Literature update week 28 (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 [1] *Nance R, Crane H, Ritchings C et al.* **Differentiation of Type 1 and Type 2 Myocardial Infarctions among HIV-infected patients requires adjudication due to overlap in risk factors**. AIDS research and human retroviruses 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29984593
ABSTRACT
BACKGROUND: The Universal Myocardial infarction (MI) definition divides MIs into different types. Type 1 MIs (T1MI) result spontaneously from atherosclerotic plaque instability. Type 2 MIs (T2MI) are due to secondary causes of myocardial oxygen demand/supply mismatch such as occurs with sepsis. T2MI are much more common among those with HIV than in the general population. T1MI and T2MI have different mechanisms, risk factors and potential treatments suggesting that they should be distinguished to achieve a better scientific understanding of MIs in HIV. We sought to determine whether MI type could be accurately predicted by patient characteristics without adjudication in HIV-infected individuals. METHODS: We developed a statistical model to predict T2MI versus T1MI using adjudicated events from 6 sites utilizing demographic characteristics, traditional cardiovascular and HIV-related risk factors. Validation was assessed in a 7th site via mean calibration, and discrimination level was assessed by the area under the curve (AUC). RESULTS: Of 812 MIs, 388 were T2MI. HIV-related factors including hepatitis C infection were predictive of T2MI, whereas traditional cardiovascular risk factors including total cholesterol predicted T1MI. The score predicted 69 T2MI in the validation sample resulting in poor calibration, given that 90 T2MIs were observed. The development sample AUC was 0.75 versus 0.65 in the validation sample, suggesting relatively poor discrimination. CONCLUSIONS: The level of discrimination to predict MI type based on patient characteristics is insufficient for individual level prediction. Adjudication is required to distinguish MI types which is necessary to advance understanding of this important outcome among HIV populations.

[2] *Schaumeier MJ, Hawkins AT, Hevelone ND et al.* **Association of Treatment for Critical Limb Ischemia with Gender and Hospital Volume**. The American surgeon 2018; 84:1069-1078.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29981651
ABSTRACT
Critical limb ischemia (CLI) is a frequent and major vascular problem and can lead to amputation and death despite surgical revascularization. Women have been shown to have 3 to 4 per cent lower revascularization rates for CLI compared with men as well as inferior

outcomes. We hypothesize that this difference is a result of women being more likely admitted to low-volume hospitals, which in turn perform fewer revascularizations. Prospective cohort study. Data from the Nationwide Inpatient Sample 2007 to 2010 were used to identify admissions with primary International Classification of Diseases-9 codes for CLI (International Classification of Diseases-9 codes: 440.22, 440.23, 440.24, 707.1, 707.10-707.15, or 707.19). Hospitals were grouped in quintiles by annual revascularization procedures. Bivariate analyses were performed and multivariable logistic regression was used to analyze the odds of revascularization, amputation, and mortality while controlling for patient and hospital-level factors. Of 113,631 admissions, 54,370 (47.8%) were women, who were more likely admitted to low-volume hospitals (very low: 49.6% vs very high: 47.1%; P < 0.001). Revascularization rates were lower in women (31.6% vs 35.1%, P < 0.001) across all volume quintiles, whereas the difference was greatest in the use of open surgical revascularization (12.5% vs 16.0%, P < 0.001). In multivariable analysis, female gender [odds ratio (OR) 0.87, 95% confidence interval (CI) 0.83-0.92, P < 0.001] and very-low hospital volume (OR 0.21, 95% CI 0.17-0.26, P < 0.001) were both significantly associated with lower rates of revascularization. Women had lower odds of major amputation compared with men (OR 0.75, 95% CI 0.69-0.82, P < 0.001), whereas treatment in a very high-volume hospital was associated with increased odds for amputation (OR 1.37, 95% CI 1.09-1.73, P = 0.008). Neither gender nor hospital volume were independently associated with in-hospital mortality in the multivariable regression model. Women are more likely to be admitted to low-volume hospitals for treatment of CLI. Because of this, they are less likely to undergo revascularization, although they also had lower rates of major amputation.

[3] *Lee JY, Kang MJ, Choi JY et al.* **Apolipoprotein B binds to enolase-1 and aggravates inflammation in rheumatoid arthritis**. Annals of the rheumatic diseases 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29997113

ABSTRACT

OBJECTIVE: Immune cells from patients with rheumatoid arthritis (RA) express more enolase-1 (ENO1) on their surface than those from healthy subjects, and they elicit an enhanced inflammatory response. This study is aimed to identify the ligands of ENO1 that could promote inflammatory loops in vitro and enhance the arthritis severity in vivo. METHODS: ENO1-binding proteins in RA synovial fluid were identified by mass spectromety, and affinity to ENO1 was evaluated by means of a ligand blotting and binding assay, surface plasmon resonance and confocal microscopy. Proinflammatory response by the interaction between ENO1 and apolipoprotein B (apoB) was tested in vitro and in vivo using peripheral blood mononuclear cells and a K/BxN serum transfer arthritis model and low-density lipoproteins receptor (LDLR) knockout mice. RESULTS: ApoB in the synovid fluid of patients with RA was identified as a specific ligand to ENO1 with a higher affinity than plasminogen, a known ENO1 ligand. ApoB binding to ENO1 on monocytes elicited the production of tumour necrosis factor-alpha, interleukins (IL)-1beta and IL-6 through both p38 mitogen-activated protein kinase and NF-kappaB pathways. In the K/BxN serum transfer arthritis model, administration of apoB increased the production of proinflammatory cytokines and exaggerated arthritis severity. The severity of K/BxN serum transfer arthritis in LDLR knockout mice was comparable with wild-type mice. CONCLUSIONS: A key component of atherogenic lipids, apoB, aggravated arthritis by potentiating the inflammatory response via its interaction with ENO1 expressed on the surface

of immune cells. This suggests a novel mechanism by which lipid metabolism regulates chronic inflammation in RA.

[4] *Khambhati J, Engels M, Allard-Ratick M et al.* **Immunotherapy for the prevention of atherosclerotic cardiovascular disease: Promise and possibilities**. Atherosclerosis 2018; 276:1-9.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30006321
ABSTRACT
Cardiovascular disease remains the leading cause of death worldwide with coronary atherosclerotic heart disease being the largest contributor. The mechanisms behind the presence and progression of atherosclerosis remain an area of intense scientific focus. Immune dysregulation and inflammation are key contributors to the development of an atherosclerotic plaque and its progression to acute coronary syndromes. Increased circulating levels of biomarkers of systemic inflammation including hsCRP are correlated with a higher cardiovascular risk. Targeting specific inflammatory pathways implicated in atherosclerotic plaque formation is an exciting area of ongoing research. Target specific therapies directed at pro-inflammatory cytokines such as IL-1beta, IL-6, TNFalpha, and CCL2 have demonstrated slowing in the progression of atherosclerosis in animal models and improved cardiovascular outcomes in human subjects. Most notably, treatment with the monoclonal antibody canakinumab, which directly targets and neutralizes IL-1beta, was recently shown to be associated with reduced risk of adverse cardiovascular events compared to placebo in a randomized, placebo-controlled trial. Several other therapies including colchicine, methotrexate and leukotriene inhibitors demonstrate the potential for lowering cardiovascular risk through immunomodulation, though further studies are needed. Understanding the role of inflammation in atherosclerosis and the development of targeted immunotherapies continues to be an evolving area of research that is rapidly becoming clinically relevant for the 21st century cardiac patient.

[5] *Tokuhisa H, Murai H, Okabe Y et al.* **Differential effects of lipophilic and hydrophilic statins on muscle sympathetic nerve activity in heart failure with preserved left ventricular ejection fraction**. Autonomic neuroscience : basic & clinical 2018; 213:8-14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30005743
ABSTRACT
Augmented sympathetic nerve activity is associated with heart failure with preserved left ventricular ejection fraction (HFpEF). Lipophilic statins reduce sympathetic nerve activity in patients with heart failure with reduced left ventricular ejection fraction. However, little is known about whether all types of statins, regardless of solubility, reduce sympathetic nerve activity in HFpEF. We evaluated the effect of atorvastatin, a lipophilic statin, and rosuvastatin, a hydrophilic statin, on muscle sympathetic nerve activity (MSNA) in HFpEF patients. This study was conducted as a prospective, randomized, open-label, crossover trial. Ten HFpEF patients with untreated hyperlipidemia participated in this study. Subjects were assigned to either the atorvastatin (lipophilic) or the rosuvastatin (hydrophilic) group with each drug administered for 8weeks. Atorvastatin and rosuvastatin treatment resulted in a similar reduction in low-density lipoprotein cholesterol (LDL-C) levels. There was no difference in the effect of either treatment

on blood pressure, heart rate, or left ventricular function. Atorvastatin significantly decreased MSNA frequency compared with baseline (31.5+/-6.3 vs. 47.5+/-10.7bursts/min, p<0.01), but rosuvastatin had no effect on MSNA (40.9+/-7.3bursts/min). MSNA was significantly lower in the atorvastatin group than rosuvastatin group (p<0.05). However, the reduction in MSNA seen in either group did not correlate with the reduction in LDL-C. No significant differences were observed in either the baroreflex control of heart rate or MSNA between the two groups. These results suggest that lipophilic statins have a favorable effect on sympathetic nerve activity beyond lowering LDL-C in HFpEF, but hydrophilic statins do not.

[6] *Gao J, Wang HB, Xiao JY et al.* **Association between proprotein convertase subtilisin/kexin type 9 and late saphenous vein graft disease after coronary artery bypass grafting: a cross-sectional study**. BMJ open 2018; 8:e021951.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29991632
ABSTRACT
OBJECTIVE: The study aims to explore the association between serum proprotein convertase subtilisin/kexin type 9 (PCSK9) level and saphenous vein grafts disease (SVGD) after coronary artery bypass grafting (CABG). DESIGN: A cross-sectional study. SETTING: A secondary hospital in Tianjin City, China. PARTICIPANTS: A total of 231 participants were included in the study. Inclusion criteria were as follows: age >/=18 years, previous CABG surgery at least 12 months ago, at least one SVG for bypass during CABG, abnormal non-invasive test results or recurrent stable angina pectoris by coronary angiography indications, and willing to participate and sign informed consent. Participants with any of the following were excluded from the study: congenital valvular disease, decompensated heart failure, anaemia defined as a haemoglobin level of <12 g/dL in women or <13 g/dL in men, malignant neoplasms, renal failure, severe hepatic disease, thyroid disease, acute or chronic inflammatory disease and chronic obstructive lung disease. PRIMARY OUTCOME MEASURE: SVGD was defined as at least one SVG with significant stenosis (>/=50%). Circulating PCSK9 levels were measured using commercial ELISA kits according to the manufacturer's instructions. RESULTS: The mean PCSK9 level in the SVGD group was significantly higher than that in the patent group (275.2+/-38.6 vs 249.3+/-37.7, p<0.01). The multivariate logistic regression model revealed a significant association between serum PCSK9 and SVGD (OR 2.08, 95% CI 1.46-2.95) per 1 SD increase in serum PCSK9. CONCLUSIONS: The present study is the first to identify an independent association between PCSK9 and late SVGD after adjustment for established cardiovascular risk factors. A multicentre prospective cohort study with large sample size should be conducted in the future to further research this relationship.

[7] *Zhang Y, An X, Lin Q et al.* **Splenectomy had no significant impact on lipid metabolism and atherogenesis in Apoe deficient mice fed on a severe atherogenic diet**. Cardiovasc Pathol 2018; 36:35-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30007210
ABSTRACT
BACKGROUND: For a long time, our major understanding of the spleen is to function as a blood filter for the removal of aged erythrocytes and circulating microorganisms. Splenectomy, therefore, has been widely performed in case of trauma and a variety of hematologic disorders.

Although some studies have indicated an increased rate of developing hyperlipidemia and atherosclerotic cardiovascular diseases in splenectomized patients, our recognition of the splenic regulation on lipid metabolism and atherogenesis is still lacking. Here we explored this issue in Apoe deficient (Apoe-/-) mice fed on an atherogenic diet containing 0.5% cholesterol and 20% fat. METHODS: 7-week-old male Apoe-/- mice were randomly divided into splenectomy group and sham operation group. After 1-week recovery from the surgery, mice were subjected to the atherogenic diet for the next 8 weeks. RESULTS: The atherogenic diet induced a severe hypercholesterolemia (about 1500 mg/dl), steatohepatitis and accelerated atherogenesis in the Apoe-/- mice. Splenectomy, compared to sham operation, did not alter plasma lipid levels or lipoprotein profiles; it also did not alter hepatic or adipose lipid deposition. Meanwhile, splenectomy did not alter atherosclerotic plaque burden or composition; it also did not alter aortic gene expression associated with macrophage inflammatory responses. CONCLUSIONS: Our data suggested that splenectomy had no significant impacts on lipid metabolism and atherogenesis in Apoe-/- mice fed on a severe atherogenic diet.

[8] *Cochain C, Ait-Oufella H, Zernecke A*. **Neutrophils promote atherosclerotic plaque destabilization in a mouse model of endotoxinemia**. Cardiovascular research 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992257
ABSTRACT

[9] *Rao AS, Lindholm D, Rivas MA et al.* **Large-Scale Phenome-Wide Association Study of PCSK9 Variants Demonstrates Protection Against Ischemic Stroke**. Circulation. Genomic and precision medicine 2018; 11:e002162.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29997226
ABSTRACT
BACKGROUND: PCSK9 inhibition is a potent new therapy for hypercholesterolemia and cardiovascular disease. Although short-term clinical trial results have not demonstrated major adverse effects, long-term data will not be available for some time. Genetic studies in large biobanks offer a unique opportunity to predict drug effects and provide context for the evaluation of future clinical trial outcomes. METHODS: We tested the association of the PCSK9 missense variant rs11591147 with predefined phenotypes and phenome-wide, in 337 536 individuals of British ancestry in the UK Biobank, with independent discovery and replication. Using a Bayesian statistical method, we leveraged phenotype correlations to evaluate the phenome-wide impact of PCSK9 inhibition with higher power at a finer resolution. RESULTS: The T allele of rs11591147 showed a protective effect on hyperlipidemia (odds ratio, 0.63+/-0.04; P=2.32x10(-38)), coronary heart disease (odds ratio, 0.73+/-0.09; P=1.05x10(-6)), and ischemic stroke (odds ratio, 0.61+/-0.18; P=2.40x10(-3)) and was associated with increased type 2 diabetes mellitus risk adjusted for lipid-lowering medication status (odds ratio, 1.24+/-0.10; P=1.98x10(-7)). We did not observe associations with cataracts, heart failure, atrial fibrillation, and cognitive dysfunction. Leveraging phenotype correlations, we observed evidence of a protective association with cerebral infarction and vascular occlusion. These results explore the effects of direct PCSK9 inhibition; off-target effects cannot be predicted using this approach. CONCLUSIONS: This result represents the first genetic evidence in a large cohort for the

protective effect of PCSK9 inhibition on ischemic stroke and corroborates exploratory evidence from clinical trials. PCSK9 inhibition was not associated with variables other than those related to LDL (low-density lipoprotein) cholesterol, atherosclerosis, and type 2 diabetes mellitus, suggesting that other effects are either small or absent.

[10] *Sullivan D, Bonnitcha P, Spinks C, Keech T*. **PCSK9 (Proprotein Convertase Subtilisin/Kexin 9) Status and Protection Against Ischemic Stroke: PheWAS, TreWAS, and More**. Circulation. Genomic and precision medicine 2018; 11:e002247.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29997228
ABSTRACT

[11] *Alkhalil M*. **Letter by Alkhalil Regarding Article, "Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)"**. Circulation 2018; 138:220-221.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986969
ABSTRACT

[12] *Bonaca MP, Sabatine MS*. **Response by Bonaca and Sabatine to Letters Regarding Article, "Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)"**. Circulation 2018; 138:222-223.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986970
ABSTRACT

[13] *Calabro P, Gragnano F, Cesaro A*. **Letter by Calabro et al Regarding Article, "Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)"**. Circulation 2018; 138:218-219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986968
ABSTRACT

[14] *Carroll MD, Mussolino ME, Wolz M, Srinivas PR*. **Trends in Apolipoprotein B, Non-High-Density Lipoprotein, and Low-Density Lipoprotein for Adults 60 Years and Older by Use of Lipid-Lowering Medications: United States, 2005 to 2006 Through 2013 to 2014**. Circulation 2018; 138:208-210.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986963
ABSTRACT

[15] *Filler G, Taheri S, McIntyre C et al.* **Chronic kidney disease stage affects small, dense low-density lipoprotein but not glycated low-density lipoprotein in younger chronic kidney disease patients: a cross-sectional study**. Clinical kidney journal 2018; 11:383-388.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992019

ABSTRACT

Background: Small, dense low-density lipoprotein (sd-LDL) and glycated LDL (g-LDL) have been associated with cardiovascular disease (CVD) in chronic kidney disease (CKD) in patients >60 years of age. Since young adult and paediatric patients have shorter exposure to Framingham-type risk factors, our study aims to determine whether younger CKD patients exhibit the same sd-LDL and g-LDL pattern. Methods: After ethics board approval, this cross-sectional study was conducted at two universities with 44 patients (mean +/- standard deviation age 12.6 +/- 4.9, range 2-24 years) with CKD stage of 1-5. Laboratory parameters studied were Cystatin C (CysC), CysC estimated glomerular filtration rate (eGFR) (calculated from the Filler formula), sd-LDL, g-LDL and albumin. Lipid samples were measured for sd-LDL and g-LDL using ELISA. Non-linear correlation analysis was performed to determine the relationship between g-LDL, sd-LDL and eGFR. Clinical Trials Registration is at clinicaltrials.gov, NCT02126293, https://clinicaltrials.gov/ct2/show/NCT02126293. Results: Triglycerides, but not total cholesterol and calculated LDL, were associated with CKD stages (ANOVA P = 0.0091). As in adults, sd-LDL was significantly associated with CKD stages (ANOVA P = 0.0133), CysC eGFR (r = -0.6495, P < 0.00001), and body mass index (r = -0.3895, P = 0.0189), but not with age. By contrast, there was no significant correlation between g-LDL and CKD stages or CysC eGFR (P = 0.9678). Conclusions: Our study demonstrates that only triglycerides and sd-LDL were associated with CKD stages in this young cohort without confounding Framingham-type CVD risk factors. While larger studies are needed, this study suggests that lowering sd-LDL levels may be a potential target to ameliorate the long-term CVD risks in paediatric CKD patients.

[16] *Bezin J, Mansiaux Y, Noize P et al.* **Use of lipid-lowering drugs and the risk of cataract: a population-based nested case-control study**. Clinical pharmacology and therapeutics 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992538

ABSTRACT

Eye lens membrane cells require high cholesterol concentrations that might be counteracted by lipid-lowering drugs. Using a nationwide database, we conducted a nested case-control study to evaluate the risk of cataract development associated with the use of lipid-lowering drugs. Patients aged 45 years and over with first cataract surgery in 2014 (cases) and up to four controls matched on age, gender, diabetes, hypothyroidism, glucocorticoid use, cardiovascular risk and area of residence were included in the study. Among the 2,811 cases and 11,106 matched controls included, analyses showed a significantly increased risk of cataract surgery for a cumulative exposure to fibrates exceeding five years (adjusted odds ratio (aOR) 1.58, 95% confidence interval 1.17-2.15), unlike cumulative exposure to statins whatever the dose or duration of treatment (aORs from 1.00 to 1.08, none being significant). This study highlighted an increased risk of cataract surgery with prolonged use of fibrates, but not of statins. This article is protected by copyright. All rights reserved.

[17] *Brown WV*. **Clinical Lipidology and the Prevention of Vascular Disease: Time for Personalized Therapy**. Clinical pharmacology and therapeutics 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29998536

ABSTRACT

Genetic, metabolic, and lifestyle modifications can cause elevations of lipoproteins that contribute to atherosclerotic lesions over time. In the modern world with life extension from many improvements in medicine and public health, most humans live long enough to develop atherosclerosis with concentrations of blood plasma lipoproteins that are very common. Familial abnormalities are prevalent and provide additional challenges in identifying unhealthy but treatable values of low-density (LDL) and very low-density lipoproteins (VLDL). Multiple community studies and clinical trials have provided guidance on selecting targets and new tools that make possible effective goals of treatment. Lipid-lowering drugs are making it possible to achieve those goals and place responsibility on physicians to master the art of preventing atherosclerotic events. Lipoprotein management remains a very focused effort and requires an artful individualized approach for each patient. Few skills are more important for healthcare providers in primary care and cardiovascular medicine.

[18] *Naumovska Z, Nestorovska AK, Grozdanova A et al.* **Evaluation of statin utilization in the Republic of Macedonia during 2013-2016**. Clinicoecon Outcomes Res 2018; 10:339-347.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29983582
ABSTRACT
Purpose: A rational use of statins has a major and increasing importance in public health and allocation of financial resources by the health insurance funds (HIFs). The aim of this study was to evaluate the market share and utilization trends of statins in the Republic of Macedonia (R. Macedonia) from 2013 to 2016. Materials and methods: A retrospective analysis and data comparison for the utilization of HMG-CoA inhibitors (C10AA) in R. Macedonia from 2013 to 2016 were conducted. The data obtained from HIF, IMS Health, pharmaceutical industry and marketing authorization holders (MAHs) were evaluated through defined daily doses per 1000 insurers per day (DDD/TID). Results: Cardiovascular drugs are the most commonly prescribed and utilized drugs in R. Macedonia. The HIF cost for cardiovascular disease (CVD) increased to euro2,243,777.00 in the period from 2013 to 2016. Since 2012, the reimbursement shows that atorvastatin accounts for the highest expenditure reaching euro2,162,958.00 while rosuvastatin reached euro1,645,860.00 in 2016. The increased consumption of statins is confirmed from the records obtained from IMS Health databases in the evaluated period in R. Macedonia suggesting increased expenditures with total growth of 35.65% reaching euro4,421,280.24 in 2016. Evident growth of statin consumption is confirmed from the data obtained from the pharmaceutical industry and MAH. The statin use increased from 42.347 DDD/TID in 2013 to 71.697 DDD/TID in 2016, although it is lower in comparison to other European Union (EU) countries (1.1-2.5-fold). Conclusion: The rapid increase in the consumption of statins can be attributed mostly to an increase in the consumption volume. It is inevitable to widen the price reduction concept with initiatives that may control statin consumption amounts with measures such as educational programs for rational drug utilization and targeting eligible population.

[19] *Evans MC, Stalam T, Miller M*. **Cardiovascular Risk Assessment in Patients with Hypertriglyceridemia**. Current cardiology reports 2018; 20:71.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992480
ABSTRACT

PURPOSE OF REVIEW: Assessing the cardiovascular risk associated with hypertriglyceridemia can be challenging due to frequent confounding conditions such as hypertension, diabetes mellitus, and hyperlipidemia. We sought to quantify this risk by examining several meta-analyses as well as subgroup analyses of previously published major randomized controlled trials that focused on the treatment of hyperlipidemia. RECENT FINDINGS: Recent trials measuring the effects of PCSK9 inhibitors such as evolocumab and alirocumab on cardiovascular outcomes have demonstrated a high degree of residual cardiovascular risk even after profound reductions in low-density-lipoprotein cholesterol (LDL-C). Despite optimization of LDL-C through the use of statins, PCSK9 inhibitors and adjunctive therapies such as ezetimibe, bile acid sequestrants and niacin, residual cardiovascular risk remains significant. Several ongoing trials are assessing the efficacy of pemafibrate and omega-3 fatty acids for the treatment of hypertriglyceridemia and their effects on major cardiovascular outcomes.

[20] *Tzoulaki I, Iliou A, Mikros E, Elliott P*. **An Overview of Metabolic Phenotyping in Blood Pressure Research**. Curr Hypertens Rep 2018; 20:78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992526
ABSTRACT
PURPOSE OF THE REVIEW: This review presents the analytical techniques, processing and analytical steps used in metabolomics phenotyping studies, as well as the main results from epidemiological studies on the associations between metabolites and high blood pressure. RECENT FINDINGS: A variety of metabolomic approaches have been applied to a range of epidemiological studies to uncover the pathophysiology of high blood pressure. Several pathways have been suggested in relation to blood pressure including the possible role of the gut microflora, inflammatory, oxidative stress, and lipid pathways. Metabolic changes have also been identified associated with blood pressure lowering effects of diets high in fruits and vegetables and low in meat intake. However, the current body of literature on metabolic profiling and blood pressure is still in its infancy, not fully consistent and requires careful interpretation. Metabolic phenotyping is a promising approach to uncover metabolic pathways associated with high blood pressure and throw light into the complex pathophysiology of hypertension.

[21] *Bastida JM, Giros ML, Benito R et al.* **Sitosterolemia: diagnosis, metabolic and hematological abnormalities, cardiovascular disease and management**. Curr Med Chem 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29984642
ABSTRACT
Sitosterolemia is a recessive inherited metabolic disorder of unknown prevalence, characterized by increased levels of plasma plant sterols. It is caused by 28 and 31 variants in ABCG5 and ABCG8 genes, respectively, and is characterized by a predisposition to hyperabsorption and accumulation of toxic levels of plant sterols in plasma. Its clinical picture is extremely heterogeneous. The main clinical features are tendinous and cutaneous xanthomas, arthritis or arthralgia, premature cardiovascular disease and atherosclerosis. These characteristics are shared with familial hypercholesterolemia (FH), making it possible for sitosterolemia to be misdiagnosed as homozygous FH, especially in pediatric patients. In such cases, a specific chromatography-based laboratory method is essential to differentiate sitosterol and

cholesterol. Hematological abnormalities (hemolytic anemia and macrothrombocytopenia) may be present in 25-35% of patients, in whom it is usually associated with the main clinical features, as occurs in the 70% of the cases. In this context, the peripheral blood smear is essential and reveals giant platelets and stomatocytes. Only 21 causative variants in ABCG5/ABCG8 are associated with macrothrombocytopenia. Most physicians still do not recognize these hematological abnormalities or relate them to sitosterolemia. Patients may suffer long-term misdiagnosis of immune thrombocytopenia and be at high risk of receiving harmful therapies or of not benefitting from a low-cholesterol diet and/or from the gold standard treatment with ezetimibe. This drug reduces levels of plasma plant sterols, provokes regression of xanthomas, and can alleviate hematological abnormalities. Finally, to identify genetic defects, recent advances in high-throughput sequencing, especially in the use of targeted sequencing of pre-specified genes, have begun to be incorporated into the first-line approach in the field of genetic disorders.

[22] *Cofan M, Ros E*. **Use of plant sterol and stanol fortified foods in clinical practice**. Curr Med Chem 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29984649
ABSTRACT
Plant sterols and stanols (PS) are natural, non-nutritive molecules that play a structural role in plant membranes similar to that of cholesterol in animal membranes and abound in seeds and derived oils. PS exert their physical effect of interference with micellar solubilization of cholesterol within the intestinal lumen and are marginally absorbed by enterocytes, with negiglible increases in circulating levels. The physiological role of PS in plants and their natural origin and non-systemic action, together with their cholesterol-lowering effect, make them an attractive option as non-pharmacological agents for the management of hypercholesterolemia. Recent meta-analyses have summarized the results of >100 controlled clinical trials and have firmly established that consumption of PS-supplemented foods in different formats at doses of 2-3 g per day results in LDL-cholesterol reductions of 9-12%. PS are both effective and safe cholesterol-lowering agents and have many clinical applications: adjuncts to a healthy diet, treatment of common hypercholesterolemia, combination therapy with statins and other lipid-lowering drugs, and treatment of metabolic syndrome and diabetes. The cholesterol-lowering efficacy is similar in all clinical situations. PS are also useful agents for treatment of hypercholesterolemic children who are not yet candidates to statins or are receive low-doses of these agents. In the setting of statin treatment, the average LDL-cholesterol reduction obtained with PS is equivalent to up- titrating twice the statin dose. However, information is still scarce on the efficacy of PS as add-on therapy to ezetimibe, fibrates, omega-3 fatty acids, or bile acid binding resins. The consistent scientific evidence on the cholesterol-lowering efficacy and safety of functional foods supplemented with PS has led several national and international scientific societies to endorse their use for the non-pharmacologic treatment of hypercholesterolemia as adjuncts to a healthy diet. There is, however, a lack of clinical trials of PS with outcomes on cardiovascular events.

[23] *Bede K, Tang WHW*. **New biomarker strategies to enable precision cardiovascular medicine**. Current opinion in cardiology 2018.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29994808
ABSTRACT
PURPOSE OF REVIEW: Precision medicine is the concept of disease treatment and prevention using an individual's genomic profile in addition to personal and environmental factors. This review outlines examples of new biomarker strategies that enable the practice of precision cardiovascular medicine. RECENT FINDINGS: Although commonly attributed to identifying causative genetic variants, mono-genetic causes of cardiovascular diseases (CVD) are not common and largely focused on lipoprotein analyses. Nevertheless, rare clinical presentations in families with extreme phenotypes can sometimes identify novel pathways that can serve as therapeutic targets, such as the discovery of PCSK9 inhibitors for familial hypercholesterolemia or small molecular inhibitors of myosin ATPase activities for hypertrophic cardiomyopathy. Polygenetic risks scores can also identify high-risk cohorts before their clinical manifestations. Novel metabolomic insights can also lead to unexpected modulators of CVD susceptibility, such as nutrient-induced gut microbiota-derived metabolic pathways. SUMMARY: Adequate knowledge systems and data infrastructure are necessary for clinicians to take into account both genetic and environmental factors to operationalize precision medicine and to prevent CVD.

[24] *Filippatos TD, Christopoulou EC, Elisaf MS*. **Pleiotropic effects of proprotein convertase subtilisin/kexin type 9 inhibitors?** Current opinion in lipidology 2018; 29:333-339.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29994840
ABSTRACT
PURPOSE OF REVIEW: Current data suggest that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may affect many metabolic pathways beyond lowering LDL cholesterol. The aim of the present manuscript is to present these so-called pleiotropic effects of PCSK9 inhibitors. RECENT FINDINGS: PCSK9 may affect the activity of other receptors beyond LDL receptors (LDLR), such as cluster of differentiation 36 (CD36), very-low-density-lipoprotein (VLDL) receptors, apolipoprotein (Apo) E receptors, LDLR-related protein 1 (LRP-1) and ATP-Binding Cassette Transporter (ABCA1). Thus, a role of PCSK9 in the development of atherosclerosis, in vascular wall inflammation and in platelet function has been suggested. Additionally, PCSK9 inhibitors may affect lipid variables beyond LDL cholesterol, carbohydrate variables, as well as they may affect brain and kidney function. Additionally, a controversial role of PCSK9 in sepsis, hepatitis C infection and Alzheimer's disease has been suggested. SUMMARY: These possible pleiotropic effects of PCSK9 inhibitors need further research, as they may affect cardiovascular risk and provide further insights in the development of atherosclerosis and other diseases such as Alzheimer's disease or chronic viral infection and sepsis.

[25] *Danielak D, Karazniewicz-Lada M, Glowka F*. **Assessment of the Risk of Rhabdomyolysis and Myopathy During Concomitant Treatment with Ticagrelor and Statins**. Drugs 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30003466
ABSTRACT
The introduction of ticagrelor, one of the first directly-acting oral antiplatelet drugs, provided new possibilities in the prevention of thrombotic events in patients with acute coronary

syndromes (ACS). Current guidelines recommend ticagrelor in dual antiplatelet therapy with aspirin over clopidogrel for prevention of stent thrombosis in patients with ACS. Moreover, in the management of ACS, lipid-lowering treatment with high-intensity statin therapy is advised for secondary prevention of cardiovascular events over the long term. Despite the apparent advantages of combined antiplatelet and lipid-lowering treatments, a possible interaction between statins and ticagrelor may lead to myopathy and rhabdomyolysis. In this review, relevant information was gathered on the ticagrelor-statin interaction that might lead to this life-threatening condition. This review focuses on the most widely used statins-simvastatin, atorvastatin, and rosuvastatin. Possible mechanisms of this interaction are discussed, including CYP3A4 isoenzymes, organic anion transporter polypeptide (OATPs), P-glycoprotein and glucuronidation. PubMed database was searched for relevant case reports and all data gathered from the introduction of ticagrelor to March 2018 are presented and discussed. In summary, co-administration of statins and ticagrelor was found to be relatively safe in routinely prescribed doses. However, caution should be exercised, especially in elder populations.

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[38] Bhatt D, Tannock L. Risk of Fasting and Non-Fasting Hypertriglyceridemia in Coronary Vascular Disease and Pancreatitis. In: Endotext. Edited by: De Groot LJ, Chrousos G, Dungan K *et al.* South Dartmouth (MA): MDText.com, Inc.; 2000.

[39] *Da Dalt L, Ruscica M, Bonacina F et al.* **PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor**. European heart journal 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29982592
ABSTRACT
Aims: PCSK9 loss of function genetic variants are associated with lower low-density lipoprotein cholesterol but also with higher plasma glucose levels and increased risk of Type 2 diabetes mellitus. Here, we investigated the molecular mechanisms underlying this association. Methods and results: Pcsk9 KO, WT, Pcsk9/Ldlr double KO (DKO), Ldlr KO, albumin AlbCre+/Pcsk9LoxP/LoxP (liver-selective Pcsk9 knock-out mice), and AlbCre-/Pcsk9LoxP/LoxP mice were used. GTT, ITT, insulin and C-peptide plasma levels, pancreas morphology, and cholesterol accumulation in pancreatic islets were studied in the different animal models. Glucose clearance was significantly impaired in Pcsk9 KO mice fed with a standard or a high-fat diet for 20 weeks compared with WT animals; insulin sensitivity, however, was not affected. A detailed analysis of pancreas morphology of Pcsk9 KO mice vs. controls revealed larger islets with increased accumulation of cholesteryl esters, paralleled by increased insulin intracellular levels and decreased plasma insulin, and C-peptide levels. This phenotype was completely reverted in Pcsk9/Ldlr DKO mice implying the low-density lipoprotein receptor (LDLR) as the proprotein convertase subtilisin/kexin Type 9 (PCSK9) target responsible for the phenotype observed. Further studies in albumin AlbCre+/Pcsk9LoxP/LoxP mice, which lack detectable circulating PCSK9, also showed a complete recovery of the phenotype, thus indicating that circulating, liver-derived PCSK9, the principal target of monoclonal antibodies, does not impact beta-cell function and insulin secretion. Conclusion: PCSK9 critically controls LDLR expression in pancreas perhaps contributing to the maintenance of a proper physiological balance to limit cholesterol overload in beta cells. This effect is independent of circulating PCSK9 and is probably related to locally produced PCSK9.

[40] *Ruuth M, Nguyen SD, Vihervaara T et al.* **Susceptibility of low-density lipoprotein particles to aggregate depends on particle lipidome, is modifiable, and associates with future cardiovascular deaths**. European heart journal 2018; 39:2562-2573.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29982602
ABSTRACT
Aims: Low-density lipoprotein (LDL) particles cause atherosclerotic cardiovascular disease (ASCVD) through their retention, modification, and accumulation within the arterial intima. High plasma concentrations of LDL drive this disease, but LDL quality may also contribute. Here, we focused on the intrinsic propensity of LDL to aggregate upon modification. We examined whether inter-individual differences in this quality are linked with LDL lipid composition and coronary artery disease (CAD) death, and basic mechanisms for plaque growth and destabilization. Methods and results: We developed a novel, reproducible method to assess the susceptibility of LDL particles to aggregate during lipolysis induced ex vivo by human recombinant secretory sphingomyelinase. Among patients with an established CAD, we found that the presence of aggregation-prone LDL was predictive of future cardiovascular deaths, independently of conventional risk factors. Aggregation-prone LDL contained more sphingolipids and less phosphatidylcholines than did aggregation-resistant LDL. Three

interventions in animal models to rationally alter LDL composition lowered its susceptibility to aggregate and slowed atherosclerosis. Similar compositional changes induced in humans by PCSK9 inhibition or healthy diet also lowered LDL aggregation susceptibility. Aggregated LDL in vitro activated macrophages and T cells, two key cell types involved in plaque progression and rupture. Conclusion: Our results identify the susceptibility of LDL to aggregate as a novel measurable and modifiable factor in the progression of human ASCVD.

[41] *Turner AW, Wong D, Dreisbach CN, Miller CL*. **GWAS Reveal Targets in Vessel Wall Pathways to Treat Coronary Artery Disease**. Frontiers in cardiovascular medicine 2018; 5:72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29988570
ABSTRACT
Coronary artery disease (CAD) is the leading cause of mortality worldwide and poses a considerable public health burden. Recent genome-wide association studies (GWAS) have revealed >100 genetic loci associated with CAD susceptibility in humans. While a number of these loci harbor gene targets of currently approved therapies, such as statins and PCSK9 inhibitors, the majority of the annotated genes at these loci encode for proteins involved in vessel wall function with no known drugs available. Importantly many of the associated genes linked to vascular (smooth muscle, endothelial, and macrophage) cell processes are now organized into distinct functional pathways, e.g., vasodilation, growth factor responses, extracellular matrix and plaque remodeling, and inflammation. In this mini-review, we highlight the most recently identified loci that have predicted roles in the vessel wall and provide genetic context for pre-existing therapies as well as new drug targets informed from GWAS. With the development of new modalities to target these pathways, (e.g., antisense oligonucleotides, CRISPR/Cas9, and RNA interference) as well as the computational frameworks to prioritize or reposition therapeutics, there is great opportunity to close the gap from initial genetic discovery to clinical translation for many patients affected by this common disease.

[42] *Marques AC, Busanello ENB, de Oliveira DN et al.* **Coenzyme Q10 or Creatine Counteract Pravastatin-Induced Liver Redox Changes in Hypercholesterolemic Mice**. Frontiers in pharmacology 2018; 9:685.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29997512
ABSTRACT
Statins are the preferred therapy to treat hypercholesterolemia. Their main action consists of inhibiting the cholesterol biosynthesis pathway. Previous studies report mitochondrial oxidative stress and membrane permeability transition (MPT) of several experimental models submitted to diverse statins treatments. The aim of the present study was to investigate whether chronic treatment with the hydrophilic pravastatin induces hepatotoxicity in LDL receptor knockout mice (LDLr(-/-)), a model for human familial hypercholesterolemia. We evaluated respiration and reactive oxygen production rates, cyclosporine-A sensitive mitochondrial calcium release, antioxidant enzyme activities in liver mitochondria or homogenates obtained from LDLr(-/-) mice treated with pravastatin for 3 months. We observed that pravastatin induced higher H2O2 production rate (40%), decreased activity of aconitase (28%), a superoxide-sensitive Krebs cycle enzyme, and increased susceptibility to Ca(2+)-induced MPT (32%) in liver mitochondria. Among several antioxidant enzymes, only glucose-6-phosphate dehydrogenase (G6PD) activity

was increased (44%) in the liver of treated mice. Reduced glutathione content and reduced to oxidized glutathione ratio were increased in livers of pravastatin treated mice (1.5- and 2-fold, respectively). The presence of oxidized lipid species were detected in pravastatin group but protein oxidation markers (carbonyl and SH- groups) were not altered. Diet supplementation with the antioxidants CoQ10 or creatine fully reversed all pravastatin effects (reduced H2O2 generation, susceptibility to MPT and normalized aconitase and G6PD activity). Taken together, these results suggest that 1- pravastatin induces liver mitochondrial redox imbalance that may explain the hepatic side effects reported in a small number of patients, and 2- the co-treatment with safe antioxidants neutralize these side effects.

[43] *Gibson MS, Domingues N, Vieira OV*. **Lipid and Non-lipid Factors Affecting Macrophage Dysfunction and Inflammation in Atherosclerosis**. Front Physiol 2018; 9:654.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29997514

ABSTRACT

Atherosclerosis is a chronic inflammatory disease and a leading cause of human mortality. The lesional microenvironment contains a complex accumulation of variably oxidized lipids and cytokines. Infiltrating monocytes become polarized in response to these stimuli, resulting in a broad spectrum of macrophage phenotypes. The extent of lipid loading in macrophages influences their phenotype and consequently their inflammatory status. In response to excess atherogenic ligands, many normal cell processes become aberrant following a loss of homeostasis. This can have a direct impact upon the inflammatory response, and conversely inflammation can lead to cell dysfunction. Clear evidence for this exists in the lysosomes, endoplasmic reticulum and mitochondria of atherosclerotic macrophages, the principal lesional cell type. Furthermore, several intrinsic cell processes become dysregulated under lipidotic conditions. Therapeutic strategies aimed at restoring cell function under disease conditions are an ongoing coveted aim. Macrophages play a central role in promoting lesional inflammation, with plaque progression and stability being directly proportional to macrophage abundance. Understanding how mixtures or individual lipid species regulate macrophage biology is therefore a major area of atherosclerosis research. In this review, we will discuss how the myriad of lipid and lipoprotein classes and products used to model atherogenic, proinflammatory immune responses has facilitated a greater understanding of some of the intricacies of chronic inflammation and cell function. Despite this, lipid oxidation produces a complex mixture of products and with no single or standard method of derivatization, there exists some variation in the reported effects of certain oxidized lipids. Likewise, differences in the methods used to generate macrophages in vitro may also lead to variable responses when apparently identical lipid ligands are used. Consequently, the complexity of reported macrophage phenotypes has implications for our understanding of the metabolic pathways, processes and shifts underpinning their activation and inflammatory status. Using oxidized low density lipoproteins and its oxidized cholesteryl esters and phospholipid constituents to stimulate macrophage has been hugely valuable, however there is now an argument that only working with low complexity lipid species can deliver the most useful information to guide therapies aimed at controlling atherosclerosis and cardiovascular complications.

[44] *Kajani S, Curley S, McGillicuddy FC*. **Unravelling HDL-Looking beyond the Cholesterol Surface to the Quality Within**. International journal of molecular sciences 2018; 19.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986413
ABSTRACT
High-density lipoprotein (HDL) particles have experienced a turbulent decade of falling from grace with widespread demotion from the most-sought-after therapeutic target to reverse cardiovascular disease (CVD), to mere biomarker status. HDL is slowly emerging from these dark times due to the HDL flux hypothesis wherein measures of HDL cholesterol efflux capacity (CEC) are better predictors of reduced CVD risk than static HDL-cholesterol (HDL-C) levels. HDL particles are emulsions of metabolites, lipids, protein, and microRNA (miR) built on the backbone of Apolipoprotein A1 (ApoA1) that are growing in their complexity due to the higher sensitivity of the respective “omic” technologies. Our understanding of particle composition has increased dramatically within this era and has exposed how our understanding of these particles to date has been oversimplified. Elucidation of the HDL proteome coupled with the identification of specific miRs on HDL have highlighted the “hormonal” characteristics of HDL in that it carries and delivers messages systemically. HDL can dock to most peripheral cells via its receptors, including SR-B1, ABCA1, and ABCG1, which may be a critical step for facilitating HDL-to-cell communication. The composition of HDL particles is, in turn, altered in numerous disease states including diabetes, auto-immune disease, and CVD. The consequence of changes in composition, however, on subsequent biological activities of HDL is currently poorly understood and this is an important avenue for the field to explore in the future. Improving HDL particle quality as opposed to HDL quantity may, in turn, prove a more beneficial investment to reduce CVD risk.

[45] *Alghamdi J, Matou-Nasri S, Alghamdi F et al.* **Risk of neuropsychiatric adverse effects of lipid-lowering drugs: a Mendelian Randomization study**. The international journal of neuropsychopharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986042
ABSTRACT
Background: Recent studies have highlighted the possible risk of neuropsychiatric adverse effects during lipid-lowering medications. However, there are still controversies that require a novel genetic-based approach to verify whether the impact of lipid-lowering drug treatment results in neuropsychiatric troubles including insomnia, depression, and neuroticism. Thus, we applied Mendelian randomization (MR) to assess any potential neuropsychiatric adverse effects of conventional lipid-lowering drugs such as Statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and ezetimibe. Methods: a two-sample MR study was conducted based on summary statistics from genome-wide association studies (GWAS) for lipids, insomnia, depression, and neuroticism. Single-nucleotide polymorphisms (SNPs) located in or near drug target genes of HMGCR, PCSK9 and NPC1L1 were used as proxies for Statins, PCSK9 inhibitors, and ezetimibe therapy; respectively. To assess the validity of the genetic risk score, their associations with coronary artery disease (CAD) were used as a positive control. Results: The MR analysis showed a statistically significant (p-value < 0.004) increased risk of depression after correcting for multiple testing with both Statins (odds ratio [OR] = 1.15, 95% CI: 1.04-1.19) and PCSK9 inhibitor treatment (OR = 1.19, 95%CI: 1.1-1.29). The risk of neuroticism was slightly

reduced with Statins therapy (OR = 0.9, 95%CI: 0.83-0.97). No significant adverse effects were associated with ezetimibe treatment. As expected, the three medications significantly reduced the risk of a CAD. Conclusion: Using a genetic-based approach, this study showed an increased risk of depression during Statins and PCSK9 inhibitor therapy while their association with insomnia risk was not significant.

[46] *Muhlbacher AC, Kaczynski A, Dippel FW, Bethge S*. **PATIENT PRIORITIES FOR TREATMENT ATTRIBUTES IN ADJUNCTIVE DRUG THERAPY OF SEVERE HYPERCHOLESTEROLEMIA IN GERMANY: AN ANALYTIC HIERARCHY PROCESS**. International journal of technology assessment in health care 2018; 34:267-275.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29987994
ABSTRACT
OBJECTIVES: Severe hypercholesterolemia is a major cause of death in coronary heart disease. New adjunctive drug therapies have passed authorization processes and been launched recently. So far it is not known which properties of the new treatment options generate the highest benefit for patients. The aim was to evaluate patient priorities in the field of adjunctive drug therapy with apheresis. Therapy characteristics were examined as to their relevance to hypercholesterolemia patients. METHODS: To identify all potential patient-relevant treatment characteristics, a systematic literature review and ten interviews with patients were conducted. Seven key characteristics were identified from the patient perspective. Patients' priorities were elicited using an analytic hierarchy process (AHP). RESULTS: In total, N = 61 patients diagnosed with severe hypercholesterolemia and undergoing apheresis participated in the study. The analysis showed predominance for the attribute "reduction of LDL-C level in blood" (Wglobal:0.362). The "risk of myopathy" (Wglobal:0.164), "risk of neurocognitive impairment" (Wglobal:0.161) and "frequency of apheresis" (Wglobal:0.119) were ranked second, third and fourth. Subgroup analyses revealed that "frequency of apheresis" is of greater importance to younger patients, men and/or patients who indicated a reduction in quality of life due to apheresis. CONCLUSIONS: The essential decision criteria for optimal therapy from the patients' perspective were obtained. "Reduction of lipoprotein in blood" was ranked highest compared with the "mode of administration" and "side effects" characteristics. The study offers a transparent approach for the identification of patient priorities for adjunctive PCSK9-inhibitor therapy in apheresis-treated hypercholesterolemia. The project can be used by healthcare decision makers to understand the importance of each patient-relevant endpoint.

[47] *Shahreyar M, Salem SA, Nayyar M et al.* **Hyperlipidemia: Management with Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors**. Journal of the American Board of Family Medicine : JABFM 2018; 31:628-634.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29986989
ABSTRACT
Coronary artery disease is the leading cause of death in United States. Hyperlipidemia is an independent and potentially reversible risk factor for coronary artery disease. The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, collectively known as statins, have been the mainstay of pharmacologic therapy. Their availability, ease of administration, low cost, and strong evidence behind safety and efficacy makes them one of the most widely prescribed lipid-

lowering agents. However, some patients may be intolerant to statins, and few others suffer from very high serum levels of cholesterol in which statin therapy alone or in combination with other cholesterol-lowering agents is insufficient in reducing serum lipid levels to achieve desired levels. In 2015, the Food and Drug Administration approved a new family of lipid-lowering agents, collectively known as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.PCSK9 inhibitors are biologically active molecules that decrease serum low-density lipoprotein cholesterol compared with statin therapy alone. They serve as an alternative to statins for patients who are intolerant to statin or as supplemental therapy in those patients for whom lower levels in serum low-density lipoprotein cholesterol are not achieved by statins alone. This article discusses PCSK9 inhibitors, their mechanism of action, indications, efficacy, safety, costs and limitations.

[48] *Ji T, Zhao Y, Wang J et al.* **Effect of Low-Dose Statins and Apolipoprotein E Genotype on Cerebral Small Vessel Disease in Older Hypertensive Patients: A Subgroup Analysis of a Randomized Clinical Trial**. Journal of the American Medical Directors Association 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30006015

ABSTRACT

OBJECTIVES: To investigate the effect of low-dose statins and apolipoprotein E (APOE) genotypes on cerebral small vessel disease (CSVD) to prevent CSVD in older hypertensive patients. DESIGN: A subgroup analysis of a randomized clinical trial. SETTING: Shandong area, China. PARTICIPANTS: Hypertensive patients aged >/=60 years were recruited from April 2008 to November 2010. MEASUREMENTS: Patients were randomly assigned to rosuvastatin (10 mg/day) or placebo groups. APOE genotypes were categorized as epsilon4 carriers and non-epsilon4 carriers. White matter hyperintensities (WMH), Fazekas scale, lacunes, and microbleeds were assessed. RESULTS: After an average of intervention period of 61.8 months, WMH volume increased 1.45 +/- 0.52 mL. There were 107 new-incident Fazekas scale >/=2, 65 new-incident lacunes, and 63 new-incident microbleeds. The increase in WMH volume was significantly lower in the rosuvastatin group than in the placebo group and was higher in APOE epsilon4 carriers than in non-epsilon4 carriers (all adjusted P < .001). The risk of new-incident Fazekas scale >/=2 was higher in the placebo group than in the rosuvastatin group (hazard ratio 2.150, 95% confidence interval 1.443-3.203; P < .001). APOE epsilon4 carriers were associated with an increased risk of new-incident Fazekas scale >/=2 compared with non-epsilon4 carriers (hazard ratio 1.973, 95% confidence interval 1.334-2.920; P = .001). There were no statistically significant differences in the risk of new-incident cerebral microbleeds between the rosuvastatin and placebo groups or between APOE epsilon4 carriers and non-epsilon4 carriers. There were no significant interactions between rosuvastatin use and APOE epsilon4 status regarding increased WMH volume (F = 1.020, P = .313) or for new-incident Fazekas scale >/=2 (P = .377), lacunes (P = .232), and microbleeds (P = .362). CONCLUSIONS/IMPLICATIONS: Low-dose rosuvastatin is an effective and safe therapy for CSVD. The presence of APOE epsilon4 allele may not be able to predict rosuvastatin treatment outcomes for preventing and/or treating CSVD in older hypertensive patients.

[49] *Zhou L, Liu X, Wang ZQ et al.* **Simvastatin Treatment Protects Myocardium in Non-coronary Artery Cardiac Surgery by Inhibiting Apoptosis Through miR-15a-5p Targeting**. Journal of cardiovascular pharmacology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29985281
ABSTRACT
Simvastatin treatment is cardioprotective in patients undergoing non-coronary artery cardiac surgery. However, the mechanisms by which simvastatin treatment protects the myocardium under these conditions are not fully understood. Seventy patients undergoing noncoronary cardiac surgery, 35 from a simvastatin treatment group and 35 from a control treatment group, were enrolled in our clinical study. Simvastatin (20 mg/d) was administered pre-operatively for 5-7 days. Myocardial tissue biopsies were taken before and after surgery. Apoptosis was detected by TUNEL staining. The expressions of Bcl-2 and Bak in myocardial tissue were detected by immunoblotting. The expressions of miRNA and Bcl-2 mRNA were detected by quantitative polymerase chain reaction (qRT-PCR) assays. Cardiomyocytes were isolated from rat and cultured. MiR-15a-5p mimic was transfected into cardiomyocytes and the Bcl-2 was detected by immunoblotting. TUNEL staining showed significantly less myocardial apoptosis in the simvastatin treatment group when compared with the control treatment group. Protein expression of Bcl-2 was increased in the simvastatin treatment group before surgery and Bak expression was increased in the control treatment group after surgery. Further comparisons showed that Bcl-2/Bak ratios were reduced in the control treatment group but were not significantly changed in the simvastatin treatment group after surgery. Furthermore, microarray assays revealed that miR-15a-5p was significantly decreased by simvastatin treatment. This was validated by qRT-PCR analysis. MiR-15a-5p was predicted to target Bcl-2 mRNA at nucleotide positions 2529-2536. This was validated by luciferase binding assays. Coincident with the change in miR-15a-5p, the mRNA expression of Bcl-2 was increased in the simvastatin treatment group. MiR-15a-5p mimic significantly inhibited Bcl-2 expression in cardiomyocytes. Our findings strongly suggest that simvastatin treatment pre-operatively protected the myocardium in patients undergoing noncoronary artery cardiac surgery, at least in part, by inhibiting apoptosis via suppressing miR-15a-5p expression leading to increasing expression of Bcl-2 and decreasing expression of Bak.

[50] *Macarie RD, Vadana M, Ciortan L et al.* **The expression of MMP-1 and MMP-9 is up-regulated by smooth muscle cells after their cross-talk with macrophages in high glucose conditions**. Journal of cellular and molecular medicine 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992758
ABSTRACT
Patients with diabetes mellitus have an increased risk of myocardial infarction and coronary artery disease-related death, exhibiting highly vulnerable plaques. Many studies have highlighted the major role of macrophages (MAC) and smooth muscle cells (SMC) and the essential part of metalloproteases (MMPs) in atherosclerotic plaque vulnerability. We hypothesize that in diabetes, the interplay between MAC and SMC in high glucose conditions may modify the expression of MMPs involved in plaque vulnerability. The SMC-MAC cross-talk was achieved using trans-well chambers, where human SMC were grown at the bottom and human MAC in the upper chamber in normal (NG) or high (HG) glucose concentration. After

cross-talk, the conditioned media and cells were isolated and investigated for the expression of MMPs, MCP-1 and signalling molecules. We found that upon cross-talk with MAC in HG, SMC exhibit: (i) augmented expression of MMP-1 and MMP-9; (ii) significant increase in the enzymatic activity of MMP-9; (iii) higher levels of soluble MCP-1 chemokine which is functionally active and involved in MMPs up-regulation; (iv) activated PKCalpha signalling pathway which, together with NF-kB are responsible for MMP-1 and MMP-9 up-regulation, and (v) impaired function of collagen assembly. Taken together, our data indicate that MCP-1 released by cell cross-talk in diabetic conditions binds to CCR2 and triggers MMP-1 and MMP-9 over-expression and activity, features that could explain the high vulnerability of atherosclerotic plaque found at diabetic patients.

[51] *Mayne J, Ooi TC, Tepliakova L et al.* **Associations Between Soluble LDLR and Lipoproteins in a Caucasian Cohort and The Effect of PCSK9 Loss-of-Function**. The Journal of clinical endocrinology and metabolism 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29982529
ABSTRACT
Context: Elevated circulating cholesterol-rich low density lipoprotein (LDL) particles increase coronary artery disease (CAD) risk. Cell surface hepatic LDL receptors (LDLRs) clear 70% of these particles from circulation. The ectodomain of LDLR is shed into circulation, preventing it from removing LDL particles. The role that LDLR ectodomain shedding plays as a regulatory mechanism is unknown. Objective: Herein, we described LDLR shedding via the relationships between circulating soluble LDLR (sLDLR) and serum lipoproteins, serum proprotein convertase subtilin/kexin like 9 (PCSK9; a negative regulator of LDLR), and clinical parameters in a Caucasian Canadian population. Design: Population based, cross-sectional study. Settings: Clinical Research Center, The Ottawa Hospital and Faculty of Medicine, University of Ottawa. Participants: 273 Caucasian Canadians. Intervention: None. Main Outcome Measures: Soluble LDLR measured by ELISA. Serum lipids and PCSK9, PCSK9 genotypes and clinical parameters were from previous analyses. Results: Soluble LDLR strongly correlated with triglycerides (TG; $r=0.624$, $p<0.0001$), and moderately with LDL cholesterol (LDLC; $r=0.384$, $p<0.0001$), and high density lipoprotein cholesterol (HDLC; $r=-0.307$, $p=0.0003$). Only TG correlations were unaffected by PCSK9 variation. Levels of sLDLR were significantly elevated in those with TG >50th or LDLC >75th percentiles. Conclusions: Serum sLDLR levels correlate with several lipoprotein parameters, especially TG and the presence of PCSK9 LOF variants alters sLDLR levels and correlations, except for TG. Ectodomain LDLR shedding has a role in LDL metabolism, distinct from PCSK9, with interplay between these two pathways that regulate cell surface LDLR. Findings suggest alteration of LDLR shedding can emerge as a target to treat dyslipidemia.

[52] *Bellinge JW, Francis RJ, Majeed K et al.* **In search of the vulnerable patient or the vulnerable plaque: (18)F-sodium fluoride positron emission tomography for cardiovascular risk stratification**. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29992525
ABSTRACT

Cardiovascular disease (CVD) remains a leading cause of death. Preventative therapies that reduce CVD are most effective when targeted to individuals at high risk. Current risk stratification tools have only modest prognostic capabilities, resulting in over-treatment of low-risk individuals and under-treatment of high-risk individuals. Improved methods of CVD risk stratification are required. Molecular imaging offers a novel approach to CVD risk stratification. In particular, (18)F-sodium fluoride ((18)F-NaF) positron emission tomography (PET) has shown promise in the detection of both high-risk atherosclerotic plaque features and vascular calcification activity, which predicts future development of new vascular calcium deposits. The rate of change of coronary calcium scores, measured by serial computed tomography scans over a 2-year period, is a strong predictor of CVD risk. Vascular calcification activity, as measured with (18)F-NaF PET, has the potential to provide prognostic information similar to consecutive coronary calcium scoring, with a single-time-point convenience. However, owing to the rapid motion and small size of the coronary arteries, new solutions are required to address the traditional limitations of PET imaging. Two different methods of coronary PET analysis have been independently proposed and here we compare their respective strengths, weaknesses, and the potential for clinical translation.

[53] *Genser L, Aguanno D, Soula HA et al.* **Increased jejunal permeability in human obesity is revealed by a lipid challenge and is linked to inflammation and type 2 diabetes**. The Journal of pathology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29984492
ABSTRACT
Obesity and its metabolic complications are characterized by subclinical systemic and tissue inflammation. In rodent models of obesity, inflammation and metabolic impairments are linked with intestinal barrier damage. However, whether intestinal permeability is altered in human obesity remains to be investigated. In a cohort of 122 severely obese and non-obese patients, we analyzed intestinal barrier function combining in vivo and ex vivo investigations. We found tight junction impairments in the jejunal epithelium of obese patients, evidenced by a reduction of occludin and tricellulin. Serum levels of zonulin and LPS-Binding Protein, two markers usually associated with intestinal barrier alterations, were also increased in obese patients. Intestinal permeability per se was assessed in vivo by quantification of urinary lactitol/mannitol (L/M) and measured directly ex vivo on jejunal samples in Ussing chambers. In the fasting condition, L/M ratio and jejunal permeability were not significantly different between obese and non-obese patients, but high jejunal permeability to small molecules (0.4 kDa) was associated with systemic inflammation within the obese cohort. Altogether, these results suggest that intestinal barrier function is subtly compromised in obese patients. We thus tested whether this barrier impairment could be exacerbated by dietary lipids. To this end, we challenged jejunal samples with lipid micelles and showed that a single exposure increased permeability to macromolecules (4 kDa). Jejunal permeability after the lipid load was two-fold higher in obese patients compared to non-obese controls and correlated with systemic and intestinal inflammation. Moreover, lipid-induced permeability was an explicative variable of type 2 diabetes. In conclusion, intestinal barrier defects are present in human severe obesity and exacerbated by a lipid challenge. This paves the way to the development of novel therapeutic approaches to modulate intestinal barrier function or personalize nutrition therapy to decrease

lipid-induced jejunal leakage in metabolic diseases. This article is protected by copyright. All rights reserved.

[54] *Turner RM, Fontana V, Bayliss M et al.* **Development, validation and application of a novel HPLC-MS/MS method for the quantification of atorvastatin, bisoprolol and clopidogrel in a large cardiovascular patient cohort**. Journal of pharmaceutical and biomedical analysis 2018; 159:272-281.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30005242
ABSTRACT
Cardiovascular disease is a leading cause of morbidity, mortality, and healthcare expenditure worldwide. Importantly, there is interindividual variation in response to cardiovascular medications, leading to variable efficacy and adverse events. Therefore a rapid, selective, sensitive and reproducible multi-analyte HPLC-MS/MS assay for the quantification in human plasma of atorvastatin, its major metabolites 2-hydroxyatorvastatin, atorvastatin lactone and 2-hydroxyatorvastatin lactone, plus bisoprolol and clopidogrel-carboxylic acid has been developed, fully validated, and applied to a large patient study. Fifty microliter plasma samples were extracted with a simple protein precipitation procedure involving acetonitrile with acetic acid (0.1%, v/v). Chromatographic separation was via a 2.7mum Halo C18 (50x2.1mm ID, 90A) column and gradient elution at a flow rate of 500muL/min consisting of a mobile phase of water (A) and acetonitrile (B), each containing 0.1% formic acid (v/v), over a 6.0min run time. The six analytes and their corresponding six deuterated internal standards underwent positive ion electrospray ionisation and were detected with multiple reaction monitoring. The developed method was fully validated with acceptable selectivity, carryover, dilution integrity, and within-run and between-run accuracy and precision. Mean extraction recovery for the analytes was 92.7-108.5%, and internal standard-normalised matrix effects had acceptable precision (coefficients of variation 2.2-12.3%). Moreover, all analytes were stable under the tested conditions. Atorvastatin lactone to acid interconversion was assessed and recommendations for its minimisation are made. The validated assay was successfully applied to analyse 1279 samples from 1024 patients recruited to a cardiovascular secondary prevention prospective study.

[55] *McDermott MM, Criqui MH*. **Ankle-Brachial Index Screening and Improving Peripheral Artery Disease Detection and Outcomes**. Jama 2018; 320:143-145.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29998324
ABSTRACT

[56] **QuickStats: Percentage of Adults Aged >/=20 Years Told Their Cholesterol Was High Who Were Taking Lipid-Lowering Medications,* by Sex and Age Group - National Health and Nutrition Examination Survey, 2005-2006 to 2015-2016**. MMWR. Morbidity and mortality weekly report 2018; 67:771.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30001561
ABSTRACT

Literature update week 28 (2018)

[57] *Wang L, Smith J, Breton C et al.* **Meganuclease targeting of PCSK9 in macaque liver leads to stable reduction in serum cholesterol**. Nature biotechnology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29985478
ABSTRACT
Clinical translation of in vivo genome editing to treat human genetic diseases requires thorough preclinical studies in relevant animal models to assess safety and efficacy. A promising approach to treat hypercholesterolemia is inactivating the secreted protein PCSK9, an antagonist of the LDL receptor. Here we show that single infusions in six non-human primates of adeno-associated virus vector expressing an engineered meganuclease targeting PCSK9 results in dose-dependent disruption of PCSK9 in liver, as well as a stable reduction in circulating PCSK9 and serum cholesterol. Animals experienced transient, asymptomatic elevations of serum transaminases owing to the formation of T cells against the transgene product. Vector DNA and meganuclease expression declined rapidly, leaving stable populations of genome-edited hepatocytes. A second-generation PCSK9-specific meganuclease showed reduced off-target cleavage. These studies demonstrate efficient, physiologically relevant in vivo editing in non-human primates, and highlight safety considerations for clinical translation.

[58] *Mackey RH, Kuller LH, Moreland LW*. **Update on Cardiovascular Disease Risk in Patients with Rheumatic Diseases**. Rheumatic diseases clinics of North America 2018; 44:475-487.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30001787
ABSTRACT
Cardiovascular disease (CVD) risk is 1.5-fold higher in rheumatoid arthritis (RA), partly due to subclinical atherosclerosis that develops before the diagnosis of RA. Dyslipidemia in RA is better quantified by lipoproteins and apolipoproteins than by cholesterol levels. Current risk factors likely underestimate CVD risk by underestimating prior risk factor levels. Some of the 2-fold higher risk of heart failure and total mortality in RA may be due to myocardial disease caused by inflammation. Per recent recommendations, to reduce CVD risk in RA, control disease activity, reduce inflammation, and aggressively treat CVD risk factors.

[59] *Grin PM, Dwivedi DJ, Chathely KM et al.* **Low-density lipoprotein (LDL)-dependent uptake of Gram-positive lipoteichoic acid and Gram-negative lipopolysaccharide occurs through LDL receptor**. Scientific reports 2018; 8:10496.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30002483
ABSTRACT
Lipoteichoic acid (LTA) and lipopolysaccharide (LPS) are bacterial lipids that stimulate pro-inflammatory cytokine production, thereby exacerbating sepsis pathophysiology. Proprotein convertase subtilisin/kexin type 9 (PCSK9) negatively regulates uptake of cholesterol by downregulating hepatic lipoprotein receptors, including low-density lipoprotein (LDL) receptor (LDLR) and possibly LDLR-related protein-1 (LRP1). PCSK9 also negatively regulates Gram-negative LPS uptake by hepatocytes, however this mechanism is not completely characterized and mechanisms of Gram-positive LTA uptake are unknown. Therefore, our objective was to elucidate the mechanisms through which PCSK9 regulates uptake of LTA and LPS by investigating the roles of lipoproteins and lipoprotein receptors. Here we show that plasma PCSK9 concentrations increase transiently over time in septic and non-septic critically ill

patients, with highly similar profiles over 14 days. Using flow cytometry, we demonstrate that PCSK9 negatively regulates LDLR-mediated uptake of LTA and LPS by HepG2 hepatocytes through an LDL-dependent mechanism, whereas LRP1 and high-density lipoprotein do not contribute to this uptake pathway. Bacterial lipid uptake by hepatocytes was not associated with cytokine production or hepatocellular injury. In conclusion, our study characterizes an LDL-dependent and LDLR-mediated bacterial lipid uptake pathway regulated by PCSK9, and provides evidence in support of PCSK9 inhibition as a potential therapeutic strategy for sepsis.

[60] *Grosse GM, Bascunana P, Schulz-Schaeffer WJ et al.* **Targeting Chemokine Receptor CXCR4 and Translocator Protein for Characterization of High-Risk Plaque in Carotid Stenosis Ex Vivo**. Stroke 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30002148
ABSTRACT
BACKGROUND AND PURPOSE: This pilot study aims to demonstrate the feasibility of targeting molecular characteristics of high-risk atherosclerotic plaque in symptomatic and asymptomatic carotid stenosis (CS), that is, upregulation of the translocator protein (TSPO) and the chemokine receptor type 4 (CXCR4), by means of molecular imaging. METHODS: In a translational setting, specimens of carotid plaques of patients with symptomatic and asymptomatic CS obtained by carotid endarterectomy were analyzed for the presence of TSPO and CXCR4 by autoradiography, using the positron emission tomography tracers (18)F-GE180 and (68)Ga-Pentixafor and evaluated by histopathology. In addition, (68)Ga-Pentixafor positron emission tomography/computed tomography was performed in a patient with high-grade CS. RESULTS: Distinct patterns of upregulation of TSPO ((18)F-GE180 uptake) and CXCR4 ((68)Ga-Pentixafor uptake) were identified in carotid plaque by autoradiography. The spatial distribution was associated with specific histological hallmarks that are established features of high-risk plaque: TSPO upregulation correlated with activated macrophages infiltration, whereas CXCR4 upregulation also corresponded to areas of intraplaque hemorrhage. (68)Ga-Pentixafor uptake was significantly higher in plaques of symptomatic compared with asymptomatic CS. Clinical positron emission tomography revealed marked (68)Ga-Pentixafor uptake in carotid plaque of a patient with high-grade CS. CONCLUSIONS: Clinical imaging of molecular signatures of high-risk atherosclerotic plaque is feasible and may become a promising diagnostic tool for comprehensive characterization of carotid disease. This methodology provides a platform for future studies targeting carotid plaque.

[61] *Safouris A, Katsanos AH, Kerasnoudis A et al.* **Statin Pretreatment and Microembolic Signals in Large Artery Atherosclerosis: A Systematic Review and Meta-Analysis**. Stroke 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29991656
ABSTRACT
BACKGROUND AND PURPOSE: Scarce data indicate that statin pretreatment (SP) in patients with acute cerebral ischemia because of large artery atherosclerosis may be related to lower risk of recurrent stroke because of a decreased incidence of microembolic signals (MES) during transcranial Doppler monitoring. METHODS: We performed a systematic review and meta-analysis of available observational studies reporting MES presence/absence or MES burden, categorized according to SP status, in patients with acute cerebral ischemia because of

symptomatic (>/=50%) large artery atherosclerosis. In studies with partially-published data, authors were contacted for previously unpublished information. We also performed a sensitivity analysis of studies with data on MES burden categorized according to SP status, and an additional subgroup analysis in patients receiving higher-dose SP (atorvastatin 80 mg or rosuvastatin 40 mg daily). RESULTS: Seven eligible study protocols were identified (610 patients, 54% with SP). SP was associated with a reduced risk of MES detection during transcranial Doppler monitoring (risk ratio=0.67; 95% CI, 0.45-0.98), with substantial heterogeneity between studies (I(2)=52%). In studies reporting MES burden (n=4), a significantly lower number of MES were identified in patients with compared with those without SP (mean difference=-0.92; 95% CI, -1.64 to -0.19), with no evidence of heterogeneity between studies (I(2)=49%). Subgroup analysis revealed that higher-dose SP reduced the risk of detecting MES (risk ratio=0.23; 95% CI, 0.06-0.88), with no evidence of heterogeneity between studies (I(2)=0%). CONCLUSIONS: SP seems to be associated with a lower incidence and burden of MES in patients with acute cerebral ischemia because of large artery atherosclerosis.

[62] *Pedicino D, Giglio AF, Ruggio A et al.* **Inflammasome, T Lymphocytes and Innate-Adaptive Immunity Crosstalk: Role in Cardiovascular Disease and Therapeutic Perspectives**. Thrombosis and haemostasis 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=29991092
ABSTRACT
Over the past few decades, lot of evidences have shown atherosclerosis as a chronic progressive disease with an exquisite inflammatory feature. More recently, the role of innate immune response in the onset and progression of coronary artery disease (CAD) and an adaptive immunity imbalance, mostly involving T cell sub-sets, have been documented. Therefore, like in many other inflammatory and autoimmune disorders, an altered innate-adaptive immunity crosstalk could represent the key of the inflammatory burden leading to atherosclerotic plaque formation and progression and to the breakdown of plaque stability. In this review, we will address the role of inflammasome in innate immunity and in the imbalance of adaptive immunity. We will discuss how this altered immune crosstalk is related to CAD onset and progression. We will also discuss how unravelling the key molecular mechanisms is of paramount importance in the development of therapeutic tools to delay the chronic progression and prevent the acute destabilization of atherosclerotic plaque.

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.

Literature update week 28 (2018)

[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.

[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

Literature update week 28 (2018)

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.

Literature update week 28 (2018)

[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.

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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.