing gluconeogenic precursors that are critical for survival during muscle wasting conditions (i.e. AIDS). Recent interest in the potential anabolic action of n-3 PUFA is based on findings from experimental studies that measured acute changes in the stimulation of muscle protein synthesis (MPS) and/or chronic changes in muscle mass

and strength in response to fish oil-derived n-3 PUFA supplementation. Key findings include a potentiated response of MPS to amino acid provision or resistance-based exercise with n-3 PUFA in healthy older adults that extrapolated to longer-term changes in muscle mass and strength. The key mechanism(s) underpinning this enhanced response of MPS remains to be fully elucidated, but is likely driven by the incorporation of exogenous n-3 PUFA into the muscle phospholipid membrane and subsequent up-regulation of cell signalling proteins known to control MPS. In conclusion, multiple lines of evidence suggest that dietary n-3 PUFA provide an essential link between musculoskeletal and cardio-metabolic health in older adults. Given that western diets are typically meagre in n-3 PUFA content, nutritional recommendations for maintaining muscle health with advancing age should place greater emphasis on dietary n-3 PUFA intake.

[48] *Adachi T, Hori M, Ishimaru Y et al.* **Preferences for health information in middle-aged Japanese workers based on health literacy levels: a descriptive study**. Public health 2019; 174:18-21.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31301551
ABSTRACT
OBJECTIVES: To describe the health information preferences in middle-aged Japanese workers based on health literacy (HL) levels and presence of medications. STUDY DESIGN: A cross-sectional study. METHODS: We performed a web-based questionnaire survey with Japanese workers aged below 60 years. HL was assessed using the total score of communicative skills (five items) and critical skills (four items) from the 14-item Health Literacy Scale. Regarding their health information preferences, participants were asked about the health information they wanted (four items), could easily understand (six items), or easily use (two items) and answered on a 4-point scale (strongly agree/agree/disagree/strongly disagree). The percentages of the affirmative responses (strongly agree or agree) were compared among tertiles based on the HL score. RESULTS: We obtained data from a total of 3387 volunteers, of whom 510 participants were on either antihypertensive, lipid-lowering, or antidiabetic drugs. Compared with the high HL and middle HL groups, low HL had fewer affirmative responses to most health information items. Health information items received 70% of affirmative responses even in the low HL level. They were visually shown by figures or pictures, highlighted by colors for important points, could be read in 1-2 min, and were accessed on the Internet, regardless of the presence of medications. Additionally, the explanation for mechanisms of medications or lifestyle to prevent or improve diseases showed high affinity in all HL levels, only for those on medications. CONCLUSIONS: This result generates a hypothesis that low HL individuals have a low interest in health information. Our data showed several possible forms of health information with high affinity based on HL levels that would help plan future population approaches.

[49] *Guijarro C, Camafort M*. **PCSK9 inhibitors: Ratification of the role of LDL cholesterol in cardiovascular prevention. Towards a convergence of European and North American prevention guidelines?** Revista clinica espanola 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31280888
ABSTRACT

The epidemiological association of cholesterol associated with low density lipoproteins (LDL-c) levels and the development of atherosclerotic vascular disease has been ratified by mendelian randomization studies. Paradoxically, the success of statins led to the underestimation of other lipid-lowering therapies and even the measurement of LDL-c. Recent studies show that the reduction of LDL-c to extraordinarily low levels through absorption inhibition, and, in a particularly intensive manner, with monoclonal antibodies against pro-protein convertase subtilisine kexine (PCSK9) continues to offer cardiovascular protection. However, the high cost and limited experience with PCSK-9 inhibitors advised a prudent use of them. An appropriate selection of patients most likely to benefit from treatment with PCSK9 inhibitors emerges as the basis for consensus of international guidelines: the combination of a high absolute vascular risk and a greater expected profit by the starting LDL-c levels.

[50] *Butt S, Hasan SMF, Hassan MM et al.* **Directly compressed rosuvastatin calcium tablets that offer hydrotropic and micellar solubilization for improved dissolution rate and extent of drug release**. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society 2019; 27:619-628.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31297015
ABSTRACT
The objective was to use caffeine and Soluplus(R) to improve the dissolution rate and to maintain a concentration of BCS Class II rosuvastatin calcium that exceeds its solubility. Caffeine and Soluplus(R) together substantially improved the dissolution rate and the extent of rosuvastatin release. Formulations for direct compression tablets included Formulation F1, a control with drug but with neither caffeine nor Soluplus(R) present; F2 with drug-caffeine complex; F3 with drug and Soluplus(R) and F4 with drug-caffeine complex and Soluplus(R). Each formulation blend provided satisfactory flow properties. Tablets were comparable in mass, hardness and friability. A marked decrease in disintegration time occurred when the hydrotropic or micellar agent was included in the formulation. Assay (98-100%) and content uniformity (99-100%) results met requirements. Release studies in pH 1.2, 6.6, and 6.8 buffers revealed the superiority of F4. At 45min sampling time, F3 and F4 tablets each provided a cumulative drug release greater than 70% in each medium. F2 tablets exhibited compliance to official standards in pH 6.6 and 6.8 buffers but not in pH 1.2 buffer, whereas tablets based on F1 failed in each medium. Two-factor ANOVA of the release data revealed a statistical difference across the four formulations in each release medium. Pairwise comparison of release profiles demonstrated that, of the four formulations, F4 provided the most effectively enhanced dissolution rate, improvement to the extent of drug release and support of a concentration higher than the solubility of rosuvastatin calcium.

[51] *Zhang X, Shen L, Huang YG*. **[Effects of Simvastatin on Diabetic Neuropathic Pain and Systematic Inflammation in Diabetic Rat Models and Their Molecular Mechanisms]**. Zhongguo yi xue ke xue yuan xue bao. Acta Academiae Medicinae Sinicae 2019; 41:283-290.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31282320
ABSTRACT
Objective To investigate the effects of simvastatin on diabetic neuropathic pain and systematic inflammation in diabetic rats and explore their molecular mechanisms.Methods Totally 24 rats

were equally randomized into the normal+vehicle(NV)group,diabetic+vehicle(DV)group,and diabetic+simvastatin(DS)group using the random number table.Streptozotocin(STZ)was used to establish the rat models of diabetes.Blood glucose,body mass,paw withdrawal mechanical threshold(PWMT),and paw withdrawal thermal latency(PWTL)in each group were observed on days 7,14,21,and 28 after STZ injection.On day 28 after STZ injection,rats were sacrificed,and the lumbar spinal dorsal horn and serum were collected.Western blotting was used to detect the expression of receptor for advanced glycation end products(RAGE)and the phosphorylation levels of protein kinase B(AKT),extracellular signal-regulated kinase(ERK),p38,and c-Jun N-terminal kinase(JNK)in the spinal dorsal horn of rats in each group.Enzyme-linked immunosorbent assay was performed to determine the serum concentrations of oxidized low density lipoprotein(ox-LDL)and interleukin-1beta(IL-1beta).Results On days 14,21 and 28 after STZ injection,the PWMT in DV group were(8.6 +/- 0.8),(7.1 +/- 1.6),and(7.8 +/- 0.8)g respectively,which were significantly lower than (12.0 +/- 0.9)(q=8.482,P =0.000),(11.6 +/- 1.5)(q=11.309,P =0.000),and(11.7 +/- 1.5)g(q=9.801,P =0.000)in NV group.The PWMT in DS group on days 21 and 28 were(9.4 +/- 1.4)(q=5.780,P =0.000)and(9.7 +/- 0.9)g(q=4.775,P =0.003),respectively,which were significantly improved comparing with those of DV group.On days 7,14,21,and 28,there were no significant differences in PWTL among these three groups (all P<0.05).The expression of RAGE in the spinal dorsal horn of DV group was significantly higher than those of NV group(q=6.299,P =0.000)and DS group(q=2.891,P =0.025).The phosphorylation level of AKT in the spinal dorsal horn of DV group was significantly higher than those of NV group(q=8.915,P=0.000)and DS group(q=4.103,P=0.003).The phosphorylation levels of ERK(q =8.313,P=0.000),p38(q =2.965,P =0.022),and JNK(q=7.459,P =0.000)in the spinal dorsal horn of DV group were significantly higher than those of NV group;the phosphorylation level of JNK in the spinal dorsal horn of DS group was significant lower than that of DV group(q=3.866,P =0.004);however,there were no significant differences in the phosphorylation levels of ERK(q=1.987,P=0.122)and p38(q=1.260,P=0.375)in the spinal dorsal horn between DS group and DV group.The serum concentrations of ox-LDL and IL-1beta in DV group were(41.86 +/- 13.40)ng/ml and(108.16 +/- 25.88)pg/ml,respectively,which were significantly higher than those in NV group [(24.66 +/- 7.87)ng/ml(q=3.606,P=0.003)and(49.32 +/- 28.35)pg/ml(q=5.079,P=0.000)] and DS group [(18.81 +/- 5.62)ng/ml (q=4.833,P =0.000)and(32.73 +/- 11.73)pg/ml(q=6.510,P =0.000)].Conclusions Simvastatin can relieve the mechanical allodynia of diabetic rats possibly by inhibiting the activation of RAGE/AKT and the phosphorylation of JNK in the spinal dorsal horn.Simvastatin can also decrease the serum concentrations of ox-LDL and IL-1beta in diabetic rats,which may contribute to the relief of systematic inflammation.