Literature update week 27 (2018)

[1] *Ruscica M, Ferri N, Macchi C et al.* **Lipid Lowering Drugs and Inflammatory Changes: an Impact on Cardiovascular Outcomes?** Annals of medicine 2018:1-46.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29976096

ABSTRACT
Inflammatory changes are responsible for maintenance of the atherosclerotic process and may underlie some of the most feared vascular complications. Among the multiple mechanisms of inflammation, the arterial deposition of lipids and particularly of cholesterol crystals is the one responsible for activation of inflammasome NLRP3, followed by the rise of circulating markers, mainly C-reactive protein (CRP). Elevation of lipoproteins, LDL but also VLDL and remnants, associates with increased inflammatory changes and coronary risk. Lipid lowering medications can reduce cholesterolemia and CRP: patients with elevations of both are at greatest cardiovascular (CV) risk and receive maximum benefit from therapy. Evaluation of the major drug series indicates that statins exert the largest LDL and CRP reduction, accompanied by reduced CV events. Other drugs, mainly active on the triglyceride/HDL axis, e.g. PPAR agonists, may improve CRP and the lipid pattern, especially in patients with metabolic syndrome. The newest most potent medications, i.e. PCSK9 antagonists, do not induce significant changes in inflammatory markers, but patients with the highest baseline CRP levels show the best CV risk reduction. Parallel evaluation of lipids and inflammatory changes clearly indicates a significant link, both guiding to patients at highest risk, and to the best pharmacological approach.

[2] *Rallidis LS, Kiouri E, Katsimardos A, Kotakos C*. **Extreme-risk category: High prevalence among stable coronary patients and an emerging widening treatment gap in achieving LDL-cholesterol less than 55mg/dL**. Atherosclerosis 2018; 275:262-264.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29980053

ABSTRACT
BACKGROUND AND AIMS: The latest guidelines from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) proposed a new "extreme-risk" category of patients, for whom a low-density lipoprotein cholesterol (LDL-C) level <55mg/dL (1.4mmol/L) is advised. We aimed to identify the proportion of patients with stable coronary artery disease (CAD), who are at extreme cardiovascular (CV) risk, and explore how achievable is the new LDL-C goal. METHODS: We enrolled 1629 consecutive patients </=80 years with stable CAD. Fasting lipids were determined and patients having probable or definite heterozygous familial hypercholesterolaemia (HeFH) were identified using the Dutch Lipid Clinic Network algorithm. RESULTS: The prevalence of risk factors/characteristics suggesting an extreme CV risk were as follows: 32% diabetes mellitus, 33% premature CAD and 9.2% HeFH. In total, 895 (55%) patients had at least one of those risk factors/characteristics and formed the extreme CV risk category. Among patients at extreme risk, 87% were on lipid-lowering therapy, of whom 20.3% had LDL-C <70mg/dL (1.8mmol/L) and only 5.3% had LDL-C <55mg/dL. CONCLUSIONS: More than half of all patients with stable CAD are at extreme CV risk and very few (approximately 5%) achieve LDL-C levels <55mg/dL. Using maximally-tolerated high-intensity statin combined with ezetimibe, if necessary, is imperative to bridge the treatment gap, while in selected cases the addition of PCSK9 inhibitors will be required.

Literature update week 27 (2018)

[3] *Zanoni P, Velagapudi S, Yalcinkaya M et al.* **Endocytosis of lipoproteins**. Atherosclerosis 2018; 275:273-295.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29980055
ABSTRACT
During their metabolism, all lipoproteins undergo endocytosis, either to be degraded intracellularly, for example in hepatocytes or macrophages, or to be re-secreted, for example in the course of transcytosis by endothelial cells. Moreover, there are several examples of internalized lipoproteins sequestered intracellularly, possibly to exert intracellular functions, for example the cytolysis of trypanosoma. Endocytosis and the subsequent intracellular itinerary of lipoproteins hence are key areas for understanding the regulation of plasma lipid levels as well as the biological functions of lipoproteins. Indeed, the identification of the low-density lipoprotein (LDL)-receptor and the unraveling of its transcriptional regulation led to the elucidation of familial hypercholesterolemia as well as to the development of statins, the most successful therapeutics for lowering of cholesterol levels and risk of atherosclerotic cardiovascular diseases. Novel limiting factors of intracellular trafficking of LDL and the LDL receptor continue to be discovered and to provide drug targets such as PCSK9. Surprisingly, the receptors mediating endocytosis of high-density lipoproteins or lipoprotein(a) are still a matter of controversy or even new discovery. Finally, the receptors and mechanisms, which mediate the uptake of lipoproteins into non-degrading intracellular itineraries for re-secretion (transcytosis, retroendocytosis), storage, or execution of intracellular functions, are largely unknown.

[4] *Zhang W, Sun S, Zhang W, Shi Z*. **Polymorphisms of ABCG2 and its impact on clinical relevance**. Biochem Biophys Res Commun 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29964015
ABSTRACT
Human ABCG2 is one of the most important ATP-binding cassette (ABC) transporters. This protein functions as a xenobiotic transporter of large, hydrophobic, both positively or negatively charged molecules, a wide variety anticancer drugs, fluorescent dyes, and different toxic compounds found in normal food. SNPs in ABCG2 may affect absorption and distribution of these substrates, altering the accumulation, effectiveness and toxicity of compounds or drugs in large populations. Its transport properties have been implicated clinically and ABCG2 expression is linked with different disease states. We reviewed the SNPs of ABCG2 in clinical relevance about gout, acute myeloid leukemia, solid tumors, and other diseases.

[5] *van Stee MF, de Graaf AA, Groen AK*. **Actions of metformin and statins on lipid and glucose metabolism and possible benefit of combination therapy**. Cardiovascular diabetology 2018; 17:94.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29960584
ABSTRACT
Patients with diabetes type 2 have an increased risk for cardiovascular disease and commonly use combination therapy consisting of the anti-diabetic drug metformin and a cholesterol-lowering statin. However, both drugs act on glucose and lipid metabolism which could lead to adverse effects when used in combination as compared to monotherapy. In this review, the

proposed molecular mechanisms of action of statin and metformin therapy in patients with diabetes and dyslipidemia are critically assessed, and a hypothesis for mechanisms underlying interactions between these drugs in combination therapy is developed.

[6] *Liu ZJ, Hu GP, Fei MY et al.* **Effects of Short-term High Dose Atorvastatin on Left Ventricular Remodeling in Patients with First Time Attack of Anterior Acute Myocardial Infarction**. Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih 2018; 33:84-90.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29976277
ABSTRACT
Objects The aim of this trial was to evaluate the effect of short-term high-dose atorvastatin therapy on levels of high-sensitivity C-reactive protein (hs-CRP), malonaldehyde (MDA), endothelin-1(ET-1), matrix metalloproteinases (MMPs), and left ventricular (LV) remodeling in patients with first time attack of acute anterior myocardial infarction (AAMI) .Methods A hundred and three patients with first time attack of AAMI who underwent successful primary percutaneous coronary intervention were randomized to receive atorvastatin 40 mg once daily for 1 week followed by 20 mg once daily (intensive treatment group, IT group, n=49), or atorvastatin 20 mg once daily (standard treatment group, ST group, n=54). Plasma levels of hs-CRP, MDA, ET-1, MMP-2 and MMP-9 were measured on admission, at 1 week, 2 weeks and 6 months follow up and compared between the IT group and ST group. Echocardiography was performed on admission, at 2 week, and 1 year follow up. The left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were measured at each echocardiographic examination and compared between the IT group and ST group.Results Plasma levels of hs-CRP (F=7.718, P=0.009), ET-1 (F=7.882, P=0.006), MMP-9 (F=4.834, P=0.028) and pro-BNP (F=4.603, P=0.032) were significantly lower at 1 week after initial onset of AAMI in the IT group compared with the ST group. The changes of LVEDV, LVESV, and LVEF at the 1 year follow-up from the admission did not differ between the IT group and the ST group (t=0.722, P=0.444; t=1.228, P=0.221; t=1.354, P=0.187, repectively).Conclusions Short-term high-dose atorvastatin treatment for AAMI was associated with lower hs-CRP, ET-1 and MMP-9 levels compared to the standard dose treatment. However, this beneficial effect is not likely to related to the left ventricular remodeling.

[7] *Fujino A, Hao H, Shimodai S et al.* **Atherosclerotic Plaque Component as a Risk Factor for Distal Embolization During Percutaneous Coronary Intervention- Pathology of Tissue Obtained by Distal Protection Device**. Circulation journal : official journal of the Japanese Circulation Society 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29962392
ABSTRACT
BACKGROUND: Embolism during percutaneous coronary intervention (PCI) causes microcirculation impairment. The aim of this study was to clarify the relationship between the pathological characteristics of tissue captured by distal protection device (DPD) and amount of tissue accumulated in DPD.Methods and Results:A total of 671 consecutive lesions in PCI using DPD were examined. The amount of necrotic debris, fibrous tissue, calcified particle, platelet thrombus and organized thrombus in the DPD baskets was histologically evaluated. The DPD tissue amount was assessed semi-quantitatively, and the relationship between the captured

DPD tissue characteristics and tissue amount was investigated. On pathology, 40.7% of the lesions had necrotic debris, 41.4% had fibrous tissue, and 18.0% had calcified particle. The prevalence of lesions in patients with acute coronary syndrome (ACS) was 62.1%. Tissue amount score distribution was as follows: score 1 (tissue invisible), 3.9%; score 2 (tissue clinging to the basket), 52.0%; score 3 (tissue accumulated at the bottom of the basket), 38.5%; and score 4 (tissue accumulated in more than half of the basket), 5.7%. On multivariate analysis, necrotic debris and fibrous tissue were associated with greater tissue amount as well as clinical presentation of ACS. CONCLUSIONS: The presence of atherosclerotic plaque component, such as necrotic debris and fibrous tissue, might be a risk for distal embolism during PCI.

[8] *Lorenzatti AJ, Eliaschewitz FG, Chen Y et al.* **Rationale and design of a randomized study to assess the efficacy and safety of evolocumab in patients with diabetes and dyslipidemia: the BERSON clinical trial**. Clinical cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29962050
ABSTRACT
BACKGROUND: Type 2 diabetes mellitus (T2DM) is a major independent risk factor for cardiovascular disease, and diabetic dyslipidemia is a major contributor to cardiovascular risk in these patients. Here we report the rationale and design of a phase 3, double-blind study specifically designed to evaluate the lipid-lowering efficacy of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab in patients with T2DM and hyperlipidemia or mixed dyslipidemia who are on background statin therapy. METHODS: In the BERSON (evolocumaB Efficacy for LDL-C Reduction in subjectS with T2DM On background statiN) trial, patients with T2DM, a screening low-density lipoprotein cholesterol (LDL-C) level of >/= 2.6 mmol/L (>/= 100 mg/dL) or >/= 3.4 mmol/L (>/= 130 mg/dL), and with or without statin treatment at screening, respectively, were enrolled and started on atorvastatin 20 mg/day for a lipid stabilization period of at least 4 weeks. Then, patients were randomly assigned in a 2:2:1:1 ratio to receive atorvastatin 20 mg once daily plus either evolocumab 140 mg every 2 weeks (Q2W), evolocumab 420 mg every month (QM), placebo Q2W, or placebo QM. The co-primary outcome measures were the percentage change from baseline in LDL-C at week 12 and the percentage change from baseline in LDL-C at the mean of weeks 10 and 12. RESULTS: The BERSON trial has completed enrollment. CONCLUSION: The study completed in the first half of 2018. This study will provide information on the efficacy and safety of evolocumab in patients with T2DM and dyslipidemia.

[9] *Perez Garcia L*. **Familial hypercholesterolemia: Experience in the Lipid Clinic of Alava**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29980385
ABSTRACT
INTRODUCTION: Familial hypercholesterolaemia (FH) is the autosomal dominant genetic disorder most frequently associated with premature cardiovascular disease (CVD). MATERIAL AND METHODS: A retrospective, observational study was conducted to determine the clinical characteristics, analytical parameters and cardiovascular risk factors of 133 patients with a genetically confirmed diagnosis of FH on follow-up in the Lipid Clinic of Alava. RESULTS: CVD

was observed in 8.30% of the patients (ischaemic heart disease in 100% of the cases). The LDL concentration goal was achieved in 40.6% (45.50% in primary prevention and 27.30% in secondary prevention). The large majority (81.80%) of patients with coronary heart disease (CHD) were male. The odds ratio (OR) of males having CHD compared to females is 4.97 (1.03-23.93, P=.03). The OR of developing CHD in patients with a family history of premature CVD is 6.86 (1.32-35.67, P=.02). A statistically significant association was found between smoking and the risk of CVD (P=.005), and also between having diabetes and the risk of CVD (P=0.0001). If the treatment with statins begins at older than 40 years, the OR of suffering CHD is 6.40 (1.53-26.5) (P=.009). The mean time from diagnosis to the cardiovascular event in the group of ex-smokers is 10.80+/-5.80 years, and in the non-smoking group it is 17.50+/-2.50 years (P=.011). CONCLUSIONS: In our reference population with FH, it was found that there was an increased risk of suffering a cardiovascular event in male patients, with a family history of premature CVD, diabetics, and in those in whom lipid lowering treatment was started after 40 years of age.

[10] *Wah-Suarez MI, Galarza-Delgado DA, Azpiri-Lopez JR et al.* **The best cardiovascular risk calculator to predict carotid plaques in rheumatoid arthritis patients**. Clinical rheumatology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29967925
ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in patients with rheumatoid arthritis (RA). Chronic inflammation and traditional risk factors increase cardiovascular risk (CVR) in these patients. Several CVR calculators are used in general population and in RA patients to predict cardiovascular outcomes and tailor therapy but the precision of these calculators in RA patients has yet to be determined. The aim of this study is to determine which risk calculator correlates best with carotid ultrasound (US) findings, specifically carotid plaque (CP) and carotid intima-media thickness (CIMT) in RA patients without clinical manifestations. This was a cross-sectional observational study relating CVR scores in RA patients with the presence of carotid US findings. A total of 97 patients 40 to 75 years old who fulfilled the 2010 ACR/EULAR and/or the 1987 ACR classification criteria for RA were selected. Clinical assessment of cardiovascular risk was performed using seven calculators and carotid US measurement of intima-media thickness and plaque. The tests with the highest sensitivity for CIMT were the Framingham BMI, Framingham lipids, ACC/AHA 2013, and QRISK2. In CP, the highest sensitivity was in QRISK2, SCORE, and ACC/AHA 2013. RA patients should be comprehensively evaluated to detect cardiovascular risk. Carotid US may be routinely recommended to detect subclinical atherosclerosis in RA patients. A lower cutoff point in CVR scales may be necessary to identify patients with a low and intermediate CVR to detect subclinical atherosclerosis earlier and personalize therapy.

[11] *Alzghari SK*. **An Unnecessary Pain: Using Pharmacogenetics for Statin-related Skeletal Muscle Toxicity**. Cureus 2018; 10:e2557.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29974012
ABSTRACT
Statins are an important class of medications in reducing the risk of cardiovascular events as well as overall mortality. However, a well-known adverse effect of statins is skeletal muscle

toxicity, which may lead to abrupt discontinuation of the statin. In turn, patients may miss out on the benefits of statin therapy. An important factor to consider is a patient's solute carrier organic anion transporter 1B1 (SLCO1B1) gene T521C polymorphism status. Herein, an overview of the pharmacogenetics of SLCO1B1 is provided as well as recommendations for use in practice.

[12] *Kusunoki M, Natsume Y, Miyata T et al.* **Effects of Concomitant Administration of a Dipeptidyl Peptidase-4 Inhibitor in Japanese Patients with Type 2 Diabetes Showing Relatively Good Glycemic Control Under Treatment with a Sodium Glucose Co-Transporter 2 Inhibitor**. Drug research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29966149
ABSTRACT
We conducted this study to determine whether additional administration of a dipeptidyl peptidase-4 (DPP-4) inhibitor might provide further improvement of the glycemic control in Japanese type 2 diabetes patients showing relatively good glycemic control under treatment with a sodium glucose co-transporter 2 (SGLT2) inhibitor. Five SGLT2 inhibitor (luseogliflozin, dapagliflozin, tofogliflozin, empagliflozin and canagliflozin) preparations and five DPP-4 inhibitor (sitagliptin, vildagliptin, alogliptin, anagliptin and linagliptin) preparations were used. The results showed that monotherapy with SGLT2 inhibitor produced significant decreases of the body weight and BMI, hemoglobin A1c (HbA1c) also decreased, but not to a significant extent. However, decreases of the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (gamma-GTP) and uric acid were observed in this group. On the other hand, in type 2 diabetes patients treated concomitantly with a DPP-4 inhibitor and SGLT2 inhibitor, significant decrease of the HbA1c was observed, indicating the favorable effect of the concomitant therapy. The body weight and BMI decreased. As for the serum lipid profile, elevation of the serum HDL-cholesterol (HDL-C) was observed. Furthermore, AST, ALT, gamma-GTP and uric acid decreased in the combined treatment group. Then, the therapeutic responses to concurrent administration with SGLT2 inhibitor of each of the 5 individual DPP-4 inhibitors used in this study were analyzed. The results showed that concomitant administration of sitagliptin, a DPP-4 inhibitor, with the SGLT2 inhibitor yielded the best results in terms of the lowering of the HbA1c and improvement of the serum lipid profile.

[13] *Kroger K, Espinola-Klein C, Hoffmann U et al.* **[Peripheral Arterial Disease: When is a PCSK9 Inhibitor Useful?]**. Deutsche medizinische Wochenschrift (1946) 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29972852
ABSTRACT
The guideline of the European Society of Cardiology recommends an LDL-C target < 70 mg/dL or a 50 % reduction in patients with manifest peripheral arterial disease (PAD) as well as in CHD or cerebrovascular disease when the baseline LDL-C is between 70 and 135 mg/dL. Application of a PCSK9 inhibitor allows target attainment for those patients who do not achieve this under maximal conventional therapy with a statin in combination with ezetemib. In the Fourier study, patients with PAOD who had neither a myocardial infarction nor a stroke at admission of the study had a significant risk reduction (RR) of both cardiovascular (RR = 0.67, 0.47 - 0.96, p = 0.0283) as well as extremity endpoints (RR = 0.43 (0.19 - 0.99; p = 0.042). In Germany these

patients are primarily seen by angiologists. This group of vascular specialists is specifically mentioned in the decision of the Federal Joint Committee as one of those who may indicate treatment with PCSK9 inhibitors.

[14] *Li F, Aji G, Wang Y et al.* **Thyroid Peroxidase Antibody is Associated with Plasma Homocysteine Levels in Patients with Graves' Disease**. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29966154
ABSTRACT
PURPOSE: Homocysteine is associated with cardiovascular, inflammation and autoimmune diseases. Previous studies have shown that thyroid peroxidase antibody is associated with homocysteine levels in hypothyroidism. The relationship between thyroid antibodies and homocysteine in hyperthyroidism remains unclear. In this study, we aimed to investigate the association of thyroid antibodies with homocysteine in patients with Graves' disease. METHODS: This was a cross-sectional study including 478 Graves' disease patients who were consecutively admitted and underwent radioiodine therapy. Homocysteine, thyroid hormones, thyroid antibodies, glucose and lipids were measured. RESULTS: Patients with homocysteine levels above the median were older and had unfavorable metabolic parameters compared to patients with homocysteine levels below the median. Thyroglobulin antibody or thyroid peroxidase antibody was associated with homocysteine levels (beta=0.56, 95%CI 0.03-1.08, p=0.04; beta=0.75, 95%CI 0.23-1.27, p=0.005). The relationship between thyroid peroxidase antibody and homocysteine remained significant when additionally adjusting for free triiodothyronine (beta=0.76, 95%CI 0.24-1.28, p=0.004). The presence of a homocysteine level above the median increased significantly with increasing thyroid peroxidase antibody quartiles in the logistic regression (OR=1.74, 95%CI 1.27-2.39, P for trend=0.001). Homocysteine levels increased significantly with increasing thyroid peroxidase antibody quartiles (p=0.005). Thyroid peroxidase antibody had no significant effect on other traditional cardiovascular risk factors. CONCLUSIONS: Thyroid peroxidase antibody is independently and positively associated with homocysteine levels in patients with Graves' disease. Thyroid peroxidase antibody may be associated with the cardiovascular risk of patients with Graves' disease through its effect on homocysteine.

[15] *Fitzgerald G, Kiernan T*. **PCSK9 inhibitors and LDL reduction: pharmacology, clinical implications and future perspectives**. Expert review of cardiovascular therapy 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29979908
ABSTRACT
INTRODUCTION: PCSK9 inhibitors are monoclonal antibodies to proprotein convertase-subtilisin/kexin type 9 which significantly reduce LDL cholesterol concentration in vivo by inhibiting degradation of the LDL receptor in hepatocytes. The introduction of PCSK9 inhibitors heralded a new era of intensive LDL-C reduction with LDL-C concentrations lowered below levels ever thought possible with conventional treatments such as statins. With their introduction considerations regarding cost, clinical outcomes and long-term safety are paramount. Areas covered: This review examines the pharmacology of PCSK9 inhibitors and

summarises the current evidence base for use in clinical practise from an efficacy, safety and cardiovascular outcome perspective including recently presented data on alirocumab. It also examines the potential role of these agents into the future. Potential issues with PCSK9 inhibitors are examined and future pharmacologic targets are examined including siRNA and PCSK9 vaccination. Expert commentary: It is clear that the PCSK9 inhibitors are highly effective in the lowering of LDL cholesterol. However, this reduction comes at a large financial cost, and although early outcome data has been positive, the role of PCSK9 inhibition remains confined to limited patient groups at present. As more long-term data is gathered on clinical outcomes and safety, the role for these agents may expand.

[16] *Zhang T, Lu D, Yang W et al.* **HMG-CoA Reductase Inhibitors Relieve Endoplasmic Reticulum Stress by Autophagy Inhibition in Rats With Permanent Brain Ischemia**. Frontiers in neuroscience 2018; 12:405.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29970982
ABSTRACT
Exploring and expanding the indications of common clinical drugs, such as statins, is important to improve the prognosis of patients with permanent cerebral infarction. It has been suggested that reversing the defects in cellular autophagy and ER stress with statin therapy may be a potential treatment option for reducing ischemic damage. Male Sprague-Dawley rats underwent permanent middle cerebral artery occlusion (PMCAO) by electrocoagulation surgery. Atorvastatin (ATV, 10 mg/kg/day) or vehicle was administered intraperitoneally. Rats were divided into the vehicle-treated (SHAM), ATV pretreatment for MCAO (AMCAO), and 3-methyladenine (3MA) combined with ATV pretreatment (3MAMCAO) groups. Magnetic resonance imaging, as well as immunohistochemical and Western blot assessments, were performed 24 h after MCAO. Each ATV-treated group demonstrated significant reductions in infarct volume compared with that in the vehicle-treated group at 24 h after MCAO, which was associated with autophagy reduction and ER stress attenuation in neurons and neovascularization. Next, Western blotting was used to detect the levels of the autophagy-related proteins LC3B and P62 and of ER stress pathway proteins. However, 3MA significantly partially inhibited the ER stress pathway via limiting the autophagic flux in the AMCAO group. In conclusion, our results imply that the neuroprotective function of ATV depends on autophagic activity to diminish ER stress-related cell apoptosis in rats with PMCAO and suggest that compounds that inhibit autophagic activity might reduce the neuroprotective effect of ATV after brain ischemia.

[17] *Nose D, Shiga Y, Ueda Y et al.* **Association between plasma levels of PCSK9 and the presence of coronary artery disease in Japanese**. Heart Vessels 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29974199
ABSTRACT
The ability of pro-protein convertase subtilisin/kexin type 9 (PCSK9) levels to predict the presence or severity of coronary artery disease (CAD) remains controversial. The purpose of this study was to investigate these associations. We enrolled 393 patients who were clinically suspected to have CAD or who had at least one cardiac risk factor and underwent multidetector-row computed tomography coronary angiography. The presence of CAD (>/=50%

coronary stenosis), the number of significantly stenosed coronary vessels, and plasma levels of PCSK9 by ELISA were analyzed. Plasma PCSK9 levels (log-transformed data) were significantly associated with the presence of CAD. Next, we divided the patients into two groups (non-statin and statin groups) according to statin treatment. PCSK9 levels in the non-statin group were significantly lower than those in the statin group. There were no significant differences in PCSK9 levels between the absence and presence of CAD in the statin group. However, in the non-statin group, PCSK9 levels in patients with CAD were significantly higher than those in patients without CAD. PCSK9 levels, in addition to age, gender, BMI, DM and HDL-C, were independently associated with the presence of CAD by a multivariable analysis. In conclusion, our results demonstrated that plasma PCSK9 levels may be a marker for evaluating the presence of CAD.

[18] *Bansal M, Agarwala R*. **Have we reached the bottom of the bottomless pit- lessons from the recent lipid-lowering trials?** Indian Heart J 2018; 70:331-334.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29961445
ABSTRACT

[19] *Wang Y, Ping Yen Yan B, Tomlinson B et al.* **Clinical and Economic Analysis of Lipid Goal Attainments in Chinese Patients with Acute Coronary Syndrome Who Received Post-Percutaneous Coronary Intervention**. Journal of atherosclerosis and thrombosis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29962381
ABSTRACT
AIM: The recommended low-density lipoprotein cholesterol (LDL-C) levels of the guideline may be appropriate for Caucasian patients but not for other ethnic groups. METHODS: A cohort study was conducted in Hong Kong, and acute coronary syndrome (ACS) patients who received percutaneous coronary intervention (PCI) between 2005 and 2015 were enrolled. The primary outcomes of interest were the total cost of care and cardiovascular-related cost during one-year follow-up. The cost difference by lipid goal attainments was analyzed by Poisson regression with multivariate treatment effects. The clinical outcomes achieved by lipid goal attainments in terms of major adverse cardiovascular events were analyzed by multivariate Cox regression. RESULTS: Among the 4638 patients, 79.50%, 48.64%, and 36.14% attained the LDL-C goals of 2.6, 2.0, and 1.8 mmol/L for one year, respectively. Only about 16% patients achieved the >/=50% reduction from baseline. None of these lipid goals was associated with a significant reduction in the total cost of care. We only identified the clinical benefits associated with the lipid goal of 2.6 mmol/L. Other more stringent lipid goals seemed to bring a significant economic burden on cardiovascular-related cost, but their clinical benefits were uncertain. CONCLUSIONS: Lowering LDL-C to achieve the guideline-recommended target levels for post-PCI ACS patients may lead to fewer cardiovascular events, but it may not necessarily lead to economic benefits within one year of follow-up.

[20] *Bajko Z, Maier S, Rusu S, Motataianu A*. **Acute Ischaemic Stroke Secondary to a Mobile Thrombus in the Common Carotid Artery - Case Report**. Journal of critical care medicine (Universitatea de Medicina si Farmacie din Targu-Mures) 2015; 1:68-70.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29967818
ABSTRACT

A mobile thrombus in the carotid arteries is a very rare ultrasonographic finding and is usually diagnosed after a neurological emergency, such as a transient ischemic attack or cerebral infarction. We present the case of a 54-year-old man with vascular risk factors (a heavy smoker, untreated hypertension) who was admitted to the emergency unit with right sided hemiparesis and aphasia. A cerebral CT scan showed a left middle cerebral artery territory infarction. The duplex ultrasound examination revealed mild atherosclerotic changes in the right common and internal carotid arteries, right-sided complete subclavian steal phenomenon and a complicated hypoechoic atherosclerotic plaque in the left common carotid artery with a large mobile thrombus. Due to the high embolization risk, the patient was hospitalised and prescribed Aspirin together with low molecular weight Heparin. We recorded an improvement in the patient's neurological status and the control duplex scan revealed disappearance of the thrombus. The presence of floating thrombus in a patient with clinical and imagistic evidence of stroke is a major therapheutic challenge for the neurologist. The treatment strategies are not standardized and must be individualized, however in our case parenteral anticoagulation proved to be successful.

[21] *Psarros C, Economou EK, Koutsilieris M, Antoniades C*. **Statins as Pleiotropic Modifiers of Vascular Oxidative Stress and Inflammation**. Journal of critical care medicine (Universitatea de Medicina si Farmacie din Targu-Mures) 2015; 1:43-54.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29967815
ABSTRACT
Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world and in the future is expected to be the number one killer worldwide. The main cause underlying CVD is atherosclerosis. A key event in atherosclerosis initiation and progression is oxidative stress through the production of reactive oxygen species as well as endothelial dysfunction. Several pro- inflammatory and anti-inflammatory cytokines and proteins are involved in this process, complemented by activation of adhesion molecules that promote leukocyte rolling, tethering and infiltration into the sub-endothelial space. Statins represent the agent of choice since numerous clinical trials have verified that their pharmacological action extends beyond lipid lowering. Statins demonstrate direct anti-oxidant effects by scavenging free radicals and stimulating anti-oxidant enzymes while acting as regulators for cytokine, protein and adhesion molecule expression, all of which are involved in the atherosclerotic process. Statin use is considered one of the most efficient currently used interventions in managing CVD with the likely hood of remaining so in the near future.

[22] *Qin N, Bayat AR, Trevisi E et al.* **Dietary supplement of conjugated linoleic acids or polyunsaturated fatty acids suppressed the mobilization of body fat reserves in dairy cows at early lactation through different pathways**. Journal of dairy science 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29960784
ABSTRACT
To investigate the metabolic changes in the adipose tissue (AT) of dairy cows under milk fat depression (MFD), 30 cows were randomly allocated to a control diet, a conjugated linoleic acid (CLA)-supplemented diet, or a high-starch diet supplemented with a mixture of sunflower and fish oil (2:1; as HSO diet) from 1 to 112 d in milk. Performance of animals, milk yield, milk

composition, energy balance, and blood metabolites were measured during lactation. Quantitative PCR analyses were conducted on the AT samples collected at wk 3 and 15 of lactation. The CLA and HSO diets considerably depressed milk fat yield and milk fat content at both wk 3 and 15 in the absence of significant changes in milk protein and lactose contents. In addition, the HSO diet lowered milk yield at wk 15 and decreased dry matter intake of cows from wk 3 to 15. Compared with the control, both CLA and HSO groups showed reduced body weight loss, improved energy balance, and decreased plasma concentrations of nonesterified fatty acids and beta-hydroxybutyrate at early lactation. The gene expression analyses reflected suppressed lipolysis in AT of the CLA and HSO groups compared with the control at wk 3, as suggested by the downregulation of hormone-sensitive lipase and fatty acid binding protein 4 and the upregulation of perilipin 2. In addition, the HSO diet promoted lipogenesis in AT at wk 15 through the upregulation of 1-acylglycerol-3-phosphate O-acyltransferase 2, mitochondrial glycerol-3-phosphate acyltransferase, perilipin 2, and peroxisome proliferator-activated receptor gamma. The CLA diet likely regulated insulin sensitivity in AT as it upregulated the transcription of various genes involved in insulin signaling, inflammatory responses, and ceramide metabolism, including protein kinase B2, nuclear factor kappa B1, toll-like receptor 4, caveolin 1, serine palmitoyltransferase long chain base subunit 1, and N-acylsphingosine amidohydrolase 1. In contrast, the HSO diet resulted in little or no change in the pathways relevant to insulin sensitivity. In conclusion, the CLA and HSO diets induced a shift in energy partitioning toward AT instead of mammary gland during lactation through the regulation of different pathways.

[23] *Roelfsema F, Yang RJ, Veldhuis JD*. **Differential Effects of Estradiol and Progesterone on Cardiovascular Risk Factors in Postmenopausal Women**. Journal of the Endocrine Society 2018; 2:794-805.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29978153
ABSTRACT
Context: Controlled, blinded studies of sex-hormone replacement in postmenopausal women using natural estradiol (E2) and native progesterone (P) are few. Objective: To delineate the effect of E2 alone or with P on lipids and inflammatory markers. Design: A placebo-controlled, double-masked, prospectively randomized study of 40 healthy, postmenopausal volunteers assigned to four treatment groups: placebo, intramuscular E2, and/or micronized oral P for 23 (+/-2) days. Results: Treatment with E2 alone compared with placebo lowered total cholesterol (TC; P = 0.006), non-high-density lipoprotein cholesterol (nonHDL-C; P = 0.004), low-density lipoprotein cholesterol (LDL-C; P = 0.012), and apolipoprotein B (Apo B; P = 0.02) levels, and raised HDL-C levels (P = 0.03 vs the 3 other groups). Conversely, addition of P to E2 reduced HDL-C levels (P = 0.015). Triglyceride concentrations manifested no effect on E2 or P. High-sensitivity C-reactive protein (hsCRP) level was highest in women with E2 and P replacement (P = 0.018 vs placebo). Leptin and IL-6 concentrations did not vary. P treatment decreased adiponectin levels (P = 0.019). Serum E2 levels correlated linearly with TC, LDL-C, nonHDL-C, Apo B (all negatively), and SHBG (positively) concentrations. P level correlated negatively with TC (P = 0.029), HDL-C (P = 0.002), and adiponectin (P = 0.002) levels. Conclusion: In this study, there were individual and interactive effects of E2 and P on key lipids in postmenopausal individuals.

[24] *Ireland R, Schwarz B, Nardone G et al.* **Unique Francisella Phosphatidylethanolamine Acts as a Potent Anti-Inflammatory Lipid**. Journal of innate immunity 2018:1-15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29969788
ABSTRACT
Virulent Francisella tularensis subsp. tularensis (Ftt) is a dynamic, intracellular, bacterial pathogen. Its ability to evade and rapidly suppress host inflammatory responses is considered a key element for its profound virulence. We previously established that Ftt lipids play a role in inhibiting inflammation, but we did not determine the lipid species mediating this process. Here, we show that a unique, abundant, phosphatidylethanolamine (PE), present in Francisella, contributes to driving the suppression of inflammatory responses in human and mouse cells. Acyl chain lengths of this PE, C24: 0 and C10: 0, were key to the suppressive capabilities of Francisella PE. Addition of synthetic PE 24: 0-10: 0 resulted in the accumulation of PE in host cells for up to 24 h of incubation, and recapitulated the inhibition of inflammatory responses observed with native Ftt PE. Importantly, this novel PE significantly inhibited inflammatory responses driven by a medically and globally important flavivirus, dengue fever virus. Thus, targeting these lipids and/or the pathways that they manipulate represents a new strategy to combat immunosuppression engendered by Ftt, but they also show promise as a novel therapeutic intervention for significant viral infections.

[25] *Benedek P, Eriksson M, Duvefelt K et al.* **Genetic Testing for Familial Hypercholesterolemia among Survivors of Acute Coronary Syndrome**. Journal of internal medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29974534
ABSTRACT
BACKGROUND: Familial hypercholesterolemia could be prevalent among acute coronary syndrome patients. OBJECTIVE: To investigate both the frequency of causative mutations for familial hypercholesterolemia (FH) and the optimal selection of patients for genetic testing among patients with an acute coronary syndrome (ACS). METHODS: 116 patients with an ACS during 2009-2015 were identified through the SWEDEHEART registry. Patients who had either a high total cholesterol level >/=7 mmol/L combined with a triglyceride level </=2.6 mmol/L, or were treated with lipid-lowering medication and had a total cholesterol level >4.9 mmol/L and a triglyceride level </=2.6 mmol/L were included. Genetic testing was performed first with a regionally designed FH-mutation panel (118 mutations), followed by testing with a commercially available FH genetic analysis (Progenika Biopharma). RESULTS: A total of 6.9% (8/116) patients had a FH-causative mutation, all in the LDL-receptor. Five patients were detected on the panel, and further testing of the remaining 111 patients detected an additional 3 FH-causative mutation. Baseline characteristics were similar in FH positive and negative patients with respect to age, gender, prior ACS and diabetes. Patients with a FH-causative mutation had higher Dutch Lipid Clinical Network-score (DLCN-score) (5.5 (5.0 - 6.5) vs 3.0 (2.0 - 5.0), p<0.001) and a higher low-density lipoprotein-level (5.7 (4.7 - 6.5) vs 4.9 (3.5 - 5.4), p= 0.030). The Dutch Lipid Clinical Network (DLCN) score had a good discrimination with an area under the curve of 0.856 (95% CI 0.763-0.949). CONCLUSION: Genetic testing for FH should be considered in patients with ACS and high DLCN-score.

[26] *Miyazaki-Anzai S, Masuda M, Kohno S et al.* **Simultaneous inhibition of FXR and TGR5 exacerbates atherosclerotic formation**. Journal of lipid research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29976576
ABSTRACT
Simultaneous activation of bile acid receptors Farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (TGR5) by INT-767 significantly reduces atherosclerotic formation. In this study, we investigated the effect of simultaneous inactivation of these bile acid receptors in atherosclerosis and which bile acid receptor mediates the anti-atherogenic effect of INT-767. To investigate the role of simultaneous inactivation of FXR and TGR5 in vivo, we generated LDL receptor (LDLR) knockout (KO) mice with FXR and TGR5 dual deficiency, which exhibited severe atherosclerosis and aortic inflammation through NF-kappaB activation. The lipid-lowering effects of INT-767 were completely blocked by FXR single deficiency but not TGR5 single deficiency. INT-767 was able to block atherosclerotic formation and decrease levels of aortic cytokines and chemokines in LDLR KO mice under either FXR or TGR5 single deficiency. Dual deficiency of FXR and TGR5 completely blocked the anti-atherogenic and anti-inflammatory effects of INT-767 in LDLR KO mice. We demonstrated that 1) FXR and TGR5 dual deficiency exacerbated the development of atherosclerosis and 2) the anti-atherogenic effect of INT-767 requires the anti-inflammatory effect but not the lipid-lowering effect through the simultaneous activation of FXR and TGR5. Our results indicate that dual activation of FXR and TGR5 is a promising strategy for treating atherosclerosis.

[27] *Choo EH, Han EJ, Kim CJ et al.* **Effect of Pioglitazone in Combination with Moderate Dose Statin on Atherosclerotic Inflammation: Randomized Controlled Clinical Trial Using Serial FDG-PET/CT**. Korean circulation journal 2018; 48:591-601.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29968431
ABSTRACT
BACKGROUND AND OBJECTIVES: Non-statin therapy plus lower intensity statin might be an alternative in patients with coronary artery disease (CAD). A recent data suggested an anti-inflammatory therapy can reduce recurrent cardiovascular events and pioglitazone is also an intriguing inflammatory-modulating agent. However, limited data exist on whether pioglitazone on top of statins further attenuates plaque inflammation. METHODS: Statin-naive patients with stable CAD and carotid plaques of >/=3 mm were randomly prescribed moderate dose atorvastatin (20 mg/day), or moderate dose atorvastatin plus pioglitazone (30 mg/day) for 3 months. The primary endpoint was the change in the arterial inflammation of the carotid artery measured by (1)(8)F-fluorodeoxyglucose positron emission tomography/computed tomography ((1)(8)F-FDG-PET/CT) during 3 months. RESULTS: Of the 41 randomized patients, 33 underwent an evaluation by fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT; 17 atorvastatin plus pioglitazone and 16 atorvastatin patients). The addition of pioglitazone significantly improved the insulin sensitivity and increased the high-density lipoprotein cholesterol after 3 months. Although a reduction in the (FDG) uptake by pioglitazone on top of atorvastatin in carotid arteries with plaque showed marginally statistical significance in the entire patient group (atorvastatin plus pioglitazone; -0.10+/-0.07 and atorvastatin -0.06+/-0.04, p=0.058), pioglitazone showed a further reduction of the

fluorodeoxyglucose (FDG) uptake among patients who had a baseline FDG uptake above the median (atorvastatin plus pioglitazone; -0.14+/-0.04 and atorvastatin -0.03+/-0.03, p<0.001). CONCLUSIONS: Pioglitazone demonstrated marginally significant anti-inflammatory effects in addition to moderate dose atorvastatin. This may have been due to the lack of power of the study. However, pioglitazone may have an anti-inflammatory effect in those patients with high plaque inflammation (Trial registry at ClinicalTrials.gov, NCT01341730).

[28] *Akbari H, Asadikaram G, Jafari A et al.* **Atorvastatin, losartan and captopril may upregulate IL-22 in hypertension and coronary artery disease; the role of gene polymorphism**. Life sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29981321
ABSTRACT
AIMS: Interleukin-22 (IL-22) may be considered as an important cytokine in maintenance and progression of hypertension and coronary artery disease (CAD). The aim of the present study was to investigate the effect of treatment of hypertension and CAD on serum levels of IL-22 and the possible association of IL-22-rs1179251 gene polymorphism with hypertension and CAD. MATERIALS AND METHODS: A total of 286 subjects with suspected CAD were enrolled. Serum levels and gene polymorphism of IL-22 were investigated in hypertensive patients with no CAD (H-Tens), hypertensive patients with CAD (CAD+H-Tens); 3), CAD patients with no hypertension (CAD); and non-hypertensive with no CAD subjects as a control group (Ctr). The patients received routine medications for hypertension and CAD. Serum IL-22 levels and IL-22-rs1179251 gene polymorphism were evaluated using ELISA and RFLP-/PCR techniques, respectively. KEY FINDINGS: Findings demonstrated that there were significantly higher levels of IL-22 in case groups (H-Tens, CAD+H-Tens, and CAD) compared to the Ctr group. Moreover, atorvastatin, losartan and captopril were administered significantly more in patients compared to the Ctr group. The results indicated a decreased risk of CAD+H-Tens of rs1179251 dominant genetic model. SIGNIFICANCE: Atorvastatin, losartan and captopril may be led to upregulation of IL-22 in CAD and hypertensive patients. Meanwhile, higher levels of circulating IL-22 could contribute to alleviating the hypertension and CAD conditions. The G allele of rs1179251 may be a protective factor for concomitant hypertension and CAD.

[29] *Wang L, Wang Y, Wang H et al.* **The influence of the intestinal microflora to the efficacy of Rosuvastatin**. Lipids in health and disease 2018; 17:151.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29960598
ABSTRACT
BACKGROUND: Intestinal microflora has been shown to play essential roles in the clinical therapies of metabolic diseases. The present study is aiming to investigate the potential roles and mechanisms of how intestinal microflora mediates lipid-reduction efficacy of Rosuvastatin. METHODS: To investigate the correlation between the intestinal microflora and efficacy of Rosuvastatin, we analyzed the diversity of intestinal microflora using PCR-DGGE analysis and 16S rDNA sequencing approaches. Furthermore, we compared the blood lipid levels of rat models with dysbiosis of intestinal microflora and control rats upon the Rosuvastatin administration. RESULTS: The diversity of the intestinal flora was obviously decreased upon the antibiotic treatment, this effect could be maintained for 2 weeks after establishment of the

models. Importantly, the results from 16S rDNA sequencing demonstrated that the abundance of Lactobacillus and Bifidobacterium was remarkably diminished upon the antibiotic treatment in antibiotic+Rosuvastatin-treated group compared to that of Rosuvastatin-treated group and control group. Correspondently, the lipid-reduction efficacy of Rosuvastatin was significantly compromised. However, the diversity of the intestinal flora was recovered 4 weeks after the antibiotic treatment. Subsequently, the lipid-reduction efficacy of Rosuvastatin was also recovered to level of the control rats treated with Rosuvastatin alone. CONCLUSION: Intestinal flora could play an essential role in mediating the lipid-reduction efficacy of Rosuvastatin.

[30] *Jeyamalar R, Wan Azman WA, Nawawi H et al.* **Updates in the management of Dyslipidaemia in the high and very high risk individual for CV risk reduction**. The Medical journal of Malaysia 2018; 73:154-162.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29962499
ABSTRACT
Cardiovascular disease (CVD) has been the main cause of mortality and an important cause of morbidity in Malaysia for several years. To reduce global cardiovascular (CV) risk in the population, primary preventive strategies need to be implemented. Hypercholesterolaemia is one of the major risk factors for CVD. This paper is an expert review on the management of hypercholesterolemia focusing on high and very high risk individuals. In low and Intermediate risk individuals, therapeutic lifestyle changes (TLC) and a healthy lifestyle alone may suffice. In high and very high risk individuals, drug therapy in conjunction with TLC are necessary to achieve the target LDL-C levels which have been shown to slow down progression and sometimes even result in regression of atherosclerotic plaques. Statins are first-line drugs because they have been shown in numerous randomized controlled trials to be effective in reducing CV events and to be safe. In some high risk individuals, despite maximally tolerated statin therapy, target Low Density Lipoprotein Cholesterol (LDL-C) levels are not achieved. These include those with familial hypercholesterolaemia and statin intolerance. This paper discusses non-statin therapies, such as ezetimibe and the newer Proprotein convertase subtilisin/kexin type 9 Inhibitors (PCSK9-i).

[31] *Wang H, Wang Y, Xia T et al.* **Pathogenesis of Abnormal Hepatic Lipid Metabolism Induced by Chronic Intermittent Hypoxia in Rats and the Therapeutic Effect of N-Acetylcysteine**. Medical science monitor : international medical journal of experimental and clinical research 2018; 24:4583-4591.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29968701
ABSTRACT
BACKGROUND The pathogenesis of chronic intermittent hypoxia (CIH)-induced abnormal hepatic lipid metabolism in rats remains unclear. Here, we investigated the therapeutic effect of N-acetylcysteine (NAC) on abnormal hepatic lipid metabolism. MATERIAL AND METHODS Rats were subjected to hypoxia and NAC treatment, and evaluated in terms of hepatic lipid metabolism, hepatocyte ultrastructure, oxidative stress in hepatocytes, expression of nuclear factor-kappa B (NF-kappaB) and inflammatory cytokines (IL-1beta, IL-6, and TNFalpha), serum lipoprotein lipase (LPL) levels, and blood lipids (triglycerides and cholesterol). RESULTS Compared to the normoxic control group, animals in the hypoxic model group showed

significant body weight gain; abnormal hepatic lipid metabolism; lipid vacuolization; accumulation of lipid droplets; abundant autophagosomes and lysosomes; significant increases in oxidative stress, inflammation level, and blood lipid levels; and significantly reduced LPL levels. Compared to control animals, rats in the treatment group exhibited normal body weight gain, improved lipid metabolism, fewer lipid droplets, alleviated ultrastructural injuries, decreased oxidative stress and inflammation level, as well as elevated LPL and reduced blood lipid levels. CONCLUSIONS The harmful effects of CIH on rat liver are possibly associated with the reactive oxygen species (ROS)/NF-kappaB signaling pathway. NAC is capable of attenuating lipid metabolism alterations and abnormal body weight gain in the CIH rat model, via a possible mechanism related to inhibition of ROS/NF-kappaB signaling.

[32] *Berberich AJ, Hegele RA*. **The complex molecular genetics of familial hypercholesterolaemia**. Nature reviews. Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29973710
ABSTRACT
Familial hypercholesterolaemia is the most commonly encountered genetic condition that predisposes individuals to premature cardiovascular disease. Nevertheless, most patients are undiagnosed, and treatment is often suboptimal even when the diagnosis seems certain. Advances in molecular technologies are reshaping our understanding of this condition, including revision upwards of the population prevalence. Furthermore, the underlying pathophysiological complexity has been exposed by the range of causative genetic loci, breadth of types and classes of rare disease-causing variants, and polygenic basis of the phenotype in many patients. Genetic testing is not always helpful or definitive. Familial hypercholesterolaemia can be envisioned as a group of related disorders, of which the classic 'textbook' phenotype is a subset. Features such as clinical stigmata, family history of dyslipidaemia or cardiovascular disease, and presence of a rare pathogenic variant all increase diagnostic certainty. However, even in the absence of these elements, the essential feature remains an elevated level of plasma LDL cholesterol, which alone should prompt a dialogue between the care provider and the patient on lifestyle modification and lipid-lowering therapy as the foundation of a long-term strategy to prevent or delay the onset of cardiovascular disease.

[33] *Saliba W, Rennert HS, Barnett-Griness O et al.* **Association of statin use with spontaneous intracerebral hemorrhage: A cohort study**. Neurology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29970405
ABSTRACT
OBJECTIVE: To examine the association between statin exposure in a dose-dependent manner and intracerebral hemorrhage (ICH) in a large nationwide study. METHODS: The computerized database of the largest health care provider in Israel was used to identify diagnosed ICH among new users of statins, who started statin treatment between 2005 and 2010. We assessed a dose-response relationship between ICH and statins, using the average atorvastatin equivalent daily dose (AAEDD). Multivariable Cox proportional hazard regression models, adjusted for baseline disease risk score, were applied to estimate the hazard ratio of ICH. RESULTS: Of the 345,531 included patients, 1,304 were diagnosed with ICH during a median follow-up of 9.5

years (interquartile range 7.6-11.0). Overall, 75.3% of patients had AAEDD <10 mg/d, 19.0% had AAEDD 0-19.9 mg/d, and 5.7% had AAEDD >/=20 mg/d. The corresponding proportions were 81.0%, 15.0%, 4.0% among ICH cases, and 75.3%, 19.0%, 5.7% among non-ICH cases. Compared to those with AAEDD <10 mg/d (reference), the adjusted hazard ratio (HR) for ICH was 0.68 (95% confidence interval [CI] 0.58-0.79) in those with AAEDD 10-19.9 mg/d, and 0.62 (0.47-0.81) in those with AAEDD >/=20 mg/d. Compared to the lowest baseline total cholesterol quartile, the adjusted HR for ICH was 0.71 (95% CI 0.62-0.82), 0.55 (0.47-0.64), and 0.57 (0.49-0.67) in those in the second, third, and highest quartiles, respectively. The results were similar and robust among highly persistent statin users and after controlling for the change in cholesterol level. CONCLUSIONS: This study confirms that the risk of ICH decreases with increasing cholesterol levels, but suggests that statin use might be associated with decreased risk of ICH.

[34] *Zhang J, Liu N, Yang C*. **Effects of Rosuvastatin in combination with Nimodipine in patients with mild cognitive impairment caused by CSVD**. Panminerva medica 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29962180
ABSTRACT
BACKGROUND: To investigate the clinical efficiency and safeness of the combination of rosuvastatin and nimodipine in treating mild cognitive impairment of CSVD patients. METHODS: A total of 120 patients with mild cognitive impairment caused by CSVD were divided randomly into two groups: an observation group and a control group, each of which had 60 patients. In the observation group, patients were given rosuvastatin in combination with nimodipine, and other patients were given nimodipine in the control group. For the two groups, the course of treatment was six months. Before and after treatments, levels of TC (total cholesterol), TG (triacylglycerol), LDL-C (low density lipoprotein-cholesterol), HDL-C (high density lipoprotein-cholesterol), MMP-9 and hs-CRP (high sensitivity C reactive protein) were measured. MoCA (Montreal Cognitive Assessment) and ADL (activities of daily living) were also evaluated. Incidence of adverse reactions were compared between two groups. RESULTS: The levels of TG, TC and LDL-C were decreased after treatment in the observation group (P<0.01), and these after-treatment levels were lower than the control group. Additionally, after treatment, the levels of MMP-9 and hs-CRP were significant lower in the observation group than the control group. The MoCA and ADL scores were higher in the observation group than the control group after treatment (P<0.05). Moreover, the overall effective rate were higher in the observation group (91.7%) than the control group (65.0%) (P<0.01), while there was no significant difference of the rate of adverse reactions between the observation group and the control one (10.0% vs. 8.3%) (P>0.05). CONCLUSIONS: The combination of rosuvastatin and nimodipine was safe and effective in treating mild cognitive impairment of CSVD patients.

[35] *Lafreniere J, Laramee C, Robitaille J et al.* **Assessing the relative validity of a new, web-based, self-administered 24 h dietary recall in a French-Canadian population**. Public health nutrition 2018:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29976261
ABSTRACT

OBJECTIVE: To assess the relative validity of a new, web-based, self-administered 24 h dietary recall, the R24W, for assessment of energy and nutrient intakes among French Canadians. DESIGN: Each participant completed a 3d food record (FR) and the R24W on three occasions over a 4-week period. Intakes of energy and of twenty-four selected nutrients assessed by both methods were compared. SETTING: Quebec City metropolitan area. SUBJECTS: Fifty-seven women and fifty men (mean (sd) age: 47.2 (13.3) years). RESULTS: Equivalent proportions of under-reporters were found with the R24W (15.0%) and the FR (23.4%). Mean (sd) energy intake from the R24W was 7.2% higher than that from the FR (10 857 (3184) kJ/d (2595 (761) kcal/d) v. 10 075 (2971) kJ/d (2408 (710) kcal/d); P<0.01). Significant differences in mean nutrient intakes between the R24W and the FR ranged from -54.8% (i.e. lower value with R24W) for niacin to +40.0% (i.e. higher value with R24W) for alcohol. Sex- and energy-adjusted deattenuated correlations between the two methods were significant for all nutrients except Zn (range: 0.35-0.72; P<0.01). Cross-classification demonstrated that 40.0% of participants were classified in the same quartile with both methods, while 40.0% were classified in the adjacent quartile and only 3.6% were grossly misclassified (1st v. 4th quartile). Analysis of Bland-Altman plots revealed proportional bias between the two assessment methods for 8/24 nutrients. CONCLUSIONS: These data suggest that the R24W presents an acceptable relative validity as compared with the FR for estimating usual dietary intakes in a cohort of French Canadians.

[36] *Husain I, Akhtar M, Madaan T et al.* **Rosuvastatin alleviates high-salt and cholesterol diet-induced cognitive impairment in rats via Nrf2-ARE pathway**. Redox report : communications in free radical research 2018; 23:168-179.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29961403
ABSTRACT
OBJECTIVE: The objectives of our study were to investigate the possible effect of rosuvastatin in ameliorating high salt and cholesterol diet (HSCD)-induced cognitive impairment and to also investigate its possible action via the Nrf2-ARE pathway. METHODS: In silico studies were performed to check the theoretical binding of rosuvastatin to the Nrf2 target. HSCD was used to induce cognitive impairment in rats and neurobehavioral studies were performed to evaluate the efficacy of rosuvastatin in enhancing cognition. Biochemical analyses were used to estimate changes in oxidative markers. Western blot and immunohistochemical analyses were done to check Nrf2 translocation. TUNEL and caspase 3 tests were performed to evaluate reversal of apoptosis by rosuvastatin. RESULTS: Rosuvastatin showed good theoretical affinity to Nrf2, significantly reversed changes in oxidative biomarkers which were induced by HSCD, and also improved the performance of rats in the neurobehavioral test. A rise in nuclear translocation of Nrf2 was revealed through immunohistochemical analysis and western blot. TUNEL staining and caspase 3 activity showed attenuation of apoptosis. DISCUSSION: We have investigated a novel mechanism of action for rosuvastatin (via the Nrf2-ARE pathway) and demonstrated that it has the potential to be used in the treatment of cognitive impairment.

[37] *Al Sifri S, Al Shammeri O, Al Jaser S et al.* **Prevalence of lipid abnormalities and cholesterol target value attainment in patients with stable coronary heart disease or an acute coronary syndrome in Saudi Arabia**. Saudi medical journal 2018; 39:697-704.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29968891

ABSTRACT
OBJECTIVES: To provide an overview of the extent of hyperlipidemia in very high-risk patients, and how lipid-lowering therapy (LLT) is used in a real-world setting. Methods: In this multicenter observational study, data were collected from LLT-treated patients with stable CHD or an ACS in Saudi Arabia between 2013 and 2014. Individuals were included if they were greater than 18 years and had a full lipid profile available, recorded either prior to the baseline physician visit (CHD patients) or within 24-hours of admission to hospital (ACS patients). Results: A total of 737 patients were included in the study, 597 with stable CHD and 140 with ACS. Few patients in either group had an LDL-C level of greater than 70 mg/dl, which is advocated for very high-risk patients (24.3% and 11.4%, respectively). The median distances to this value were 19.0 mg/dl (CHD) and 25.0 mg/dl (ACS). Low doses of statins were being utilized (31 and 24 mg/day for CHD and ACS, respectively), with only minimal intensification for the ACS patients after hospital admission (41 mg/day at follow-up). Conclusions: Achievement of recommended LDL-C levels was poor for patients with stable CHD or an ACS. Statin intensity was low, indicating huge scope for intensifying the treatment of these very high-risk patients.

[38] *Ma YR, Wu YF, Duan YQ et al.* **[Effects of metoprolol or/and pravastatin on the pharmacokinetics of metformin in rats]**. Yao xue xue bao = Acta pharmaceutica Sinica 2017; 52:253-257.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29979507

ABSTRACT
This study investigates the effects of metoprolol (METO) or/and pravastatin (PRAV) on the pharmacokinetics of metformin (METF) in rats. Twenty-eight male SD rats were divided into METF group, METF+METO group, METF+PRAV group and METF+METO+PRAV group. Blood samples were collected at 10, 20, 40, 60, 90, 120, 180, 240, 360, 480 and 600 min after oral administration of metformin, and concentration of metformin in plasma was determined by HPLC. Compared to the METF group, Cmax of metformin was significantly decreased ($P < 0.01$) and MRT0-t , t1/2 and V were significantly increased in the METF+METO group; t1/2 was significantly decreased in the METF+PRAV group; Cmax was significantly decreased and MRT0-t was significantly increased in the METF+METO+PRAV group. Compared to the METF+METO group, MRT0-t of metformin was significantly decreased in the METF+METO+PRAV group. Compared to the METF+PRAV group, Cmax of metformin was significantly decreased ($P < 0.01$), and MRT0-t , t1/2 and V were significantly increased in the METF+METO+PRAV group. There exist multiple drug interactions of metformin, metoprolol and pravastatin in rats.