Literature update week 10 (2019)

[1] *Whelton SP, Dardari Z, Handy Marshall C et al.* **Relation of Isolated Low High-Density Lipoprotein Cholesterol to Mortality and Cardiorespiratory Fitness (from the Henry Ford Exercise Testing Project [FIT Project])**. The American journal of cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30827489
ABSTRACT
Isolated low high-density lipoprotein cholesterol (HDL-C) is associated with lower fitness and increased mortality. Whether the association between isolated low HDL-C and mortality differs by fitness is uncertain. Patients in the Henry Ford ExercIse Testing Project (FIT Project) completed a physician-referred treadmill stress test and those prescribed lipid-lowering medications or with known cardiovascular disease were excluded. Isolated low HDL-C was defined as HDL-C <40 mg/dl for men and <50 mg/dl for women with low-density lipoprotein cholesterol (LDL-C) and triglycerides <100 mg/dl (n=688). An optimal lipid panel was defined as HDL-C >/=40 mg/dl for men and >/=50 mg/dl for women with LDL-C and triglycerides <100 mg/dl (n=2,923). Mortality was ascertained through Social Security Death Index linkage. Patients with isolated low HDL-C had a mean age of 48.9 +/- 12.9 years and 62.9% were women. Over a mean follow-up of 10.3 +/- 5 years, 12.8% of patients with isolated low HDL-C and 8.7% with optimal lipids died. Compared to individuals with optimal lipids, those with isolated low HDL-C who achieved <6 METs had a lower survival (p=0.02), whereas there was no mortality difference for those who achieved 6 to 10 METs (p=0.13) or >/=10 METs (p=0.66). In adjusted Cox models, the mortality hazard for those with isolated low HDL-C compared with optimal lipids was 1.73 (95% confidence interval [CI] 1.18 to 2.54), 1.90 (95% CI 1.19 to 3.04), and 0.97 (95% CI 0.53 to 1.78) for the METS categories of <6, 6 to 10, and >/=10. In conclusion, individuals with isolated low HDL-C fitness significantly improved risk stratification and only those with lower fitness had an increased totality mortality risk.

[2] *Schade DS, Shey L, Eaton RP*. **Prescribing Statins to Reduce Cardiovascular Disease - Ten Common Misconceptions**. The American journal of medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30851261
ABSTRACT

[3] *Ferrari F, Stein R, Motta MT, Moriguchi EH*. **PCSK9 Inhibitors: Clinical Relevance, Molecular Mechanisms, and Safety in Clinical Practice**. Arquivos brasileiros de cardiologia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30843929
ABSTRACT
Coronary artery disease (CAD) is one of the leading causes of mortality. High circulating levels of low-density lipoprotein (LDL) in the blood are associated with cardiovascular mortality, whether through an etiological role or through its association with the progression of CAD per se. Randomized clinical trials have shown that, when LDL levels are reduced, cardiovascular risk is also reduced, which reinforces this association. The first major trial involving a hypolipidemic agent of the statin family, the Scandinavian Simvastatin Survival Study (4S), was published in 1994 and found a significant reduction in mortality in patients at high cardiovascular risk. However, even in subsequent studies with different statins, a residual risk persisted, and this seems not to have changed over time; it is speculated that this risk may be due to statin intolerance. In this scenario, the potential exists for novel hypolipidemic agents to drive a true

revolution in the therapy of dyslipidemia. The recent discovery of PCSK9 inhibitors (PCSK9i), a class of hypolipidemic monoclonal antibodies, is extremely promising. PCSK9 inhibition is capable of promoting a mean LDL reduction of up to 60%, with potential for very significant clinical repercussions, as every 38 mg/dL reduction in LDL appears to be associated with a 22% reduction in cardiovascular risk. This review addresses a brief history of PCSK9i, major trials of these drugs, cardiovascular outcomes, and aspects related to their efficacy and safety. Finally, the molecular mechanisms and possible pleiotropic effects of PCSK9i are also discussed.

[4] *Gencer B, Pagano S, Vuilleumier N et al.* **Clinical, behavioral and biomarker predictors of PCSK9 levels in HIV-infected patients naive of statin therapy: A cross-sectional analysis from the Swiss HIV cohort**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30827714
ABSTRACT
BACKGROUND AND AIMS: Better characterization of Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) profile is currently needed to tailor appropriate lipid-lowering strategies in HIV patients. METHODS: HIV-infected individuals aged>/=40 years and naive of statin therapy included in the Swiss HIV cohort study were screened for PCSK9 levels with a routine blood sample collection in 2014at the Geneva University Hospitals. An exploratory linear regression model was built including clinical (age, sex, ethnicity, cardiovascular risk factors, body mass index, low CD4 defined as </=200cells/mul, leucocytes, lymphocytes, platelet, antiretroviral therapy), behavioral (tobacco and marijuana smoking, alcohol use and physical activity) and biomarker (CRP, TNF-alpha, IL-8, Il-10 and MCP-1) to investigate association with continuous PCSK9 levels. RESULTS: We studied 239 HIV-infected individuals who met inclusion criteria and available PCSK9 levels with a mean age of 49 years. 35 subjects (14.6%) reported marijuana consumption, of whom 20 (57.1%) reported daily consumption and 15 (6.3%) occasional use. PCSK9 levels were correlated with low-density lipoprotein-cholesterol (LDL-C). Our exploratory model identified marijuana consumption (p=0.023) and low CD4 values (p=0.020) as significantly associated factors with higher PCSK9 levels. No association was found with Framingham risk score. Patients with marijuana consumption had significantly higher levels of PCSK9 with a dose-response effect ($p < 0.001$); the association persisted after adjustment for the calculated Framingham risk score (p=0.003) and additional adjustment for clinical variables (p=0.027). CONCLUSIONS: In HIV-infected individuals naive of statin treatment, marijuana consumption and low CD4 values are associated with higher PCSK9 levels independently of clinically relevant confounding factors.

[5] *Perez-Calahorra S, Laclaustra M, Marco-Benedi V et al.* **Effect of lipid-lowering treatment in cardiovascular disease prevalence in familial hypercholesterolemia**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30827715
ABSTRACT
BACKGROUND AND AIMS: The impact on heterozygous familial hypercholesterolemia (HeFH) health led by high-intensity lipid-lowering therapy (HILLT) is unknown, and the question remains if there is still an unacceptably high residual risk to justify treatment with new lipid-lowering drugs. METHODS: This observational, retrospective, multicenter, national study in Spain, whose information was obtained from a national dyslipemia registry, was designed to

establish the current prevalence of cardiovascular disease (CVD) in HeFH and to define the impact of HILLT on CVD in this population. Odds were estimated using several logistic regression models with progressive adjustment. RESULTS: 1958 HeFH, mean age 49.3+/-14.3 years, were included in the analysis. At inclusion in the registry, 295 patients (15.1%) had suffered CVD and 164 (55.6%) had suffered the first event before the onset lipid-lowering treatment. Exposition to treatment associated more than ten times lower odds for CVD than in subjects naive to treatment (OR 0.085, 95% CI 0.063-0.114, p<0.001). A first CVD event after a mean treatment period of 9.1+/-7.2 years occurred in 131 out of 1615 (8.1%) HeFH subjects, and 115 (87.8%) of them were on HILLT. CONCLUSIONS: Current prevalence of CVD among HeFH is one third of that reported before the statins era. Early initiation and prolonged lipid-lowering treatment was associated with a reduction in CVD. New cases of CVD, in spite of HILLT, appeared mostly among patients accumulating risk factors and probably they may be considered for further lipid-lowering drugs.

[6] *Aguiar C, MacLeod J, Yip A et al.* **Impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS study): rationale and design of an investigator-initiated prospective study**. BMJ open 2019; 9:e023418.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30833313
ABSTRACT
INTRODUCTION: Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-related complications including cardiovascular risk factors such as diabetes, hypertension and dyslipidaemia. Healthcare providers believe that overweight and obese cardiac surgery patients are more likely to experience adverse postoperative outcomes. The body mass index (BMI) is the primary measure of obesity in clinical practice, without accounting for a patient's level of cardiopulmonary fitness or muscle mass. The objective of this study is to determine whether fitness capacity of obese cardiac surgical patients and biomarkers, alone or in combination, will help identify patients at risk for adverse outcomes when undergoing cardiac surgery. METHODS AND ANALYSIS: Patients between the ages of 18 and 75 years undergoing elective cardiac surgery are consented to participate in this prospective observational study. Patients will be invited to participate in measures of obesity, functional capacity and exercise capacity assessments, quality of life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated are measures other than BMI that could be predictive of short-term and long-term postoperative outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids, amino acids) and inflammation (adipokines, cytokines and chemokines). ETHICS AND DISSEMINATION: This study has been approved by the institutional review board at the Horizon Health Network. On completion of the study, the results shall be disseminated through conference presentations and publications in peer-reviewed journals. Additionally, the report shall also be diffused more broadly to the general public and the cardiovascular community. TRIAL REGISTRATION NUMBER: NCT03248921.

[7] *Mubanga M, Byberg L, Egenvall A et al.* **Dog ownership and cardiovascular risk factors: a nationwide prospective register-based cohort study**. BMJ open 2019; 9:e023447.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30850401

ABSTRACT

OBJECTIVE: To study the association between dog ownership and cardiovascular risk factors. DESIGN: A nationwide register-based cohort study and a cross-sectional study in a subset. SETTING: A cohort of 2 026 865 participants was identified from the Register of the Total Population and linked to national registers for information on dog ownership, prescribed medication, hospital admissions, education level, income and country of birth. Participants were followed from 1 October, 2006, to the end of the study on 31 December, 2012, assessing medication for a cardiovascular risk factor, emigration and death. Cross-sectional associations were further assessed in 10 110 individuals from the TwinGene study with additional adjustment for professional level, employment status, Charlson comorbidity index, disability and tobacco use. PARTICIPANTS: All Swedish residents aged 45-80 years on 1 October, 2006. MAIN OUTCOME MEASURES: Initiation of medication for hypertension, dyslipidaemia and diabetes mellitus. RESULTS: After adjustment for confounders, the results indicated slightly higher likelihood of initiating antihypertensive (HR, 1.02; 95% CI, 1.01 to 1.03) and lipid-lowering treatment (HR, 1.02; 95% CI, 1.01 to 1.04) in dog owners than in non-owners, particularly among those aged 45-60 years and in those owning mixed breed or companion/toy breed dogs. No association of dog ownership with initiation of treatment for diabetes was found in the overall analysis (HR, 0.98; 95% CI, 0.95 to 1.01). Sensitivity analyses in the TwinGene cohort indicated confounding of the association between dog ownership and prevalent treatment for hypertension, dyslipidaemia and diabetes mellitus, respectively, from factors not available in the national cohort, such as employment status and non cardiovascularchronic disease status. CONCLUSIONS: In this large cohort study, dog ownership was associated with a minimally higher risk of initiation of treatment for hypertension and dyslipidaemia implying that the previously reported lower risk of cardiovascular mortality among dog owners in this cohort is not explained by reduced hypertension and dyslipidaemia. These observations may suffer from residual confounding despite access to multiple important covariates, and future studies may add valuable information.

[8] *Wei W, Peng J, Shen T*. **Rosuvastatin Alleviates Ischemia/Reperfusion Injury in Cardiomyocytes by Downregulating Hsa-miR-24-3p to Target Upregulated Uncoupling Protein 2**. Cellular reprogramming 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30835496

ABSTRACT

Statins could reduce the risks of coronary heart disease death and ischemic cardiovascular events. In this study, we aim to explore the role of rosuvastatin in ischemia/reperfusion (I/R)-injured cardiomyocytes and the possible mechanism. An I/R model was established by oxygen-glucose deprivation/reperfusion (OGD/R). The protective effects of rosuvastatin pretreatment on OGD/R-injured cardiomyocytes were performed using MTT assay, lactate dehydrogenase (LDH) release assay, and quantitative real-time polymerase chain reaction (qRT-PCR). Bioinformatics software TargetScan and miRTarBase were used to predict the targeted miRNAs with uncoupling protein (UCP)2. Furthermore, verify the binding capacity of hsa-miR-24-3p and UCP2 with qRT-PCR and dual-luciferase reporter assay. The expression of UCP2, cell viability, LDH level, and apoptosis level affected by downregulated hsa-miR-24-3p were assessed using

qRT-PCR, western blotting, MTT, the LDH kit, and flow cytometry. Pretreatment with rosuvastatin could significantly augment cell viability, reduce LDH level, increase the expression of UCP2, and downregulate hsa-miR-24-3p in OGD/R-injured H9c2 cells. miR-24-3p was closely connected with UCP2, and downregulated miR-24-3p could promote UCP2 expression, which presented cell viability increasing, LDH release and cell apoptosis inhibition in OGD/R condition. Moreover, it decreased the protein expression of Cleaved-Caspase-9 and Cyto C. This is the first time our study suggests that rosuvastatin pretreatment protects cardiomyocytes from OGD/R through upregulating UCP2 through downregulation of hsa-miR-24-3p.

[9] *Gao J, Wang YY, Liu Y*. **Application of virtual histological intravascular ultrasound in plaque composition assessment of saphenous vein graft diseases**. Chinese medical journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30839353

ABSTRACT

OBJECTIVE: Saphenous vein grafts disease (SVGD) is a common complication after coronary artery bypass graft (CABG) and normally treated by percutaneous coronary intervention (PCI).The most common complication after SVG-PCI is slow or no-reflow. It is known that the no-reflow phenomenon occurs in up to 15% of the SVG-PCI and is associated with high risk of major adverse cardiac events (MACEs) and mortality, therefore it is important to investigate the factors that could predict the clinical outcome of PCI for risk stratification and guiding interventions. In recent years, the spectral analysis of IVUS radiofrequency data [Virtual histology-IVUS (VH-IVUS)] has been used to provide quantitative assessment on both plaque compositions and morphologic characteristics. DATA SOURCES: The PubMed, Embase, and Central databases were searched for possible relevant studies published from 1997 to 2018 using the following index key words: 'Coronary artery bypass grafting'; 'Saphenous venous graft disease'; 'Virtual histology-intravascular ultrasound'; 'Virtual histology-intravascular ultrasound' and ' Percutaneous coronary intervention' STUDY SELECTION:: The primary references were Chinese and English articles including original studies and literature reviews, were identified and reviewed to summarize the advances in the application of VH-IVUS techniques in situ vascular and venous graft vascular lesions. RESULTS: With different plaque components exhibiting a defined spectrum, VH-IVUS can classify atherosclerotic plaque into four types: fibrous tissue (FT), fibro fatty (FF), necrotic core (NC), and dense calcium (DC). The radiofrequency signal is mathematically transformed into a color-coded representation, including lipid, fibrous tissue, calcification, and necrotic core. Several studies have demonstrated the independent relationship between VH-IVUS-defined plaque classification or plaque composition and MACEs, but a significant association between plaque components and no-reflow after PCI in acute coronary syndrome. In recent years, VH-IVUS are applied to assess the plaque composition of SVGD, based on the similarity of pathophysiological mechanisms between coronary artery disease (CAD) and SVGD, further studies with the larger sample size, the long-term follow-up, multicenter clinical trials may be warranted to investigate the relationship between plaque composition of saphenous vein graft (SVG) by VH-IVUS and clinical outcomes in patients with SVGD undergoing PCI. CONCLUSIONS: In degenerative SVG lesions, VH-IVUS found that plaque composition was associated with clinical features, future studies need to explore the relationship between VH-IVUS defined atherosclerotic plaque components and clinical outcomes in SVGD patients undergoing PCI, an innovative prediction tool of clinical

[10] *Pradhan AD*. **A New Beginning for Triglyceride Lowering Therapies**. Circulation 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30836784

ABSTRACT

The cardiovascular community has been debating for decades whether to treat mild-tomoderate hypertriglyceridemia. Results of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)(1) position this controversy as front matter for deliberation. For lipid experts, dominating the discourse will be the strength of experimental evidence, mechanism of benefit, identification of treatment response parameters, and prioritizing treatment options. For the practitioner, the question ultimately will be whether potential gains are worth the disruption to clinical care that accompanies a new paradigm in prevention.

[11] *Coakley JC*. **Lipids in Children and Links to Adult Vascular Disease**. The Clinical biochemist. Reviews 2018; 39:65-76.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30828113

ABSTRACT

Atherosclerosis often begins in childhood or adolescence. Post-mortem studies in children have shown the presence of coronary atheroma, and there are hereditary conditions associated with hyperlipidaemia in childhood which lead to premature cardiovascular disease. Detection of hyperlipidaemia early in life can be crucial in the prevention of premature death from atherosclerosis. The circulating lipoproteins are in a constant state of flux, with passage of apolipoproteins and lipids between the various particles. Genetic variants of apolipoproteins can cause both hypercholesterolaemia and hypertriglyceridaemia. Elevated concentrations of lipoprotein(a) predispose to coronary artery disease. Another important molecule in lipid metabolism, proprotein convertase subtilisin/kexin type 9 (PCSK9), plays a crucial role in the removal of low-density lipoprotein (LDL) receptors. Reference intervals for the various lipid subfractions are now available for children, and there are guidelines regarding when to take action regarding paediatric hyperlipidaemia. The most important genetic condition in children which may lead to premature death from coronary heart disease is familial hypercholesterolaemia (FH). FH is best diagnosed and treated early in life. Most cases are due to defects in the LDL receptor. Pharmacotherapy for FH usually involves the statin group of drugs, although newer medications are now available, especially for the treatment of homozygous FH. Statin therapy has been demonstrated to be successful in preventing cardiac events in FH. Secondary dyslipidaemia in childhood can be associated with numerous diseases including diabetes, lifestyle disorders such as obesity, and drugs. Treatment of the underlying condition usually resolves the hyperlipidaemia.

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[12] *Fujii H, Kono K, Nishi S*. **Characteristics of coronary artery disease in chronic kidney disease**. Clinical and experimental nephrology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30830548
ABSTRACT
Patients with chronic kidney disease (CKD) commonly experience cardiovascular disease (CVD), and a major cause of death in these patients is CVD. Therefore, the prevention of CVD progression is very crucial in patients with CKD. Recently, this relationship between CKD and CVD has increasingly been examined, and a concept termed "cardiorenal syndrome" has been advocated. Coronary artery disease (CAD) and myocardial injury are crucial factors that contribute to the occurrence of CVD. The initial step CAD is endothelial dysfunction that can be detected as a decrease in the coronary flow reserve (CFR). The previous studies have reported that decreased CFR is significantly correlated to coronary events and mortality. Furthermore, CFR reduces with a decline in the kidney function. Another important presentation of CAD is coronary artery calcification. Vascular calcification is a crucial pathophysiological state, particularly in patients with CKD, and it affects the stability of coronary atherosclerotic plaque. In CKD, not only the traditional risk factors but also CKD-related non-traditional risk factors play key roles in CVD progression. Therefore, the mechanisms responsible for CVD progression are very complex; however, their clarification is crucial to improve the prognosis in patients with CKD.

[13] *Julius U, Tselmin S, Schatz U et al.* **Lipoprotein(a)-an interdisciplinary challenge**. Clinical research in cardiology supplements 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30838556
ABSTRACT
Lipoprotein(a) (Lp(a)) is an internationally recognized atherogenic risk factor which is inherited and not changed by nutrition or physical activity. At present, only proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may modestly decrease its concentration (but not in all patients)-leading to a certain decrease in cardiovascular events (CVE) in controlled studies. However, at present an elevation of Lp(a) is not a generally accepted indication for their use. More effective is lipoprotein apheresis (LA) therapy with respect to both lowering Lp(a) levels and reduction of CVE. In the future, an antisense oligonucleotide against apolipoprotein(a) will probably be available. Atherosclerosis in patients with an elevation of Lp(a) may affect several vessel regions (carotids, aorta, coronaries, leg arteries). Thus, Lp(a) should be measured in high-risk patients. These patients are usually cared for by their family doctors and by other specialists who should closely cooperate. Lipidologists should decide whether costly therapies like PCSK9 inhibitors or LA should be started. The main aim of current therapy is to optimize all other risk factors (LDL cholesterol, hypertension, diabetes mellitus, body weight, renal insufficiency). Patients should be regularly monitored (lab data, heart, arteries). This paper describes the duties of physicians of different specialties when caring for patients with high Lp(a) concentrations.

[14] *Julius U, Tselmin S, Schatz U et al.* **Lipoprotein(a) and proprotein convertase subtilisin/kexin type 9 inhibitors**. Clinical research in cardiology supplements 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30838555

ABSTRACT
Lipoprotein(a) (Lp(a)) is an internationally accepted independent atherogenic risk factor. Details about its synthesis, many aspects of composition and clearance from the bloodstream are still unknown. LDL receptor (LDLR) (and probably other receptors) play a role in the elimination of Lp(a) particles. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors increase the number of available LDLRs and in this way very effectively reduce the LDL cholesterol (LDL-C) concentrations. As shown in controlled studies using PCSK9 inhibitors, Lp(a) levels are decreased by 20 to 30%, though in some patients no effect was observed. So far, it has not been clarified whether this decrease is associated with an effect on the incidence of cardiovascular events (CVEs). In two recently published well-performed secondary prevention studies (FOURIER with evolocumab, ODYSSEY OUTCOMES with alirocumab) baseline Lp(a) levels were shown to have an impact on CVEs independently of baseline LDL-C concentrations. The rather modest PCSK9 inhibitor-induced decrease of Lp(a) was associated with a reduction of CVEs in both studies, even after adjusting (ODYSSEY OUTCOMES) for demographic variables (age, sex, race, region), baseline Lp(a), baseline LDL-C, change in LDL-C, and clinical variables (time from acute coronary syndrome, body mass index, diabetes, smoking history). The largest decrease of CVEs was seen in patients with relatively low concentrations of both LDL-C and Lp(a) (FOURIER). These findings will probably have an influence on the use of PCSK9 inhibitors in patients with high Lp(a) concentrations.

[15] *Reiner Z*. **Can Lp(a) Lowering Against Background Statin Therapy Really Reduce Cardiovascular Risk?** Current atherosclerosis reports 2019; 21:14.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30847681

ABSTRACT
PURPOSE OF REVIEW: The association between elevated plasma levels of lipoprotein (a) [Lp(a)] and atherosclerotic cardiovascular disease (ASCVD) has been discussed for many years. Recent genetic findings have confirmed that elevated Lp(a) similar to elevated LDL-cholesterol (LDL-C) might be causally related to premature ASCVD. Lp(a) is relatively refractory to lifestyle interventions. The results of studies with statins and their possible effect on Lp(a) are conflicting. Specific Lp(a) apheresis is used as a treatment against background statin therapy and can decrease Lp(a). The purpose of this review is to discuss whether new drugs which decrease Lp(a) can prevent ASCVD and decrease ASCVD mortality when applied in addition to statins. RECENT FINDINGS: Some new LDL-C-lowering drugs such as mipomersen and lomitapide decrease elevated Lp(a) in addition to statins but they have some unpleasant adverse effects. Recently, an antisense oligonucleotide against apo(a), AKCEA-APO(a)Rx, has been shown to selectively decrease Lp(a). The most recent advance in LDL-C lowering are PCSK9 inhibitors. Alirocumab and evolocumab do not only significantly reduce LDL-C on top of maximally tolerated statin therapy and prevent ASCVD events, but also further decrease Lp(a). There is no data to indicate whether mipomersen, lomitapide, or IONIS-APO(a)-LRx decrease ASCVD events and mortality. Conclusive evidence is still lacking as to whether the treatment with PCSK9 inhibitors against background statin therapy actually additionally reduces ASCVD risk due to the lowering of Lp(a) or simply due to lowering LDL-C to levels much lower than high-intensity statin treatment as monotherapy. Ongoing trials will probably provide an answer to these questions.

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[16] *Nicholls SJ*. **The New Face of Hyperlipidemia and the Role of PCSK9 Inhibitors**. Current cardiology reports 2019; 21:18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30828741
ABSTRACT
PURPOSE OF REVIEW: To review the clinical rationale for use of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors in clinical practice. RECENT FINDINGS: Despite widespread use of statins for lipid lowering, many patients at high cardiovascular risk continue to demonstrate unsatisfactory cholesterol levels and experience clinical events. This highlights the ongoing need to develop additional strategies to achieve more effective risk reduction in a greater number of patients. Proprotein convertase subtilisin kexin type 9 (PCSK9) plays an important role in the regulation of low-density lipoprotein metabolism. Inhibitory approaches that reduce PCSK9 activity have been demonstrated to produce substantive reductions in LDL cholesterol levels, when administered as either monotherapy or in addition to statin therapy. More recently, PCSK9 monoclonal antibodies have been reported to reduce cardiovascular event rates in large scale clinical trials. Increasing evidence suggests that PCSK9 inhibitors can produce effective lipid lowering in high risk patients. Ongoing work will identify those patients most likely to derive cost effective risk reduction with their use.

[17] *Yang Y, Yang S, Jiao X et al.* **ANGPTL3 Mutations in Unrelated Chinese Han Patients with Familial Hypercholesterolemia**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30827231
ABSTRACT
OBJECTIVE: Familial hypercholesterolemia (FH) is a severe genetic hyperlipidemia characterized by increased levels of low-density lipoprotein cholesterol (LDL-C), leading to premature atherosclerosis. Angiopoietin like protein (ANGPTL3) is a hepatocytespecific protein that can be used to lower LDL in FH. However, it was unknown whether ANGPTL3 variants are present in FH patients. This study was performed to identify ANGPTL3 variants in unrelated Chinese Han patients with FH. METHODS AND RESULTS: We screened 80 patients with FH (total cholesterol >7.8mmol/L, LDL-cholesterol >4.9mmol/L) and 77 controls using targeted next-generation sequencing (NGS) of six FH candidate genes (LDLR, ApoB100, PCSK9, ABCG5, ABCG8, and ANGPTL3). Candidate pathogenic variants identified by NGS were validated by Sanger sequencing. Mutant and wild-type plasmids containing the variant sequence were constructed and verified by Sanger sequencing. The gene expression profile was analyzed by an expression profile chip in transfected HepG2 cells using quantitative real-time (qRT)-PCR. We identified 41 variants in 28 FH patients, including two ANGPTL3 mutations: one exonic (c.A956G: p.K319R) and one in the untranslated region (c.*249G>A). Gene ontology analyses found that the cholesterol metabolic process and ANGPTL3 expression were significantly up-regulated in the ANGPTL3 K319R mutation group compared with the wild-type group. qRT-PCR findings were consistent with expression profile analysis. CONCLUSIONS: Rare ANGPTL3 variants were identified in Chinese patients with FH, including ANGPTL3: p.(Lys319Arg) which affected the expression of ANGPTL3 and the cholesterol metabolic process as determined by bioinformatics analysis.

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[18] *Chen Y, Yuan Z, Lu J et al.* **Randomised study of Evolocumab in Patients With Type 2 Diabetes and Dyslipidaemia on Background Statin: Pre-Specified Analysis of the China Population From the BERSON Clinical Trial**. Diabetes Obes Metab 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30851062

ABSTRACT
AIM: To evaluate the efficacy and safety of evolocumab with background atorvastatin in Chinese patients with type 2 diabetes mellitus (T2DM) and hyperlipidaemia or mixed dyslipidaemia. MATERIALS AND METHODS: This is a pre-specified analysis of patients in the BERSON study (ClinicalTrials.gov, NCT02662569) in China. Patients were started on background atorvastatin 20 mg/day and then were randomised 2:2:1:1 to evolocumab 140 mg every 2 weeks (Q2W) or 420 monthly (QM) or placebo Q2W or QM. Co-primary endpoints were the percentage change in LDL cholesterol (LDL-C) from baseline to week 12 and from baseline to the mean of weeks 10 and 12. Additional endpoints included atherogenic lipids, glycaemic measures, and adverse events (AEs). RESULTS: Of 453 patients randomised in China, 451 received at least one dose of study drug (evolocumab or placebo). Evolocumab significantly reduced LDL-C compared with placebo at week 12 (Q2W, -85.0%; QM, -74.8%) and at the mean of weeks 10 and 12 (Q2W, -80.4%; QM, -81.0%; adjusted P<0.0001 for all), when administered with background atorvastatin. Non-HDL-C, ApoB100, total cholesterol, Lp(a), triglycerides, HDL-C, and VLDL-C significantly improved with evolocumab versus placebo. No new safety findings were observed with evolocumab. The incidence of diabetes AEs was higher with evolocumab compared with placebo. There were no differences over time between evolocumab and placebo in measures of glycaemic control. CONCLUSIONS: In patients in China with T2DM and hyperlipidaemia or mixed dyslipidaemia receiving background atorvastatin, evolocumab significantly reduced LDL-C and other atherogenic lipids, was well tolerated, and had no notable impact on glycaemic measures.

[19] *Sanin V, Koenig W*. **[Therapy of Hypercholesterolemia in Primary Prevention]**. Deutsche medizinische Wochenschrift (1946) 2019; 144:322-328.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30836403

ABSTRACT
Atherosclerotic cardiovascular disease is the leading cause of premature mortality and morbidity worldwide. Dyslipidemia is a commonly encountered clinical condition and is an important determinant of cardiovascular disease. The causality of plasma low-density lipoprotein-cholesterol (LDL-C) in the pathophysiology of cardiovascular disease has been established beyond any reasonable doubt. In this context, individual risk estimation, the determination of target values and lipid-lowering strategies represent an essential part and a challenge in the daily clinical practice to prevent cardiovascular events. Statins are recommended as first-line therapy for patients with hypercholesterolemia in secondary prevention. Controversies remain in the context of primary prevention, however, as to which kind of subjects to treat, the magnitude of the benefit, and potential harm. This article gives a brief overview of the current evidence, guideline recommendations and strategies for lowering of LDL-C in the primary prevention of cardiovascular disease.

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[20] *Tardif JC, Rheaume E, Rhainds D, Dube MP*. **Lipoprotein (a), arterial inflammation, and PCSK9 inhibition**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30838412
ABSTRACT

[21] *Van Rompay MI, Solomon KR, Nickel JC et al.* **Prostate cancer incidence and mortality among men using statins and non-statin lipid-lowering medications**. European journal of cancer (Oxford, England : 1990) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30850323
ABSTRACT
BACKGROUND: Statins have demonstrated protection against aggressive/late-stage and/or lethal prostate cancer (PC), but prior studies are limited by small populations, short follow-up and unequal health-care access. Research has not demonstrated that non-statin lipid-lowering medications (NSLLMs) provide a similar benefit, which would support a cholesterol-based mechanism. We sought to rigorously test the hypothesis that cholesterol-lowering drugs affect PC incidence and severity. METHODS: A retrospective cohort study was conducted by abstracting prescription and health service records for 249,986 Saskatchewan men aged >/=40 years between January 1, 1990 and December 31, 2014 and comparing first-time statin and NSLLM users with age-matched non-users and glaucoma medication (GM) users for PC incidence, metastases at diagnosis and PC mortality using Cox proportional hazards regression. RESULTS: In comparing statin users to non-users, a weak association was detected with increased PC incidence (hazard ratio [HR] 1.07, 95% confidence interval [CI]: 1.02-1.12) that disappeared when compared with GM users. Substantial protective associations were observed between statin use and metastatic PC and PC mortality (HRs 0.69, 95% CI: 0.61-0.79 and 0.73, 95% CI: 0.66-0.81, respectively), which were stronger when compared with GM use (HRs 0.52, 95% CI: 0.40-0.68 and 0.51, 95% CI: 0.41-0.63, respectively). Similar associations were found for NSLLM versus GM for metastatic PC (HR 0.57, 95% CI: 0.41-0.79) and PC mortality (HR 0.66, 95% CI: 0.51-0.85). CONCLUSIONS: Our analyses provide one of the more comprehensive findings to date that statins may reduce risk of metastatic PC and PC mortality, and the first to demonstrate that NSLLM have similar effects, supporting a cholesterol-based mechanism.

[22] *Wu SY, Fang SC, Shih HJ et al.* **Mortality associated with statins in men with advanced prostate cancer treated with androgen deprivation therapy**. European journal of cancer (Oxford, England : 1990) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30827745
ABSTRACT
OBJECTIVES: Before launching large clinical trials to confirm the effects of statins in improving outcomes among men with prostate cancer (PC), the most appropriate target patient population and the type of statins need to be clearly identified. PATIENTS AND METHODS: A retrospective cohort study was conducted using the Taiwan Cancer Registry of 2008-2014. This study included 5749 men with locally advanced and metastatic PC who received only androgen deprivation therapy (ADT) in the first year after their cancer diagnosis. Statin users were defined as anyone who was prescribed statins for >28 days. An inverse probability of treatment-weighted Cox model was used to estimate the effects of statin use on all-cause

mortality and PC-specific mortality (PCSM) while treating the statin status as a time-dependent variable. RESULTS: Overall, 2259 patients died, and 1495 of them died of PC during a median follow-up of 3.6 years from 1 year after their diagnosis. Statin use was associated with significant reductions in all-cause mortality (hazard ratio [HR] = 0.78, 95% confidence interval [CI]: 0.70-0.86) and PCSM (HR = 0.76, 95% CI: 0.68-0.86) for metastatic disease and all-cause mortality (HR = 0.66, 95% CI: 0.54-0.81) for locally advanced disease. Patients who received atorvastatin, pravastatin, rosuvastatin or pitavastatin showed a stronger reduction in mortality than those who received other statins. Benefits of statins were consistently observed in men who received post-diagnostic statins, even in those with high comorbidities or an old age. CONCLUSIONS: Our results suggest that only atorvastatin, pravastatin and rosuvastatin were associated with improved survival in advanced PC patients receiving ADT.

[23] *Ruscica M, Watts GF, Sirtori CR*. **PCSK9 monoclonal antibodies and lipoprotein apheresis for lowering lipoprotein(a): making choices in an era of RNA-based therapies**. European journal of preventive cardiology 2019:2047487319833504.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30845833
ABSTRACT

[24] *Bove M, Cicero AFG, Borghi C*. **Emerging drugs for the treatment of hypercholesterolemia**. Expert opinion on emerging drugs 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30841759
ABSTRACT
Introduction Despite the consolidated role of statins and ezetimibe to treat hypercholesterolemia, often the desirable Low-Density-Lipoprotein-cholesterol (LDL-C) values are not achieved, with a consequent increase of the residual cardiovascular (CV) risk. Areas covered In this review, we summarize the main pharmacological characteristics of new lipid-lowering drugs, such as Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors, Cholesteryl-Ester-Transfer Protein inhibitors, Microsomal Triglyceride Transfer Protein inhibitors, ATP citrate lyase inhibitors, Antisense Oligonucleotides, small interfering RNA and Peroxisome Proliferator-Activated Receptors type alpha agonists. The available clinical evidence of efficacy and safety is critically discussed as well as the prospects of application, based on the different mechanisms and targets of action. Expert opinion Some of these emerging agents represent an excellent therapeutic strategy to treat patients with LDL largely out of target, resistant or intolerant to statins, trying to minimize the residual CV risk, modulating different classes of lipoproteins, not just LDL. The main challenge for the large use of emerging drugs is their cost. Thus, the correct identification of the adequate target population for treatment is a priority. This is particularly true for safe, powerful and fully developed drugs as the PCSK9 inhibitors, for which a relatively large use is potentially expected.

[25] *Yang B, Shi MQ, Li ZH et al.* **Effects of n-3 fatty acid supplements on cardiometabolic profiles in hypertensive patients with abdominal obesity in Inner Mongolia: a randomized controlled trial**. Food & function 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30839013
ABSTRACT

Literature update week 10 (2019)

Daily supplementation with n-3 fatty acid (FA) has been believed to be an adjunct or alternative to drug treatments to reduce blood pressure (BP) and triglyceride (TG) levels in western patients with high risk of cardiovascular disease. The BP-lowering effect of n-3 FA supplements among Chinese hypertensive patients has been reported in our previous 12-week, double-blind, randomized controlled trial (RCT), but the benefits on cardiometabolic profiles among obese Chinese populations are not well known. We therefore used the data from the previous RCT to investigate the effects of marine- and plant-derived n-3 FA supplements on cardiometabolic profiles in middle-aged and elderly Chinese hypertensive patients with abdominal obesity. In total, 108 eligible volunteers from Inner Mongolia, China were randomly assigned to three treatments for 12 weeks: fish oil (FO, n = 35, 2 g day-1 eicosapentaenoic acid + docosahexaenoic acid), flaxseed oil (FLO, n = 39, 2.5 g day-1 alpha-linolenic acid), and corn oil served as a control (CO, n = 34). BP, blood lipids, waist circumference (WC) and fasting glucose-insulin were measured at baseline and after 12-week intervention by using standard methods. Clustered cardiometabolic risk was expressed as a continuously distributed z-score calculated by standardizing and then summing WC, insulin, glucose, TG, HDL-cholesterol and BP values. The cardiometabolic risk scores were significantly lower in the FO group than in the CO group after the 12-week intervention (-0.41 +/- 0.92 vs. 0.02 +/- 0.95, p = 0.016), but not in the FLO group (-0.23 +/- 1.02 vs. 0.02 +/- 0.95, p = 0.109). For individual risk factors, compared with CO, FO significantly decreased LDL-cholesterol (-0.25 +/- 0.78 mmol L-1 vs. -0.05 +/- 0.65 mmol L-1, p = 0.010), ApoB (-012 +/- 0.28 mmol L-1 vs. -0.03 +/- 0.23 mmol L-1, p = 0.036), and WC (-1.58 +/- 3.67 cm vs. -0.52 +/- 3.27 cm, p = 0.031), whereas no significant difference was found between FLO and CO groups in LDL-cholesterol (p = 0.081), ApoB (p = 0.102) and WC (p = 0.093). The present findings suggest that marine n-3 FA intervention may improve the cardiometabolic traits in this Chinese hypertensive population comorbid with abdominal obesity.

[26] *Yakimenko capital O C, Maznichenko I*. **EVALUATION OF TREATMENT EFFICACY IN PATIENTS WITH NON-ALCOHOLIC-STEATOHEPATITIS AND HETEROZYGOTIC FAMILIAL HYPERCHOLESTEROLEMIA**. Georgian medical news 2019:67-72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30829592
ABSTRACT
The aim of the study was to increase the efficacy of treatment of patients with HFHC and NASH by developing a personified approach to the therapy with rosuvastatin 20 mg/day and combined hepatoprotector at the inpatient and outpatient stages of treatment. 124 patients with clinical HFHC were examined. The object of the study was 55 patients (age 55.45+/-5.5 years) with a clinical diagnosis of HFHC, NASH. All patients underwent a detailed physical examination, laboratory-instrumental (general clinical, biochemical (hepatic transaminases, lipidogram, ultrasonography of the abdominal organs), molecular genetic examination (polymorphism of the SLCO1B1 gene). Two groups of study were formed, in the first group patients received rosuvastatin 20 mg/day, in the second group - rozuvastatin 20 mg/day and combined hepatoprotector 2 capsules 3 times a day for 90 days. The patients treated with rosuvastatin 20 mg/day and hepatoprotector were revealed a reliable decrease in the level of TC by 46%, which was 5.1+/-0.59 mmol/l ($p<0.005$), the level of LDL significantly decreased by 68.5% - 2.23+/-0.58 mmol/l ($p<0.005$), the level of HDL increased by 73% and amounted to

2.56+/-0.29 mmol/l (p<0.005). On the 90th day of therapy, the activity of hepatic transaminases reached reference values: ALT 32.16+/-7.83 units/l, AST - 30.11+/-6.32 units/l (p<0.005). Based on the complex examination and determination of polymorphism of SLCO1B1, a personified dose of statin was selected.

[27] *Du H, Li X, Su N et al.* **Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: a systematic review and meta-analysis**. Heart 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30842207
ABSTRACT
BACKGROUND: To evaluate the effects of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors on major adverse cardiovascular events (MACE). METHODS: Our systematic review included randomised controlled trials if they studied PCSK9 inhibitors in patients for primary and/or secondary prevention of cardiovascular diseases or with hypercholesterolaemia/hyperlipidaemia. Dichotomous variables from individual studies were pooled by relative risks (RR) and their 95% CIs using the random-effect model. Risk difference (RD) in the 10-year frame was also estimated using the pooled RR and the estimated baseline risk using the control group. Grading of Recommendation Assessment, Development and Evaluation was used to assess the quality of evidence. RESULTS: We included 54 trials with 97 910 patients in the analysis. Compared with controls, PCSK9 inhibitors significantly reduced the risk of MACE by 16% (RR, 0.84; 95% CI 0.79 to 0.89; RD: 47 fewer per 1000 vs 286 as the baseline risk; 95% CI 32 to 59 fewer), non-fatal myocardial infarction (MI) by 17% (RR, 0.83; 95% CI 0.74 to 0.93; RD, 35 fewer per 1000 vs 207 as the baseline; 95% CI 13 to 53 fewer) and any stroke by 25% (RR, 0.75; 95% CI 0.65 to 0.85; RD, 16 fewer per 1000 vs 61 as the baseline; 95% CI 9 to 21 fewer) with moderate quality evidence. No significant differences were found between PCSK9 inhibitors and control groups in all-cause mortality, cardiovascular death, heart failure or unstable angina with low-quality evidence. CONCLUSIONS: This study demonstrated that PCSK9 inhibitors could significantly reduce the risk of MACE, non-fatal MI and stroke. TRIAL REGISTRATION: PROSPERO; CRD42017073904.

[28] *Yokoji-Takeuchi M, Tabeta K, Takahashi N et al.* **Corrigendum to "Indirect regulation of PCSK9 gene in inflammatory response by Porphyromonas gingivalis infection" [Heliyon 5 (1) (January 2019) e01111]**. Heliyon 2019; 5:e01210.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30828655
ABSTRACT
[This corrects the article DOI: 10.1016/j.heliyon.2018.e01111.].

[29] *Herr JE, Hetu MF, Li TY et al.* **Presence of Calcium-Like Tissue Composition in Carotid Plaque is Indicative of Significant Coronary Artery Disease in High-Risk Patients**. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30826224
ABSTRACT
BACKGROUND: Grayscale pixel ranges from ultrasound images, indicating differences in atherosclerotic plaque echogenicity, have been shown to represent different tissue types. Our

objective was to determine whether carotid plaque composition was correlated with severity of coronary artery disease (CAD) and risk of cardiovascular (CV) events. METHODS: A focused carotid ultrasound was performed in 522 participants who had recently undergone coronary angiography. In 468 participants found to have atherosclerotic plaque in at least one carotid artery, plaque composition was assessed for tissue-like types: grayscale ranges 0-4 (blood), 8-26 (fat), 41-76 (muscle), 112-196 (fibrous), and 211-255 (calcium). Logistic regression was used to evaluate correlations with significant CAD (>/=50% stenosis). Cox proportional hazards models were used to determine risk for 5-year CV outcomes. RESULTS: Carotid plaque percent fibrous and percent calcium increased with severity of CAD (P < .02). When adjusted for age, sex, body mass index, estimated glomerular filtration rate, and traditional cardiac risk factors, maximum plaque height and percent calcium remained independent contributors of significant CAD (P < .01). Plaque height (>/=2.74 mm), percent calcium (>/=0.11%), and percent fat (11.6%) were associated with increased risk for CV events. Combined plaque height and percent fat gave the highest risk for events (risk ratio = 2.02; CI, 1.41-2.94, P = .0002). CONCLUSIONS: Carotid plaque fibrous and calcium-like tissues are correlated with increased CAD. Increased percent fat or percent calcium is associated with risk for CV events; however, a combination of plaque height, percent calcium, and/or percent fat increases risk for CV events. Incorporating ultrasound carotid plaque composition into screening practice may improve patient risk stratification for heart disease.

[30] *Song J, Jiang X, Cao Y et al.* **Interaction between an ATP-Binding Cassette A1 (ABCA1) Variant and Egg Consumption for the Risk of Ischemic Stroke and Carotid Atherosclerosis: a Family-Based Study in the Chinese Population**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30828007

ABSTRACT

AIM: ATP-binding cassette A1 (ABCA1) plays an important role in reducing the risk of stroke. Egg is the major source of dietary cholesterol and is known to be associated with the risk of stroke and atherosclerosis. We aimed to assess the effects of interaction between an ABCA1 variant (rs2066715) and egg consumption on the risk of ischemic stroke (IS), carotid plaque, and carotid-intima media thickness (CIMT) in the Chinese population. METHODS: In total, 5869 subjects (including 1213 IS cases) across 1128 families were enrolled and divided into two groups based on the median egg consumption (4 eggs per week). In the analyses for the presence of carotid plaque and CIMT, 3171 out of 4656 IS-free controls without self-reported history of coronary heart disease and lipid-lowering medications were included. Multilevel logistic regression models were used to model the genetic association of rs2066715 with the risk of IS, and mixed-effect linear regression for the genetic association of rs2066715 with carotid plaque, and CIMT. The gene-by-egg cross-product term was included in the regression model for interaction analysis. RESULTS: We found that rs2066715 was associated with the increased risk of carotid plaque among those who consumed 4 eggs per week after adjustment (odds ratio [95% confidence interval]: 1.61 [1.08, 2.39], P =0.019). A significant effect of interaction between rs2066715 and egg consumption on the risk of carotid plaque was identified (P =0.011). CONCLUSION: rs2066715 was found to interact with egg consumption in modifying the risk of carotid plaque in the Chinese population.

Literature update week 10 (2019)

[31] *Crombag G, Schreuder F, van Hoof RHM et al.* **Microvasculature and intraplaque hemorrhage in atherosclerotic carotid lesions: a cardiovascular magnetic resonance imaging study**. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2019; 21:15.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30832656
ABSTRACT
BACKGROUND: The presence of intraplaque haemorrhage (IPH) has been related to plaque rupture, is associated with plaque progression, and predicts cerebrovascular events. However, the mechanisms leading to IPH are not fully understood. The dominant view is that IPH is caused by leakage of erythrocytes from immature microvessels. The aim of the present study was to investigate whether there is an association between atherosclerotic plaque microvasculature and presence of IPH in a relatively large prospective cohort study of patients with symptomatic carotid plaque. METHODS: One hundred and thirty-two symptomatic patients with >/=2 mm carotid plaque underwent cardiovascular magnetic resonance (CMR) of the symptomatic carotid plaque for detection of IPH and dynamic contrast-enhanced (DCE)-CMR for assessment of plaque microvasculature. K(trans), an indicator of microvascular flow, density and leakiness, was estimated using pharmacokinetic modelling in the vessel wall and adventitia. Statistical analysis was performed using an independent samples T-test and binary logistic regression, correcting for clinical risk factors. RESULTS: A decreased vessel wall K(trans) was found for IPH positive patients (0.051 +/- 0.011 min(- 1) versus 0.058 +/- 0.017 min(- 1), p = 0.001). No significant difference in adventitial K(trans) was found in patients with and without IPH (0.057 +/- 0.012 min(- 1) and 0.057 +/- 0.018 min(- 1), respectively). Histological analysis in a subgroup of patients that underwent carotid endarterectomy demonstrated no significant difference in relative microvessel density between plaques without IPH (n = 8) and plaques with IPH (n = 15) (0.000333 +/- 0.0000707 vs. and 0.000289 +/- 0.0000439, p = 0.585). CONCLUSIONS: A reduced vessel wall K(trans) is found in the presence of IPH. Thus, we did not find a positive association between plaque microvasculature and IPH several weeks after a cerebrovascular event. Not only leaky plaque microvessels, but additional factors may contribute to IPH development. TRIAL REGISTRATION: NCT01208025 . Registration date September 23, 2010. Retrospectively registered (first inclusion September 21, 2010). NCT01709045 , date of registration October 17, 2012. Retrospectively registered (first inclusion August 23, 2011).

[32] *Hurley JC*. **The Role of Endotoxin in Septic Shock**. Jama 2019; 321:902-903.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30835303
ABSTRACT

[33] *Mani P, Puri R, Schwartz GG et al.* **Association of Initial and Serial C-Reactive Protein Levels With Adverse Cardiovascular Events and Death After Acute Coronary Syndrome: A Secondary Analysis of the VISTA-16 Trial**. JAMA cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30840024
ABSTRACT
Importance: Higher baseline high-sensitivity C-reactive protein (hsCRP) levels after an acute coronary syndrome (ACS) are associated with adverse cardiovascular outcomes. The usefulness

of serial hsCRP measurements for risk stratifying patients after ACS is not well characterized. Objective: To assess whether longitudinal increases in hsCRP measurements during the 16 weeks after ACS are independently associated with a greater risk of a major adverse cardiac event (MACE), all-cause death, and cardiovascular death. Design, Setting, and Participants: Secondary analysis of the double-blind, multicenter, randomized clinical Vascular Inflammation Suppression to Treat Acute Coronary Syndromes for 16 Weeks (VISTA-16) trial conducted between June 1, 2010, and March 7, 2012 (study termination on March 9, 2012), which included 5145 patients from 362 academic and community hospitals in Europe, Australia, New Zealand, India, and North America assigned to receive varespladib or placebo on a background of atorvastatin treatment beginning within 96 hours of presentation with an ACS. The present study evaluated data from patients with available baseline and longitudinal hsCRP levels measured at weeks 1, 2, 4, 8, and 16 after randomization to treatment or placebo. Statistical analysis was performed from June 15, 2018, through September 15, 2018. Main Outcomes and Measures: Outcomes were MACE (composite of cardiovascular death, myocardial infarction, nonfatal stroke, or unstable angina with documented ischemia requiring hospitalization), cardiovascular death, and all-cause death after adjustment for baseline clinical, treatment, and laboratory characteristics, including baseline hsCRP levels. Results: Among 4257 patients in this study, 3141 (73.8%) were men and the mean age was 60.3 years (interquartile range [IQR], 53.5-67.8 years). The median 16-week low-density lipoprotein cholesterol level was 64.9 mg/dL (IQR, 50.3-82.3 mg/dL), and the median hsCRP level was 2.4 mg/L (IQR, 1.1-5.2 mg/L). On multivariable analysis, higher baseline hsCRP level (hazard ratio [HR], 1.36 [95% CI, 1.13-1.63]; P = .001) and higher longitudinal hsCRP level (HR, 1.15 [95% CI, 1.09-1.21]; P < .001) were independently associated with MACE. Similar significant and independent associations were shown between baseline and longitudinal hsCRP levels and cardiovascular death (baseline: HR, 1.61 per SD [95% CI, 1.07-2.41], P = .02; longitudinal: HR, 1.26 per SD [95% CI, 1.19-1.34], P < .001) and between baseline and longitudinal hsCRP levels and all-cause death (baseline: HR, 1.58 per SD [95% CI, 1.07-2.35], P = .02; longitudinal: HR, 1.25 per SD [95% CI, 1.18-1.32], P < .001). Conclusions and Relevance: Initial and subsequent increases in hsCRP levels during 16 weeks after ACS were associated with a greater risk of the combined MACE end point, cardiovascular death, and all-cause death despite established background therapies. Serial measurements of hsCRP during clinical follow-up after ACS may help to identify patients at higher risk for mortality and morbidity.

[34] *Jun BG, Cheon GJ*. **The utility of ezetimibe therapy in nonalcoholic fatty liver disease**. The Korean journal of internal medicine 2019; 34:284-285.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30840809
ABSTRACT

[35] **Comparison table: Some lipid-lowering drugs**. The Medical letter on drugs and therapeutics 2019; 61:e24-e30.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30845107
ABSTRACT

[36] **Lipid-lowering drugs**. The Medical letter on drugs and therapeutics 2019; 61:17-24.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30845106
ABSTRACT

[37] *Huang M, Zhao Z, Cao Q et al.* **PAQR3 modulates blood cholesterol level by facilitating interaction between LDLR and PCSK9**. Metabolism 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30831144
ABSTRACT
OBJECTIVE: Low-density lipoprotein cholesterol (LDL-C) is the hallmark of atherosclerotic cardiovascular diseases. The hepatic LDL receptor (LDLR) plays an important role in clearance of circulating LDL-C. PCSK9 facilitates degradation of LDLR in the lysosome and antagonizing PCSK9 has been successfully used in the clinic to reduce blood LDL-C level. Here we identify a new player that modulates LDLR interaction with PCSK9, thus controlling LDLR degradation and cholesterol homeostasis. METHODS: The blood LDL-C and cholesterol levels were analyzed in mice with hepatic deletion of Paqr3 gene. The half-life of LDLR was analyzed in HepG2 cells. The interaction of PAQR3 with LDLR and PCSK9 was analyzed by co-immunoprecipitation and immunofluorescent staining. RESULTS: The blood LDL-C and total cholesterol levels in the mice with hepatic deletion of Paqr3 gene were significantly lower than the control mice after feeding with high-fat diet ($p < 0.001$ and $p < 0.05$ respectively). The steady-state level of LDLR protein is elevated by Paqr3 knockdown/deletion and reduced by PAQR3 overexpression. The half-life of LDLR protein is increased by Paqr3 knockdown and accelerated by PAQR3 overexpression. PAQR3 interacts with the beta-sheet domain of LDLR and the P-domain of PCSK9 respectively. In addition, PAQR3 can be localized in early endosomes and colocalized with LDLR, PCSK9 and LDL. Mechanistically, PAQR3 enhances the interaction between LDLR and PCSK9. CONCLUSION: Our study reveals that PAQR3 plays a pivotal role in controlling hepatic LDLR degradation and blood LDL-C level via modulating LDLR-PCSK9 interaction.

[38] *Back M, Yurdagul A, Jr., Tabas I et al.* **Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities**. Nature reviews. Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30846875
ABSTRACT
Atherosclerosis is a lipid-driven inflammatory disease of the arterial intima in which the balance of pro-inflammatory and inflammation-resolving mechanisms dictates the final clinical outcome. Intimal infiltration and modification of plasma-derived lipoproteins and their uptake mainly by macrophages, with ensuing formation of lipid-filled foam cells, initiate atherosclerotic lesion formation, and deficient efferocytotic removal of apoptotic cells and foam cells sustains lesion progression. Defective efferocytosis, as a sign of inadequate inflammation resolution, leads to accumulation of secondarily necrotic macrophages and foam cells and the formation of an advanced lesion with a necrotic lipid core, indicative of plaque vulnerability. Resolution of inflammation is mediated by specialized pro-resolving lipid mediators derived from omega-3 fatty acids or arachidonic acid and by relevant proteins and signalling gaseous molecules. One of the major effects of inflammation resolution mediators is phenotypic conversion of pro-inflammatory macrophages into macrophages that suppress inflammation and promote healing. In advanced atherosclerotic lesions, the ratio between specialized pro-resolving mediators and pro-inflammatory lipids (in particular leukotrienes) is strikingly low, providing a

molecular explanation for the defective inflammation resolution features of these lesions. In this Review, we discuss the mechanisms of the formation of clinically dangerous atherosclerotic lesions and the potential of pro-resolving mediator therapy to inhibit this process.

[39] *Kwee RM, Qiao Y, Liu L et al.* **Temporal course and implications of intracranial atherosclerotic plaque enhancement on high-resolution vessel wall MRI**. Neuroradiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30834465
ABSTRACT
PURPOSE: Little is known about the natural history of intracranial atherosclerotic plaque enhancement and its clinical implications. Our objective was to investigate the value of follow-up high-resolution contrast-enhanced vessel wall MRI (VWMRI) for classifying culprit plaques in patients with intracranial atherosclerotic disease (ICAD). METHODS: Fourteen patients with symptomatic ICAD (50% females; median age 48 years) underwent serial 3T VWMRI. Fifty-five plaques were identified and graded based on the likelihood of having caused the ischemic event (non-culprit, indeterminate, culprit) and degree of enhancement (0, 1, 2) at baseline and follow-up (median follow-up, 140 days). For accuracy analysis, plaque enhancement at baseline and stable or increasing plaque enhancement at follow-up was tested to identify a culprit plaque, and areas under the receiver operating characteristic curves (AUCs) were compared. RESULTS: In 37/55 (67.3%) plaques, enhancement grade remained unchanged. Lack of enhancement was only seen in non-culprit plaques at baseline, and none developed enhancement over time. Enhancement never changed more than one grade. Thirty-seven percent (10/27) of non-culprit plaques that enhanced decreased in enhancement grade at follow-up, but no culprit plaques decreased in enhancement. AUC of baseline and follow-up plaque enhancement combined was significantly larger than AUC of baseline plaque enhancement alone to identify culprit plaques (0.733 vs. 0.567, p = 0.0001). CONCLUSION: Contrast enhancement of ICAD can persist months after the ischemic event. Lack of enhancement at baseline or a decrease in enhancement at follow-up suggests that the plaque is not culprit. Persistent enhancement from baseline to follow-up improves accuracy in identifying culprit plaques.

[40] *Biselli-Chicote PM, Lotierzo AT, Biselli JM et al.* **Atorvastatin increases oxidative stress and inhibits cell migration of oral squamous cell carcinoma in vitro**. Oral oncology 2019; 90:109-114.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30846168
ABSTRACT
OBJECTIVE: This study aimed to evaluate the effect of atorvastatin treatment on reactive oxygen species (ROS) production and tumor angiogenesis in oral squamous cell carcinomas. MATERIAL AND METHODS: An HN13 cell line was treated with 1microM, 5microM, and 10microM of atorvastatin. VEGF-A gene expression was evaluated by quantitative real time PCR. VEGF-A protein expression was quantified from total protein and conditioned media by ELISA. Cellular oxidative stress was measured using 2',7'-dichlorfluorescein-diacetate (DCFH-DA). Angiogenesis assay was performed using human umbilical vein endothelial cells (HUVEC). The effect of atorvastatin on cell migration was evaluated by wound healing assay. RESULTS:

5microM and 10microM of atorvastatin significantly increased VEGF-A gene expression in the HN13 cell line. Intracellular expression of the VEGF-A protein was higher in the cells treated with 5microM and 10microM than in the control cells. VEGF-A protein expression was also higher in the conditioned media from the atorvastatin-treated cells than in the media from the DMSO-treated cells. 5microM and 10microM of atorvastatin increased oxidative stress. Regarding angiogenesis assay, 5microM of atorvastatin resulted in higher numbers of branch points, compared to the solvent. 10microM of atorvastatin treatment resulted in significantly reduced cell migration. CONCLUSIONS: This study showed that atorvastatin increases the oxidative stress and angiogenesis in oral squamous cell carcinomas. The decrease of cell migration indicates atorvastatin's inhibitory effect in oral tumors. These results suggest that atorvastatin could increase the intracellular oxidative stress in these cells, leading to a toxic microenvironment and inhibiting their metastasis.

[41] *Gupta A, Stokes W, Eguchi M et al.* **Statin use associated with improved overall and cancer specific survival in patients with head and neck cancer**. Oral oncology 2019; 90:54-66.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30846177
ABSTRACT
OBJECTIVES: Studies have shown the utility of lipid-lowering agents in improving outcomes in various cancers. We aim to explore how statins affect overall survival and cancer specific survival in head and neck cancer patients using population-based datasets. PATIENTS AND METHODS: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset, we separated HNC patients into three groups: those with no hyperlipidemia (nH), those with hyperlipidemia and not taking a statin (HnS), and those with hyperlipidemia and taking a statin (H+S). Overall survival (OS) and cancer specific survival (CSS) were compared between the three groups based on disease subsite (oral cavity, oropharynx, and other) using Kaplan-Meier and multivariate Cox regression analysis (MVA), controlling for demographic, socioeconomic, staging, treatment, and comorbidity covariates. Using Pearson chi-square analysis, we also compared the incidence of cancer-related toxicity events. RESULTS: There were 495 nH, 567 HnS, and 530 H+S patients. H+S patients had superior OS and CSS (73.0, 81.2%) relative to nH (58.6, 69.1%) and HnS groups (61.7, 69.2%) ($p<0.01$). On MVA, H+S patients showed improved OS ($p<0.01$) and CSS ($p=0.04$) compared to nH (HR=1.64, 1.56) and HnS (HR=1.40, 1.37). MVA stratified by subsite yielded similar results for oral cavity and oropharyngeal disease. Toxicity-related events did not differ significantly between the groups. CONCLUSION: HNC patients with hyperlipidemia and taking a statin demonstrated improved outcomes compared to nH and HnS patients, further supporting statins' role as a potential adjuvant anti-neoplastic agent in HNC. Further prospective studies to investigate the impact of statins on HNC outcomes are warranted.

[42] *Chen K, Miller EJ, Sadeghi MM*. **PET-Based Imaging of Ischemic Heart Disease**. PET clinics 2019; 14:211-221.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30826019
ABSTRACT
PET-based cardiac nuclear imaging plays a large role in the management of ischemic heart disease. Compared with conventional single-photon emission CT myocardial perfusion imaging,

PET provides superior accuracy in diagnosis of coronary artery disease and, with the incorporation of myocardial blood flow and coronary flow reserve, adds value in assessing prognosis for established coronary and microvascular disease. This review describes these and other uses of PET in ischemic heart disease, including assessing myocardial viability in ischemic cardiomyopathy. Developments in novel PET flow tracers and molecular imaging tools to assess atherosclerotic plaque vulnerability, vascular calcification, and vascular remodeling also are described.

[43] *Fogacci F, Banach M, Mikhailidis DP et al.* **SAFETY OF RED YEAST RICE SUPPLEMENTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS**. Pharmacological research : the official journal of the Italian Pharmacological Society 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30844537

ABSTRACT

Recently, concerns regarding the safety of red yeast rice (RYR) have been raised after the publication of some case reports claiming toxicity. Since the previous meta-analyses on the effects of RYR were mainly focused on its efficacy to improve lipid profile and other cardiovascular parameters, we carried out a meta-analysis on safety data derived from the available randomized controlled clinical trials (RCTs). Primary outcomes were musculoskeletal disorders (MuD). Secondary outcomes were non-musculoskeletal adverse events (Non-MuD) and serious adverse events (SAE). Subgroups analyses were carried out considering the intervention (RYR alone or in association with other nutraceutical compounds), monacolin K administered daily dose (</=3, <3-5 and >5 mg/day), follow-up (>12 or </=12 weeks), with statin therapy or statin-intolerance and type of control treatment (placebo or statin treatment). Data were pooled from 53 RCTs comprising 112 treatment arms, which included 8535 subjects, with 4437 in the RYR arm and 4303 in the control one. Monacolin K administration was not associated with increased risk of MuD (odds ratio [OR] = 0.94, 95% confidence interval [CI] 0.53,1.65). Moreover, we showed reduced risk of Non-MuD (OR = 0.59, 95%CI 0.50, 0.69) and SAE (OR = 0.54, 95%CI 0.46, 0.64) vs. control. Subgroups analyses confirmed the high tolerability profile of RYR. Furthermore, increasing daily doses of monacolin K were negatively associated with increasing risk of Non-MuD (slope: -0.10; 95%CI: -0.17, -0.03; two-tailed p < 0.01). Based on our data, RYR use as lipid-lowering dietary supplement seems to be overall tolerable and safe in a large kind of moderately hypercolesterolaemic subjects.

[44] *Harris WS, Zotor FB*. **n-3 Fatty acids and risk for fatal coronary disease**. The Proceedings of the Nutrition Society 2019:1-6.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30837013

ABSTRACT

The purpose of this review is to consider the effects of the long-chain n-3 fatty acids found in marine foods, EPA and DHA, on risk for CVD, particularly fatal outcomes. It will examine both epidemiological and randomised controlled trial findings. The former studies usually examine associations between the dietary intake or the blood levels of EPA + DHA and CVD outcomes or, on occasion, total mortality. For example, our studies in the Framingham Heart Study and in the Women's Health Initiative Memory Study have demonstrated significant inverse relations between erythrocyte EPA + DHA levels (i.e. the Omega-3 Index) and total mortality. Recent data

from the Cardiovascular Health Study reported the same relations between plasma phospholipid n-3 levels and overall healthy ageing. As regards randomised trials, studies in the 1990s and early 2000s were generally supportive of a cardiovascular benefit for fish oils (which contain EPA + DHA), but later trials were generally not able to duplicate these findings, at least for total CVD events. However, when restricted to effects on risk for fatal events, meta-analyses have shown consistent benefits for n-3 treatment. Taken together, the evidence is strong for a cardioprotective effect of EPA + DHA, especially when consumed in sufficient amounts to raise blood levels into healthy ranges. Establishing target EPA + DHA intakes to reduce risk for cardiovascular death is a high priority.

[45] Mohan J, Zacharias SK. Acute Coronary Syndrome Catheter Interventions. In: StatPearls. Treasure Island (FL): StatPearls Publishing
StatPearls Publishing LLC.; 2019.