

Literature update week 10 (2018)

[1] *Lund J, Larsen LH, Lauritzen L. Fish oil as a potential activator of brown and beige fat thermogenesis. Adipocyte 2018:1-8.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29521565>

ABSTRACT

Numerous studies have shown that feeding rodents n-3 polyunsaturated fatty acids attenuates adiposity. Moreover, meta-analyses of human dietary intervention studies indicate that fish oil (eicosapentaenoic and docosahexaenoic acid) supplementation might reduce waist circumference. A recent line of research suggests that browning of white adipose depots and activation of uncoupled respiration in brown fat contributes to these effects. This mini-review summarizes the observations in rodents, highlights several mechanisms that might explain these observations and discusses the translational potential. Given the available in vivo evidence and the ability of human adipocytes to acquire a beige phenotype in response to eicosapentaenoic acid incubation, future studies should test the hypothesis that fish oil activates thermogenic brown and beige adipose tissue in humans.

[2] *Kosari S, Naunton M, Yee K et al. Fish Oil for Rheumatoid Arthritis: A Home Medicine Review Initiative. American journal of therapeutics 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29509551>

ABSTRACT

[3] *Wiercigroch E, Staniszewska-Slezak E, Szkaradek K et al. FT-IR Spectroscopic Imaging of Endothelial Cells Response to Tumor Necrosis Factor-alpha: To Follow Markers of Inflammation Using Standard and High-Magnification Resolution. Anal Chem 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29504750>

ABSTRACT

Two endothelial cell lines were selected as models to investigate an effect of incubation with cytokine tumor necrosis factor type alpha (TNF-alpha) using Fourier transform infrared (FT-IR) imaging spectroscopy. Both cell lines are often used in laboratories and are typical lung vascular endothelial cells (HMLVEC) derived from the fusion of umbilical vein endothelial cells with lung adenocarcinoma cells (EA.hy926). This study was focused on alteration of spectral changes accompanying inflammation at the cellular level by applying two resolution systems of FT-IR microscopy. The standard approach, with a pixel size of ca. 5.5 μm^2 , determined the inflammatory state of the whole cell, while a high-magnification resolution (pixel size of ca. 1.1 μm^2) provided information at the subcellular level. Importantly, the analysis of IR spectra recorded with different modes produced similar results overall and yielded unambiguous classification of inflamed cells. Generally, the most significant changes in the cells under the influence of TNF-alpha are related with lipids-their composition and concentration; however, segregation of cells into subcellular compartments provided an additional insight into proteins and nucleic acids related events. The observed spectral alterations are specific for the type of endothelial cell line.

[4] *Zaccardi F, Kunutsor SK, Seidu S et al. Is the lower risk of venous thromboembolism with statins related to low-density-lipoprotein reduction? A network meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis 2018; 271:223-231.*

Literature update week 10 (2018)

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29524865>

ABSTRACT

BACKGROUND AND AIMS: Meta-analyses of randomised controlled trials (RCTs) have suggested a possible benefit of statin treatment on the risk of venous thromboembolism (VTE), with potential differences by type and dose of statins. We aimed to assess differences among statins and to investigate the relationship between risk of VTE and reduction of LDL-cholesterol (LDL-c) levels. **METHODS:** We electronically searched, through November 29, 2017, RCTs comparing a statin with either placebo or another statin treatment, including 100 or more adult participants, and lasting at least 24 weeks. Data on first VTE events and LDL-c was analysed with a network meta-analysis and a meta-regression. **RESULTS:** Thirty RCTs (159,058 participants; 1431 events) were included, with 28 reporting LDL-c data. Network meta-analysis indicated a larger benefit for rosuvastatin compared to placebo and other statins; 50% of the effect of statins on VTE risk reduction, however, was explained by their different potencies in lowering LDL-c. The risk reduction in VTE was proportional to LDL-c decrease (37% relative lower risk per each 1mmol/L reduction in LDL-c), without an apparent threshold. A reduction of 1mmol/L in LDL-c would translate in 37 less VTE events per year in 100,000 people in UK, corresponding to 3162 prevented episodes per year in people between 50 and 59 years. **CONCLUSIONS:** In RCTs with statin treatment, the reduction of VTE risk was only partially related to LDL-c reduction and the benefit was larger than that observed for atherothrombotic risk. Further RCTs are warranted to clarify the relationship between statin, lipid modifications, and VTE risk.

[5] Korhonen MJ, Tiittanen P, Kastarinen H et al. **Statins do not Increase the Rate of Bleeding among Warfarin Users.** *Basic & clinical pharmacology & toxicology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29504234>

ABSTRACT

Clinical significance of potential interaction between warfarin and statins is unclear. Our objective was to determine whether use of statins as a class or use of simvastatin modulates the rate of bleeding requiring hospitalisation among new warfarin users. Using Finnish healthcare databases, we identified a cohort of 101,588 warfarin initiators between 1 January 2009 and 30 June 2012. By the end of 2012, these patients accumulated 92,695 person-years of exposure to warfarin-only and 60,253 years of exposure to warfarin-with-statin. The outcome was a composite of gastrointestinal, intracranial or other bleeding leading to hospitalisation. A Poisson generalised estimating equations model was employed to estimate rate ratios (RR) and their 95% confidence intervals (CI) for exposure to warfarin-with-statin compared to warfarin-only and to allow multiple episodes per patient and time-dependent covariates. In multivariable models, we found no difference in the bleeding rate in association with exposure to any statin (multivariable-adjusted RR=0.98, 95% CI 0.89-1.07) or to simvastatin (RR=1.01, 95% CI 0.91-1.11) with warfarin compared to exposure to warfarin-only. We conclude that concomitant use of statins and warfarin was not associated with an increased rate of bleeding requiring hospitalisation. This article is protected by copyright. All rights reserved.

[6] Pan J, Han L, Guo J et al. **AIM2 accelerates the atherosclerotic plaque progressions in ApoE-/- mice.** *Biochem Biophys Res Commun* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29510138>

ABSTRACT

Plaque formation is initiated and triggered by cell death in the vascular wall, which gradually leads to the progression of atherosclerosis. Pyroptosis is a newly discovered form of programmed cell death. Absent in melanoma 2 (AIM2), a member of the HIN-200 protein family, plays an important role in activating inflammasomes. However, the role and mechanism of AIM2 in atherosclerotic plaque progression has not been thoroughly elucidated to date. The effect of pyroptosis and the mechanism for this effect were investigated in apolipoprotein E-deficient (ApoE^{-/-}) mice. AIM2 overexpression and inhibition were studied in ApoE^{-/-} mice that were fed a high-fat diet. The specific role of AIM2 in vascular smooth muscle cells (VSMCs) was explored in vitro. The results showed that high fat diet increases the expression of AIM2, ICMA-1, GSDMD-N, which could be mediated by AIM2 expression. The plaque lesion area is larger with AIM2 overexpression. Moreover, TUNEL-positive cells were increased when AIM2 was overexpressed. With increased AIM2, macrophages were enhanced. In vitro studies showed that AIM2 and GSDMD-N expression correlated with ox-LDL levels in a concentration dependent manner. AIM2 expression is associated with NF-kappaB signaling activity and can be inhibited by NF-kappaB inhibitor. AIM2 mediated GSDMD activity through ASC, caspase1 pathway. EthD-III and TUNEL staining showed that AIM2 mediates pyroptosis in VSMCs. Our study suggests that AIM2 is not only a regular of inflammasome but also an active participant in atherosclerosis.

[7] *Nakayama H, Otsu K. Mitochondrial DNA as an inflammatory mediator in cardiovascular diseases. The Biochemical journal* 2018; 475:839-852.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29511093>

ABSTRACT

Mitochondria play a central role in multiple cellular functions, including energy production, calcium homeostasis, and cell death. Currently, growing evidence indicates the vital roles of mitochondria in triggering and maintaining inflammation. Chronic inflammation without microbial infection - termed sterile inflammation - is strongly involved in the development of heart failure. Sterile inflammation is triggered by the activation of pattern recognition receptors (PRRs) that sense endogenous ligands called damage-associated molecular patterns (DAMPs). Mitochondria release multiple DAMPs including mitochondrial DNA, peptides, and lipids, which induce inflammation via the stimulation of multiple PRRs. Among the mitochondrial DAMPs, mitochondrial DNA (mtDNA) is currently highlighted as the DAMP that mediates the activation of multiple PRRs, including Toll-like receptor 9, Nod-like receptors, and cyclic GMP-AMP synthetase/stimulator of interferon gene pathways. These PRR signalling pathways, in turn, lead to the activation of nuclear factor-kappaB and interferon regulatory factor, which enhances the transcriptional activity of inflammatory cytokines and interferons, and induces the recruitment of inflammatory cells. As the heart is an organ comprising abundant mitochondria for its ATP consumption (needed to maintain constant cyclic contraction and relaxation), the generation of massive amounts of mitochondrial radical oxygen species and mitochondrial DAMPs are predicted to occur and promote cardiac inflammation. Here, we will focus on the role of mtDNA in cardiac inflammation and review the mechanism and pathological significance of mtDNA-induced inflammatory responses in cardiac diseases.

Literature update week 10 (2018)

[8] Shi GJ, Shi GR, Zhou JY et al. **Involvement of growth factors in diabetes mellitus and its complications: A general review.** Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2018; 101:510-527.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29505922>

ABSTRACT

Diabetes mellitus (DM) is a major endocrine metabolic disease and is marked by a lack of insulin. The complication of DM is one of the most difficult problems in medicine. The initial translational studies revealed that growth factors have a major role in integrating tissue physiology and in embryology as well as in growth, maturation and tissue repair. In some tissues affected by diabetes, growth factors are induced by a relative deficit or excess. Fibroblast growth factor 21 (FGF21) is a promising regulator of glucose and lipid metabolism with multiple beneficial effects including hypoglycemic and lipid-lowering. Vascular endothelial growth factor (VEGF) is a potent angiogenic and vascular permeability factor and is implicated in both of these complications in diabetes. Increase or decrease in the production of transforming growth factor-beta1 (TGF-beta1) has been associated with diabetic nephropathy and retinopathy. The insulin-like growth factor-I (IGF-I) is a naturally-occurring single chain polypeptide which has been widely used in the treatment of diabetic glomerular and renal tubular injuries. This review summarizes the recent evidences for an involvement of growth factors in diabetic complications, focusing on their emergence in sequence of events leading to vascular complications or their potential therapeutic role in these diseases. Growth factor therapy in diabetic foot ulcers is already a clinical reality. As methods to finely regulate growth factors in a tissue and time-specific manner are further developed and tested, regulation of the growth factor to normal level in vivo may well become a therapy to prevent and treat diabetic complications.

[9] Pettersen D, Fjellstrom O. **Small molecule modulators of PCSK9 - A literature and patent overview.** Bioorganic & medicinal chemistry letters 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29519739>

ABSTRACT

Proprotein convertase subtilisin kexin like type 9 (PCSK9) has since its discovery been a key protein target for the modulation of LDL cholesterol. The interest in PCSK9 has grown even more with the positive clinical trial outcomes in cardiovascular disease recently reported for two PCSK9 antibodies. Currently, there are no PCSK9 small molecule programs active in clinical development. However, there has been a steady increase in publications and patent applications within the PCSK9 small molecule field. This digest will provide a summary of small molecule and peptide PCSK9 modulators reported both in scientific journals and in patent applications, most of them originating from the last 3-4years. As such, this digest will serve as an introduction to the field and assist further identification and discovery of small molecule PCSK9 modulators.

[10] Hajati F, Atlantis E, Bell KJL, Girosi F. **Patterns and trends of potentially inappropriate high-density lipoprotein cholesterol testing in Australian adults at high risk of cardiovascular disease from 2008 to 2014: analysis of linked individual patient data from the Australian Medicare Benefits Schedule and Pharmaceutical Benefits Scheme.** BMJ open 2018; 8:e019041.

Literature update week 10 (2018)

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29523561>

ABSTRACT

OBJECTIVES: We examine the extent to which the adult Australian population on lipid-lowering medications receives the level of high-density lipoprotein cholesterol (HDL-C) testing recommended by national guidelines. **DATA:** We analysed records from 7 years (2008-2014) of the 10% publicly available sample of deidentified, individual level, linked Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) electronic databases of Australia. **METHODS:** The PBS data were used to identify individuals on stable prescriptions of lipid-lowering treatment. The MBS data were used to estimate the annual frequency of HDL-C testing. We developed a methodology to address the issue of 'episode coning' in the MBS data, which causes an undercounting of pathology tests. We used a published figure on the proportion of unreported HDL-C tests to correct for the undercounting and estimate the probability that an HDL-C test was performed. We judged appropriateness of testing frequency by comparing the HDL-C testing rate to guidelines' recommendations of annual testing for people at high risk for cardiovascular disease. **RESULTS:** We estimated that approximately 49% of the population on stable lipid-lowering treatment did not receive any HDL-C test in a given year. We also found that approximately 19% of the same population received two or more HDL-C tests within the year. These levels of underutilisation and overutilisation have been changing at an average rate of 2% and -4% a year, respectively, since 2009. The yearly expenditure associated with test overutilisation was approximately \$A4.3 million during the study period, while the cost averted because of test underutilisation was approximately \$A11.3 million a year. **CONCLUSIONS:** We found that approximately half of Australians on stable lipid-lowering treatment may be having fewer HDL-C testing than recommended by national guidelines, while nearly one-fifth are having more tests than recommended.

[11] *Khaw KT, Sharp SJ, Finikarides L et al. Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women. BMJ open 2018; 8:e020167.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29511019>

ABSTRACT

INTRODUCTION: High dietary saturated fat intake is associated with higher blood concentrations of low-density lipoprotein cholesterol (LDL-C), an established risk factor for coronary heart disease. However, there is increasing interest in whether various dietary oils or fats with different fatty acid profiles such as extra virgin coconut oil may have different metabolic effects but trials have reported inconsistent results. We aimed to compare changes in blood lipid profile, weight, fat distribution and metabolic markers after four weeks consumption of 50 g daily of one of three different dietary fats, extra virgin coconut oil, butter or extra virgin olive oil, in healthy men and women in the general population. **DESIGN:** Randomised clinical trial conducted over June and July 2017. **SETTING:** General community in Cambridgeshire, UK. **PARTICIPANTS:** Volunteer adults were recruited by the British Broadcasting Corporation through their websites. Eligibility criteria were men and women aged 50-75 years, with no known history of cancer, cardiovascular disease or diabetes, not on lipid lowering medication, no contraindications to a high-fat diet and willingness to be randomised to consume one of the three dietary fats for 4 weeks. Of 160 individuals initially expressing an

Literature update week 10 (2018)

interest and assessed for eligibility, 96 were randomised to one of three interventions; 2 individuals subsequently withdrew and 94 men and women attended a baseline assessment. Their mean age was 60 years, 67% were women and 98% were European Caucasian. Of these, 91 men and women attended a follow-up assessment 4 weeks later. INTERVENTION: Participants were randomised to extra virgin coconut oil, extra virgin olive oil or unsalted butter and asked to consume 50 g daily of one of these fats for 4 weeks, which they could incorporate into their usual diet or consume as a supplement. MAIN OUTCOMES AND MEASURES: The primary outcome was change in serum LDL-C; secondary outcomes were change in total and high-density lipoprotein cholesterol (TC and HDL-C), TC/HDL-C ratio and non-HDL-C; change in weight, body mass index (BMI), waist circumference, per cent body fat, systolic and diastolic blood pressure, fasting plasma glucose and C reactive protein. RESULTS: LDL-C concentrations were significantly increased on butter compared with coconut oil (+0.42, 95% CI 0.19 to 0.65 mmol/L, $P<0.0001$) and with olive oil (+0.38, 95% CI 0.16 to 0.60 mmol/L, $P<0.0001$), with no differences in change of LDL-C in coconut oil compared with olive oil (-0.04, 95% CI -0.27 to 0.19 mmol/L, $P=0.74$). Coconut oil significantly increased HDL-C compared with butter (+0.18, 95% CI 0.06 to 0.30 mmol/L) or olive oil (+0.16, 95% CI 0.03 to 0.28 mmol/L). Butter significantly increased TC/HDL-C ratio and non-HDL-C compared with coconut oil but coconut oil did not significantly differ from olive oil for TC/HDL-C and non-HDL-C. There were no significant differences in changes in weight, BMI, central adiposity, fasting blood glucose, systolic or diastolic blood pressure among any of the three intervention groups. CONCLUSIONS AND RELEVANCE: Two different dietary fats (butter and coconut oil) which are predominantly saturated fats, appear to have different effects on blood lipids compared with olive oil, a predominantly monounsaturated fat with coconut oil more comparable to olive oil with respect to LDL-C. The effects of different dietary fats on lipid profiles, metabolic markers and health outcomes may vary not just according to the general classification of their main component fatty acids as saturated or unsaturated but possibly according to different profiles in individual fatty acids, processing methods as well as the foods in which they are consumed or dietary patterns. These findings do not alter current dietary recommendations to reduce saturated fat intake in general but highlight the need for further elucidation of the more nuanced relationships between different dietary fats and health. TRIAL REGISTRATION NUMBER: NCT03105947; Results.

[12] *Durham AL, Speer MY, Scatena M et al. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovascular research* 2018; 114:590-600.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29514202>

ABSTRACT

Vascular calcification is associated with a significant increase in all-cause mortality and atherosclerotic plaque rupture. Calcification has been determined to be an active process driven in part by vascular smooth muscle cell (VSMC) transdifferentiation within the vascular wall. Historically, VSMC phenotype switching has been viewed as binary, with the cells able to adopt a physiological contractile phenotype or an alternate 'synthetic' phenotype in response to injury. More recent work, including lineage tracing has however revealed that VSMCs are able to adopt a number of phenotypes, including calcific (osteogenic, chondrocytic, and

Literature update week 10 (2018)

osteoclastic), adipogenic, and macrophagic phenotypes. Whilst the mechanisms that drive VSMC differentiation are still being elucidated it is becoming clear that medial calcification may differ in several ways from the intimal calcification seen in atherosclerotic lesions, including risk factors and specific drivers for VSMC phenotype changes and calcification. This article aims to compare and contrast the role of VSMCs in driving calcification in both atherosclerosis and in the vessel media focusing on the major drivers of calcification, including aging, uraemia, mechanical stress, oxidative stress, and inflammation. The review also discusses novel findings that have also brought attention to specific pro- and anti-calcifying proteins, extracellular vesicles, mitochondrial dysfunction, and a uraemic milieu as major determinants of vascular calcification.

[13] *Ahmad F, Leake DS. Antioxidants inhibit low density lipoprotein oxidation less at lysosomal pH: A possible explanation as to why the clinical trials of antioxidants might have failed. Chemistry and physics of lipids* 2018; 213:13-24.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29518380>

ABSTRACT

Oxidised low density lipoprotein (LDL) was considered to be important in the pathogenesis of atherosclerosis, but the large clinical trials of antioxidants, including the first one using probucol (the PQRST Trial), failed to show benefit and have cast doubt on the importance of oxidised LDL. We have shown previously that LDL oxidation can be catalysed by iron in the lysosomes of macrophages. The aim of this study was therefore to investigate the effectiveness of antioxidants in preventing LDL oxidation at lysosomal pH and also establish the possible mechanism of oxidation. Probuco did not effectively inhibit the oxidation of LDL at lysosomal pH, as measured by conjugated dienes or oxidised cholesteryl esters or tryptophan residues in isolated LDL or by ceroid formation in the lysosomes of macrophage-like cells, in marked contrast to its highly effective inhibition of LDL oxidation at pH 7.4. LDL oxidation at lysosomal pH was inhibited very effectively for long periods by N,N'-diphenyl-1,4-phenylenediamine, which is more hydrophobic than probucol and has been shown by others to inhibit atherosclerosis in rabbits, and by cysteamine, which is a hydrophilic antioxidant that accumulates in lysosomes. Iron-induced LDL oxidation might be due to the formation of the superoxide radical, which protonates at lysosomal pH to form the much more reactive, hydrophobic hydroperoxyl radical, which can enter LDL and reach its core. Probuco resides mainly in the surface monolayer of LDL and would not effectively scavenge hydroperoxyl radicals in the core of LDL. This might explain why probucol failed to protect against atherosclerosis in various clinical trials. The oxidised LDL hypothesis of atherosclerosis now needs to be re-evaluated using different and more effective antioxidants that protect against the lysosomal oxidation of LDL.

[14] *Cho KI, Sakuma I, Sohn IS et al. Best Treatment Strategies With Statins to Maximize the Cardiometabolic Benefits. Circulation journal : official journal of the Japanese Circulation Society* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29503409>

ABSTRACT

Literature update week 10 (2018)

Statins are important for preventing adverse cardiovascular events in patients with both high and low risk of vascular disease, by reducing the levels of low-density lipoprotein cholesterol (LDL-C). However, statins dose-dependently increase adverse effects and increase the risk of type 2 diabetes. Previously, it was hypothesized this was caused by off-target effects, but recent studies demonstrate it is caused by on-target effects. Nonetheless, the American guidelines recommend the use of high-intensity statin therapy, and extend its use to most people at risk of vascular diseases, particularly older people. In contrast, European, Korean, and Japanese committees have expressed concerns about the potential adverse effects of using high-intensity statins for lifelong periods in a large fraction of the population. Patients who have achieved LDL-C levels below currently recommended targets may still experience cardiovascular events, resulting from residual risk. Ezetimibe, PCSK9 inhibitors, inclisiran, and ANGPTL3 antisense oligonucleotides are promising alternative non-statin drugs. Of interest, cross-talk between hypercholesterolemia and the renin-angiotensin-system exists at multiple levels of insulin resistance and endothelial dysfunction. There are still unanswered questions on how to maximize the cardiometabolic benefits of statins in patients. We will discuss the results of randomized clinical trials, meta-analysis, and recent clinicopharmacogenetic studies, and propose practical guidelines to maximize the cardiometabolic benefits while reducing adverse effects and overcoming residual risk.

[15] *Sathiyakumar V, Park J, Quispe R et al. Impact of Novel LDL-C Assessment on the Utility of Secondary Non-HDL-C and ApoB Targets in Selected Worldwide Dyslipidemia Guidelines. Circulation* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29506984>

ABSTRACT

Background -Selected dyslipidemia guidelines recommend non-high-density lipoprotein-cholesterol (non-HDL-C) and apolipoprotein B (apoB) as secondary targets to the primary target of low-density lipoprotein-cholesterol (LDL-C). We examined, after considering two LDL-C estimates that differ in accuracy: (1) how frequently non-HDL-C guideline targets could change management; and (2) utility of apoB targets after meeting LDL-C and non-HDL-C targets.

Methods -We analyzed 2,518 adults representative of the U.S. population from the 2011-2012 National Health and Nutrition Examination Survey and 126,092 patients from the Very Large Database of Lipids study with apoB. We identified all individuals as well as those with high-risk clinical features including coronary disease, diabetes, and metabolic syndrome who met very high- and high-risk guideline targets of LDL-C <70 and <100 mg/dL, using Friedewald estimation (LDL-CF) and a novel, more accurate method (LDL-CN). Next, we examined those not meeting non-HDL-C (<100, <130 mg/dL) and apoB (<80, <100 mg/dL) guideline targets. In those meeting dual LDL-C and non-HDL-C targets (<70 and <100 mg/dL, respectively, or <100 and <130 mg/dL respectively), we determined the proportion of individuals who did not meet guideline apoB targets (<80 or <100 mg/dL). Results -A total of 7-9% and 31-36% of individuals had LDL-C <70 and <100 mg/dL, respectively. Among those with LDL-CF <70 mg/dL, 14-15% had non-HDL-C \geq 100 mg/dL, and 7-8% had apoB \geq 80 mg/dL. Among those with LDL-CF <100 mg/dL, 8-10% had non-HDL-C \geq 130 mg/dL and 2-3% had apoB \geq 100 mg/dL. In comparison, among those with LDL-CN <70 or 100 mg/dL, only ~2% and ~1% of individuals, respectively, had non-HDL-C and apoB values above guideline targets. Similar trends were upheld among those with high-

Literature update week 10 (2018)

risk clinical features: ~0-3% of individuals with LDL-C<70 mg/dL had non-HDL-C \geq 100 mg/dL or apoB \geq 80 mg/dL compared to 13-38% and 9-25%, respectively, in those with LDL-C<70 mg/dL. With LDL-C or LDL-C<70 mg/dL and non-HDL-C<100 mg/dL, 0-1% had apoB \geq 80 mg/dL. Among all dual LDL-C or LDL-C<100 mg/dL and non-HDL-C<130 mg/dL individuals, 0-0.4% had apoB \geq 100 mg/dL. The above findings were robust to sex, fasting status, and lipid-lowering therapy status. Conclusions -After more accurately estimating LDL-C, guideline-suggested non-HDL-C targets could alter management in only a small fraction of individuals, including those with coronary disease and other high-risk clinical features. Furthermore, current guideline-suggested apoB targets provide modest utility after meeting cholesterol targets. Clinical Trial Registration -URL: <https://clinicaltrials.gov> Unique Identifier: NCT01698489.

[16] *Baum SJ, Cannon CP. PCSK9 inhibitor valuation: A science-based review of the two recent models. Clinical cardiology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29512936>

ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) has been extensively evaluated. Prospective cohort studies, randomized controlled trials, biology, pathophysiology, genetics, and Mendelian randomization studies, have clearly taught us that LDL-C causes atherosclerotic cardiovascular disease. The newest class of drugs to lower LDL-C, the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, have been found to safely reduce LDL-C approximately 60% when added to high-intensity statin therapy. Because their cost is much greater than that of the currently available agents, their value has been questioned. In late August, 2017, two groups assessed the value of this class of drugs looking at cost-effectiveness; however, the Institute for Clinical and Economic Review and Fonarow and colleagues found disparate results when assessing PCSK9 valuation. Herein, we review the evolution of LDL-C from hypothesis to fact, and then attempt to adjudicate the 2 models, shedding light on the complex modeling process. We find that models of cost-effectiveness are helpful adjuncts to decision making, but that their conclusions depend on many assumptions. Ultimately, clinician judgment regarding their clinical benefit, balanced by some estimation of cost, may be more productive to target the right patients for whom the benefits can be well-justified.

[17] *Wang H, Yin J, Guo Y. Atorvastatin might resist tobacco smoking-induced endothelial inflammation through the inhibition of NF-kappaB signal pathway. Clinical and experimental hypertension (New York, N.Y. : 1993)* 2018:1-4.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29509049>

ABSTRACT

Endothelial inflammation caused by tobacco smoking is widely considered as a pathogenic factor in many vascular diseases. Drugs such as atorvastatin were found to be an effective treatment in smoking-dependent vascular diseases, but the underlying mechanism is still unclear. Here, we investigated the mechanism of atorvastatin resisting endothelial inflammation caused by tobacco smoking. Firstly, isolated human umbilical vein endothelial cells (HUVECs) were divided into normal control group, cigarette smoking extract (CSE) group, and atorvastatin (AS)+CSE group. Then the expressions of inflammatory factors (vascular cell

Literature update week 10 (2018)

adhesion molecule-1 (VCAM-1) and E-selectin) and nuclear transcription factor kappa (NF-kappaB) in HUVECs were detected by western blot after separate treatments. The results showed that the expressions of VCAM-1, E-selectin, and NF-kappaB in CSE group were significantly higher than the other two groups ($P < 0.05$). We also found that the expressions of VCAM-1, E-selectin, and NF-kappaB in CSE + atorvastatin group were a little higher than the normal control group ($P < 0.05$). Our results showed that atorvastatin might partly resist tobacco smoking-induced endothelial inflammation through the inhibition of NF-kappaB signal pathway.

[18] *Adams SP, Sekhon SS, Tsang M, Wright JM. Fluvastatin for lowering lipids. The Cochrane database of systematic reviews 2018; 3:Cd012282.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29508377>

ABSTRACT

BACKGROUND: Fluvastatin is thought to be the least potent statin on the market, however, the dose-related magnitude of effect of fluvastatin on blood lipids is not known. **OBJECTIVES:** Primary objective To quantify the effects of various doses of fluvastatin on blood total cholesterol, low-density lipoprotein (LDL cholesterol), high-density lipoprotein (HDL cholesterol), and triglycerides in participants with and without evidence of cardiovascular disease. Secondary objectives To quantify the variability of the effect of various doses of fluvastatin. To quantify withdrawals due to adverse effects (WDAEs) in randomised placebo-controlled trials. **SEARCH METHODS:** The Cochrane Hypertension Information Specialist searched the following databases for randomised controlled trials up to February 2017: the Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 1), MEDLINE (1946 to February Week 2 2017), MEDLINE In-Process, MEDLINE Epub Ahead of Print, Embase (1974 to February Week 2 2017), the World Health Organization International Clinical Trials Registry Platform, CDSR, DARE, Epistemonikos and ClinicalTrials.gov. We also contacted authors of relevant papers regarding further published and unpublished work. No language restrictions were applied. **SELECTION CRITERIA:** Randomised placebo-controlled and uncontrolled before and after trials evaluating the dose response of different fixed doses of fluvastatin on blood lipids over a duration of three to 12 weeks in participants of any age with and without evidence of cardiovascular disease. **DATA COLLECTION AND ANALYSIS:** Two review authors independently assessed eligibility criteria for studies to be included, and extracted data. We entered data from placebo-controlled and uncontrolled before and after trials into Review Manager 5 as continuous and generic inverse variance data, respectively. WDAEs information was collected from the placebo-controlled trials. We assessed all trials using the 'Risk of bias' tool under the categories of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases. **MAIN RESULTS:** One-hundred and forty-five trials (36 placebo controlled and 109 before and after) evaluated the dose-related efficacy of fluvastatin in 18,846 participants. The participants were of any age with and without evidence of cardiovascular disease, and fluvastatin effects were studied within a treatment period of three to 12 weeks. Log dose-response data over doses of 2.5 mg to 80 mg revealed strong linear dose-related effects on blood total cholesterol and LDL cholesterol and a weak linear dose-related effect on blood triglycerides. There was no dose-related effect of fluvastatin on blood HDL cholesterol. Fluvastatin 10 mg/day to 80 mg/day reduced LDL cholesterol by 15% to 33%, total cholesterol by 11% to 25% and triglycerides by 3% to 17.5%.

Literature update week 10 (2018)

For every two-fold dose increase there was a 6.0% (95% CI 5.4 to 6.6) decrease in blood LDL cholesterol, a 4.2% (95% CI 3.7 to 4.8) decrease in blood total cholesterol and a 4.2% (95% CI 2.0 to 6.3) decrease in blood triglycerides. The quality of evidence for these effects was judged to be high. When compared to atorvastatin and rosuvastatin, fluvastatin was about 12-fold less potent than atorvastatin and 46-fold less potent than rosuvastatin at reducing LDL cholesterol. Very low quality of evidence showed no difference in WDAEs between fluvastatin and placebo in 16 of 36 of these short-term trials (risk ratio 1.52 (95% CI 0.94 to 2.45). **AUTHORS' CONCLUSIONS:** Fluvastatin lowers blood total cholesterol, LDL cholesterol and triglyceride in a dose-dependent linear fashion. Based on the effect on LDL cholesterol, fluvastatin is 12-fold less potent than atorvastatin and 46-fold less potent than rosuvastatin. This review did not provide a good estimate of the incidence of harms associated with fluvastatin because of the short duration of the trials and the lack of reporting of adverse effects in 56% of the placebo-controlled trials.

[19] *Lee JGH, Genga KR, Pisitsak C et al. Survival benefit of a low ratio of visceral to subcutaneous adipose tissue depends on LDL clearance versus production in sepsis. Crit Care* 2018; 22:58.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29510719>

ABSTRACT

BACKGROUND: Patients with sepsis with a high ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) have increased mortality. Our goal was to investigate the mechanism of this effect, noting that low LDL levels are also associated with increased sepsis mortality. Accordingly we tested for association between VAT/SAT, low-density lipoprotein (LDL) levels, and mortality. Then we examined the effect of statin treatment, which decreases LDL production, and the effect of PCSK9 genotype, which increases LDL clearance. **METHODS:** We performed retrospective analysis of a cohort of patients with sepsis from a tertiary care adult intensive care unit in Vancouver, Canada, who underwent abdominal computed tomography (CT) (n = 75) for clinical reasons. We compared LDL levels in patients with sepsis according to high versus low VAT/SAT and 90-day survival. We next examined the effects of statin therapy and PCSK9 loss-of-function genotype on survival. **RESULTS:** Patients with a low VAT/SAT had increased 90-day survival and were relatively protected against low LDL levels in sepsis compared to high VAT/SAT. Statin treatment abrogated the beneficial effects of low VAT/SAT; eliminating the difference in LDL levels and survival between patients with low and high VAT/SAT. PCSK9 loss-of-function genotype similarly eliminated the increased LDL levels in low VAT/SAT patients but, in contrast, increased the survival advantage of low VAT/SAT compared to high VAT/SAT. **CONCLUSIONS:** Low LDL levels per se are not simply associated with decreased sepsis survival because lowering LDL levels by inhibiting LDL production (statin treatment) is associated with adverse outcomes, while increased LDL clearance (PCSK9 loss-of-function genotype) is associated with improved outcomes in patients with low VAT/SAT.

[20] *Russell C, Sheth S, Jacoby D. A Clinical Guide to Combination Lipid-Lowering Therapy. Current atherosclerosis reports* 2018; 20:19.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29516190>

ABSTRACT

Literature update week 10 (2018)

PURPOSE OF REVIEW: We provide an overview of our current understanding of combination lipid-lowering therapies intended for dyslipidemia treatment and cardiovascular disease prevention. First, we analyze recent statin and non-statin combination therapy guidelines and clinical studies since the publication of 2013 American College of Cardiology Cholesterol Guidelines. Second, we examine the clinical utility of non-statin agents alone and in combination in terms of LDL-C lowering and ASCVD risk reduction. **RECENT FINDINGS:** Medical societies, including the American College of Cardiology (ACC), National Lipid Association (NLA), and American Association of Clinical Endocrinologists (AACE), have released guidelines to address the appropriate use of non-statin therapies. The guidelines incorporated new evidence, including the IMPROVE-IT and FOURIER clinical trials, which demonstrate that the combination of statin therapy with other non-statin agents such as ezetimibe and PCSK9 inhibitors has a significant clinical benefit. Increasing evidence that aggressive low-density lipoprotein cholesterol (LDL-C) lowering leads to lower cardiovascular disease risk supports the need for continued exploration of the role of combination lipid-lowering therapies. A review of guidelines and clinical trials evaluating non-statin agents illuminates the growing base of evidence and expert opinion supporting the use of combination lipid-lowering therapies. While the majority of clinical trial data utilizes dyslipidemia monotherapy, especially statins, combination therapies represent an opportunity for individualized, patient-centered approach to LDL-C lowering and atherosclerotic cardiovascular disease (ASCVD) risk reduction. The overview provides a perspective on lipid management intended for clinicians who seek additional information and guidance on the use of combination therapies.

[21] *Wiggins BS, Senfield J, Kassahun H et al. Evolocumab: Considerations for the Management of Hyperlipidemia. Current atherosclerosis reports* 2018; 20:17.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29511875>

ABSTRACT

PURPOSE OF REVIEW: To review the efficacy, safety, pharmacology, and pharmacokinetics of evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. **RECENT FINDINGS:** PCSK9 inhibitors are a class of lipid-lowering agents that significantly reduce low-density lipoprotein cholesterol (LDL-C) levels in patients with atherosclerotic cardiovascular disease and hyperlipidemia. Evolocumab is a monoclonal antibody that inhibits PCSK9 and has been evaluated in phase II and III studies as monotherapy, in combination with statins and other lipid-lowering therapies, in patients who are statin intolerant, and in patients with heterozygous and homozygous familial hypercholesterolemia. Data from these studies show that evolocumab significantly reduces LDL-C levels. Treatment with evolocumab also significantly improves levels of other lipid parameters (e.g., apolipoproteins A1 and B, lipoprotein(a), non-high-density lipoprotein cholesterol, and triglycerides). Recent results indicate that LDL-C reduction with evolocumab significantly reduces the risk of cardiovascular events and is also associated with atherosclerotic plaque regression. From a safety standpoint, rates of adverse events (AEs), serious AEs, and AEs leading to discontinuation were similar between evolocumab and controls in clinical trials, and no increase in AEs was observed when evolocumab was used in combination with statins. Patients with elevated LDL-C benefit from evolocumab treatment, suggesting that evolocumab could help meet an unmet medical need in

Literature update week 10 (2018)

high-risk patient populations with atherosclerotic cardiovascular disease and hyperlipidemia that are unable to reduce LDL-C levels sufficiently with statin therapy alone.

[22] *Masson W, Lobo M, Siniawski D et al. Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk. Diabetes Metab* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29523487>

ABSTRACT

BACKGROUND: Cholesteryl ester transfer protein (CETP) inhibitors are a class of drugs that targets the CETP enzyme to significantly increase serum high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C) levels. As HDL-C has potential antidiabetic properties, and the beneficial effects of CETP drugs on glucose homeostasis have not been sufficiently studied, the aims of this study were: (1) to evaluate the effect of CETP inhibitors on the incidence of diabetes; and (2) to assess the association between CETP inhibitor-induced changes in HDL-C levels and incidence of diabetes. **METHODS:** A meta-analysis was performed of randomized controlled clinical trials of CETP inhibitor therapy, either alone or combined with other lipid-lowering drugs, reporting data from new cases of diabetes with a minimum of 6 months of follow-up, after searching the PubMed/MEDLINE, Embase and Cochrane Controlled Trials databases. A fixed-effects meta-regression model was then applied. **RESULTS:** Four eligible trials of CETP inhibitors, involving a total of 73,479 patients, were considered for the analyses, including 960 newly diagnosed cases of diabetes in the CETP inhibitor group vs 1086 in the placebo group. CETP inhibitor therapy was associated with a significant 12% reduction in incidence of diabetes (OR: 0.88, 95% CI: 0.81-0.96; P=0.005). Assessment of the relationship between on-treatment HDL-C and the effect of CETP inhibitors showed a statistically non-significant trend (Z=-1.13, P=0.26). **CONCLUSION:** CETP inhibitors reduced the incidence of diabetes. The improvement in glucose metabolism may have been related, at least in part, to the increase in HDL-C concentration.

[23] *Klischies S. European Society of Cardiology Congress 2017 (August 26-30, 2017 - Barcelona, Spain). Drugs of today (Barcelona, Spain : 1998)* 2017; 53:667-670.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29517085>

ABSTRACT

The annual congress of the European Society of Cardiology (ESC) is the largest medical congress in Europe for this area of research and took place this year in Barcelona, Spain. The ESC Congress 2017 gathered more than 30,000 registered participants from over 140 countries together to share their knowledge in all cardiovascular fields, from basic science to management and prevention of cardiovascular diseases. The congress comprised 5 days of science and education with over 11,000 abstracts submitted, 500 expert sessions and over 200 exhibiting companies, making it the prime meeting platform for the profession. This year's ESC Congress Spotlight was "40 years of percutaneous coronary intervention (PCI)." PCI is a nonsurgical procedure used to treat narrowing of the coronary arteries of the heart found in coronary artery disease.

[24] *Rubio-Marin P, Michan-Dona A, Maraver-Delgado J et al. Cascade screening program for familial hypercholesterolemia. Endocrinologia, diabetes y nutricion* 2018.

Literature update week 10 (2018)

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29523491>

ABSTRACT

INTRODUCTION AND OBJECTIVE: Early detection of heterozygous familial hypercholesterolemia (HFH) is needed to prevent premature cardiovascular events. Our aim is to describe the course of an HFH screening detection day in the Northern Cadiz Health Area in Spain and to analyze the data recorded. **SUBJECTS AND METHODS:** Descriptive study of an FH cascade screening program. Index cases (ICs) and their 1st and 2nd grade relatives were appointed during a weekend by the FH Foundation. Venous blood samples were taken from the subjects for genetic, blood, and chemistry tests; specialized medical consultation and physical examination were performed. **RESULTS:** The study sample consisted of 132 subjects: 21 ICs and 111 relatives (16 under 18 years old), with a mean age of 11.4 years (SD 4.57). Mean age of subjects over 18 years was 45.2 years. A gene mutation was found in 90 relatives. Mean age at diagnosis was 25 years (SD 17.7) for relatives and for 36.4 years (SD 17.2; $P=0.01$) for ICs. Smoking rate was higher in relatives than in ICs (26.3% vs 4.8%; $P=0.02$) and corneal arcus was more common in ICs as compared to relatives (47.6% vs 12.6%; $P<0.001$). Prior myocardial infarction was recorded in 14.3% of ICs and 4.2% of relatives respectively ($P=0.07$). Maximum lipid lowering treatment was being administered to 43.1%. **CONCLUSIONS:** The screening detection approach identified the estimated 4% population with HFH in the area, and allows for diagnosing HFH 11.4 years earlier.

[25] *Oi M, Donner D, Peart J et al. Pravastatin improves risk factors but not ischaemic tolerance in obese rats. European journal of pharmacology* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29501869>

ABSTRACT

Statins are effective in management of dyslipidaemia, and a cornerstone of CVD prevention strategies. However, the impacts of their pleiotropic effects on other cardiovascular risk factors and myocardial responses to infarction are not well characterised. We hypothesised that pravastatin treatment in obesity improves lipid profiles, insulin-resistance and myocardial resistance to ischaemia/reperfusion (I/R) injury. Wistar rats were fed a control (C) chow or high carbohydrate and fat diet (HCFD) for 16 weeks with vehicle or pravastatin (prava 7.5 mg/kg/day) treatment for 8 weeks. At 16 weeks HOMAs were performed, blood samples collected and hearts excised for Langendorff perfusions/biochemical analyses. Anti-oxidant activity and proteins regulating mitochondrial fission/fusion and apoptosis were assessed. The HCFD increased body weight (736 \pm 15 vs. 655 \pm 12 g for C; $P<0.001$), serum triglycerides (2.91 \pm 0.52 vs. 1.64 \pm 0.26 mmol/L for C; $P<0.001$) and insulin-resistance (HOMA- 6.9 \pm 0.8 vs. 4.2 \pm 0.5 for C; $P<0.05$) while prava prevented diet induced changes and paradoxically increased lipid peroxidation. The HCFD increased infarct size (34.1 \pm 3.1% vs. 18.8 \pm 3.0% of AAR for C; $P<0.05$), which was unchanged by prava in C and HCFD animals. The HCFD decreased cardiac TxR activity and mitochondrial MFN-1 and increased mitochondrial DRP-1 (reducing MFN-1:DRP-1 ratio) and Bax expression, with the latter changes prevented by prava. While unaltered by diet, cytosolic levels of Bax and caspase-3 were reduced by prava in C and HCFD hearts (without changes in cleaved caspase-3). We conclude that obesity, hyper-triglyceridemia and impaired glycemic control in HCFD rats are countered by prava. Despite improved risk factors, prava did not reduce myocardial infarct size, potentially reflecting its complex pleiotropic impacts on cardiac GPX activity and MFN-1, DRP-1, caspase-3 and Bcl-2 proteins.

Literature update week 10 (2018)

[26] Zhou F, Tan Y, Chen XH et al. **Atorvastatin improves plaque stability in diabetic atherosclerosis through the RAGE pathway.** European review for medical and pharmacological sciences 2018; 22:1142-1149.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29509268>

ABSTRACT

OBJECTIVE: To study the improving effect of atorvastatin on plaque stability in diabetes mellitus (DM) mice complicated with atherosclerosis. MATERIALS AND METHODS: Apolipoprotein E (ApoE)-/- mice were used to establish the DM mouse model. Half of the mice received atorvastatin after successful modeling. ApoE-/- and C57BL/6J mice were used as controls. Oil red O staining and Masson staining were performed to detect the lipid and collagen components in mice. Immunohistochemical assay was used to observe the expressions of smooth muscle cell (SMC) and Ly-6c. The expressions of receptor for advanced glycation end products (RAGE), monocyte chemoattractant protein-1 (MCP-1) and nuclear factor-kappaB (NF-kappaB) in tissues were detected by Western blotting. Finally, the levels of serum soluble RAGE (sRAGE), advanced glycation end products (AGEs), malondialdehyde (MDA) and reduced glutathione (GSH) in mice were also detected. RESULTS: Atorvastatin reduced the area of atherosclerotic plaque and improved the stability of arterial plaque through reducing lipid deposition, the number of macrophages and SMC, increasing collagen fibers. In mice in atorvastatin group, the levels of serum AGEs and sRAGE were decreased. Moreover, atorvastatin inhibited the downstream pathway of RAGE as well as DM, thus inducing the oxidative stress. CONCLUSIONS: Atorvastatin improves plaque stability in diabetic atherosclerosis through the RAGE pathway.

[27] Ofstad AP, Atar D, Gullestad L et al. **The heart failure burden of type 2 diabetes mellitus-a review of pathophysiology and interventions.** Heart failure reviews 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29516230>

ABSTRACT

Diabetes and heart failure (HF) are both global epidemics with tremendous costs on society with increased rates of HF hospitalizations and worsened prognosis when co-existing, making it a significant "deadly duo." The evidence for pharmacological treatment of HF in patients with type 2 diabetes mellitus (T2DM) stems typically from either subgroup analyses of patients that were recruited to randomized controlled trials of HF interventions, usually in patients with reduced ejection fraction (EF), or from subgroup analyses of HF patients recruited to cardiovascular (CV) outcome trials (CVOT) of glucose lowering agents involving patients with T2DM. Studies in patients with HF with preserved EF are sparse. This review summarizes the literature on pathophysiology and interventions aiming to reduce the HF burden in T2DM and includes HF trials of ACEi, digoxin, beta-blocker, ARB, If-blocker, MRA, and ARNI involving 38,600 patients, with or without prevalent diabetes, and CV outcome trials in T2DM involving 74,351 patients, with or without prevalent HF. In all HF trials, HF outcomes by prevalent diabetes were reported with an incremental risk of HF and death confessed by prevalent diabetes and a treatment effect similar to those without diabetes. All T2DM CVOTs reported on HF outcomes with heterogeneity between trials with two reporting benefits (empagliflozin and canagliflozin) and two reporting increased risk (saxagliptin, pioglitazone). In vulnerable T2DM

Literature update week 10 (2018)

patients with concomitant HF, guideline-recommended HF drugs are effective. When choosing glucose-lowering therapy, outcomes from available CVOTs should be considered.

[28] *Ponziani MC, Karamouzis I, Mele C et al. Baseline glucose homeostasis predicts the new onset of diabetes during statin therapy: A retrospective study in real life. Hormones (Athens, Greece) 2017; 16:396-404.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29518760>

ABSTRACT

OBJECTIVE: We evaluated the risk of altered glucose levels and new-onset diabetes (NOD) associated with statins according to glucose levels at baseline in a population treated for dyslipidemia on primary prevention for >5 years. DESIGN: The retrospective study included 308 subjects (265 on statins and 43 controls on diet) with a follow-up of 5-15 years. The cohort was classified according to glucose tolerance at both baseline and follow-up. RESULTS: The cumulative incidence of NOD was 13.6% (9.3% in controls and 13.5% in treated patients). NOD was diagnosed after 3.4+/-1.8 years. In the group with normal glucose levels at baseline, a family history of diabetes (OR: 3.4, 95% CI 1.3-8.9), BMI >30 kg/m² (OR: 8.5, 95% CI 2.0-35.8), treatment with thiazide (OR: 21.9, 95% CI 1.2-384.2) and no alcohol consumption (OR: 0.3, 95% CI 0.1-0.8) reduced the risk of developing altered glucose levels or NOD. No effects of statins were seen. In the group with altered glucose levels at baseline, hypertension (OR: 5.0, 95% CI 1.0-25.3) and hypertriglyceridemia (OR: 3.5, 95% CI 1.0-11.8) increased the risk of remaining with altered glucose levels or developing NOD. Treatment with statins (OR: 7.5, 95% CI 1.5-37.4), in particular atorvastatin, was associated with an increased risk. In the whole population, statin therapy (OR: 4.0, 95% CI 1.1-14.1, p<0.020), and in particular simvastatin and atorvastatin, was associated with increased risk of altered glucose levels or NOD. Patients who developed or maintained altered glucose levels or NOD had a poor metabolic phenotype at baseline. CONCLUSIONS: Statins were associated with an increased risk of NOD or altered glucose levels, mainly in subjects with altered glucose levels before the beginning of therapy. Poor metabolic phenotype and unhealthy behaviors or family history of diabetes contributed to that risk.

[29] *Falkowski A, Goracy I, Kaczmarczyk M et al. Lipid derivatives of arachidonic acid used as markers of atherosclerotic plaque instability: a pilot study. International angiology : a journal of the International Union of Angiology 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29509372>

ABSTRACT

BACKGROUND: To compare the results of computer estimation of atherosclerotic plaque with biochemical data and ascertain any relationship with the occurrence of stroke. METHODS: The study involved 20 atherosclerotic plaques causing 70-99% stenosis of internal carotid arteries (ICA). Ultrasonographic examination (USG) images of plaques were analyzed using a computer program. A histogram was obtained for each plaque and a gray scale median (GSM) was determined for each histogram in order to measure the echogenicity of an examined plaque. Then the plaques, collected during endarterectomy, were examined with regard to the concentration of prostaglandins E₂ (PGE₂), thromboxane A₂ (TXA₂), and 8 - epi-Prostaglandin F₂alpha. This data was compared with GSM and the occurrence of stroke. RESULTS: The

Literature update week 10 (2018)

statistical analysis showed significant correlations between low GSM and the occurrence of strokes. Out of 10 plaques with GSM < 35, six (60.0%) were associated with a stroke. In contrast, out of 10 plaques with GSM > 35, only one (10.0%) had a stroke. In addition, there were significant differences in the plaque content of PGE 2, (p<0.05) and (TXA2, p<0.011) between groups. CONCLUSIONS: High levels of PGE2 and TXA2, correlated with the low GSM values, may be the features of unstable plaques and that's may be associated with a risk for stroke.

[30] *Miyauchi K, Kimura T, Shimokawa H et al. Rationale and Design of Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) Trial. Int Heart J* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29503404>

ABSTRACT

Large-scale clinical trials in patients in Western countries with coronary artery disease (CAD) have found that aggressive lipid-lowering therapy using high-dose statins reduces cardiovascular (CV) events further than low-dose statins. However, such evidence has not yet been fully established in Asian populations, including in Japan. The Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study addresses whether intensification of statin therapy improves clinical outcomes in Japanese patients with CAD. REAL-CAD is a prospective, multicenter, randomized, open-label, blinded-endpoint, physician-initiated phase 4 trial in Japan. The study will recruit up to 12,600 patients with stable CAD. Patients are assigned to receive either pitavastatin 1 mg/day or pitavastatin 4 mg/day. LDL-C levels are expected to reach approximate mean values of 100 mg/dL in the low-dose pitavastatin group and 80 mg/dL in the high-dose group. The primary endpoint is the time to occurrence of a major CV event, including CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization during an average of 5 years. The large number of patients and the long follow-up period in the REAL-CAD study should ensure that there is adequate power to definitively determine if reducing LDL-C levels to approximately 80 mg/dL by high-dose statin can provide additional clinical benefit. After the study is completed, we will have categorical evidence on the optimal statin dose and target LDL-C level for secondary prevention in Japanese patients.

[31] *He WS, Zhu H, Chen ZY. Plant Sterols: Chemical and Enzymatic Structural Modifications and Effects on Their Cholesterol-Lowering Activity. Journal of agricultural and food chemistry* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29521096>

ABSTRACT

Plant sterols have attracted more and more attention due to their excellent cholesterol-lowering activity. However, free plant sterols have some characteristics of low oil solubility, water insolubility, high melting point and low bioavailability, which greatly limit their application in foods. Numerous studies have been undertaken to modify their chemical structures in order to improve their chemical and physical properties in meeting the needs of various applications. The present review is to summarize the literature and update the progress on structural modifications of plant sterols in the following aspects: (i) synthesis of plant sterol

Literature update week 10 (2018)

esters by esterification and transesterification with hydrophobic fatty acids and triacylglycerols to improve their oil solubility; (ii) synthesis of plant sterol derivatives by coupling with various hydrophilic moieties to enhance their water solubility; and (iii) mechanisms by which plant sterols reduce plasma cholesterol and the effect of structural modifications on plasma cholesterol-lowering activity of plant sterols.

[32] *Lei L, Chen J, Liu Y et al. Dietary Wheat Bran Oil Is Equally as Effective as Rice Bran Oil in Reducing Plasma Cholesterol. Journal of agricultural and food chemistry* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29502409>

ABSTRACT

Rice bran oil (RBO) possesses a plasma cholesterol-lowering activity, while effect of wheat bran oil (WBO) on plasma cholesterol remains unknown. The present study compared the cholesterol-lowering activity of WBO with that of RBO in hamsters. Fifty-four male hamsters were divided into seven groups fed either a noncholesterol diet (NCD) or one of six high-cholesterol diets, namely HCD diet (0.2% cholesterol +9.5% lard), HCD+C diet (0.2% cholesterol +9.5% lard +0.5% cholestyramine), WL diet (0.2% cholesterol +4.8% Lard +4.8% WBO), WH diet (0.2% cholesterol +9.5% WBO), RL diet (0.2% cholesterol +4.8% Lard +4.8% RBO), and RH diet (0.2% cholesterol +9.5% RBO). Plasma total cholesterol (TC) in HCD group was 327.4 +/- 31.8 mg/dL, while plasma TC in two WBO and two RBO groups was 242.2 +/- 20.8, 243.1 +/- 31.7, 257.1 +/- 16.3, and 243.4 +/- 46.0 mg/dL, respectively, leading to a decrease in plasma TC by 22-26% (P < 0.01). No significant difference in cholesterol-lowering potency was seen between WBO and RBO. Plasma cholesterol-lowering activity of WBO and RBO was accompanied by down-regulation of hepatic 3-hydroxy-3-methylglutaryl-CoA reductase and fatty acid synthase, while up-regulation of cholesterol-7alpha-hydroxylase. WL, WH, RL, and RH diets increased the fecal excretion of total neutral sterols by 72.8%, 106.9%, 5.4%, and 36.8% (P < 0.01) respectively. Results indicated WBO and RBO could inhibit cholesterol absorption via down-regulation of intestinal Niemann-Pick C1 like 1 protein, acyl CoA:cholesterol acyltransferase 2, and ATP binding cassette transporter 5. In summary, WBO was equally effective as RBO in decreasing plasma cholesterol in hypercholesterolemia hamsters.

[33] *Kim CH, Wang S, Park JB et al. Assessing Impact of High-Dose Pitavastatin on Carotid Artery Elasticity with Speckle-Tracking Strain Imaging. Journal of atherosclerosis and thrombosis* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29515050>

ABSTRACT

AIM: Speckle-tracking imaging has been introduced for the precise assessment of vessel mechanics. However, there are no data on the role of this imaging tool in assessing the changes in vasculature with statin therapy, which is known to enhance vascular elasticity. METHODS: This study was a prospective study including 48 statin-naive patients (age, 58.2+/-8.4 years; 29.2% male) with hypercholesterolemia. Circumferential carotid artery strain (CAS) and stiffness index (beta2) were measured using speckle-tracking imaging before and after 3 months of high-dose pitavastatin treatment (4 mg daily). For the comparison, we measured conventional carotid elasticity parameters and intima-media thickness using B-mode ultrasound at the same time points. RESULTS: Compared with baseline, there was significant improvement

Literature update week 10 (2018)

in circumferential CAS (2.98% \pm 1.18% to 3.40% \pm 1.43%, $p=0.008$) and beta2 (0.19 \pm 0.07 to 0.17 \pm 0.08, $p=0.047$) after statin therapy. Contrariwise, there were no significant changes in all conventional carotid elasticity metrics and intima-media thickness. When stratifying patients into two subgroups by 10 year atherosclerotic cardiovascular disease (ASCVD) risk, speckle-tracking-derived circumferential CAS and beta2 improved significantly only in patients with ASCVD risk $\geq 7.5\%$. CONCLUSIONS: Short-term treatment with high-dose pitavastatin improved carotid artery elasticity measured by speckle-tracking method, but not conventional parameters by B-mode ultrasound. Speckle-tracking-based measurements may allow the early noninvasive assessment of statin effects on vascular function in hypercholesterolemic patients.

[34] *Dobrzynski JM, Kostis JB, Sargsyan D et al. Effect of cholesterol lowering with statins or proprotein convertase subtilisin/kexin type 9 antibodies on cataracts: A meta-analysis.*

Journal of clinical lipidology 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29501393>

ABSTRACT

BACKGROUND: It is not known whether statins or proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies are associated with cataract and whether very low achieved low-density lipoprotein cholesterol (LDL-C) lowering may cause cataract. OBJECTIVE: To examine two questions: whether statins and/or PCSK9 antibodies cause or prevent cataracts and whether very low LDL-C is associated with increased risk of cataract. METHODS: Systematic searches of PubMed, ClinicalTrials.gov, Web of Science, The Cochrane Library, and an Federal Drug Administration report were used to perform random effects meta-analyses on the relationship of statins and/or PCSK9 antibodies with cataract. These meta-analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. RESULTS: Prespecified analyses indicated no significant effect of statins or PCSK9 antibodies (odds ratio [OR] 0.99, 95% confidence interval [CI] 0.83-1.17, $P = .8889$) or differences between the effects of statins (OR 0.89, 95% CI 0.66-1.19, $P = .4349$) and PCSK9 antibodies (OR 1.04, 95% CI 0.85-1.28, $P = .7042$) on the development of cataract. Also, there was no significant effect of LDL-C lowering to different levels with respect to cataract (OR 1.06, 95% CI 0.92-1.22, $P = .4317$). Meta-regression of the log OR for cataract vs LDL-C during treatment did not show a statistically significant relationship (P for slope = .3972). CONCLUSION: There was no significant effect of cholesterol lowering with statins or PCSK9 antibodies or differences between these two medication classes in causing or preventing cataracts. However, it is difficult to make definitive statements regarding PCSK9 antibodies because there is no long-term experience with these agents. Very low LDL-C was not associated with higher risk of cataract.

[35] *Yanai H, Masui Y, Katsuyama H et al. An Improvement of Cardiovascular Risk Factors by Omega-3 Polyunsaturated Fatty Acids.* *Journal of clinical medicine research* 2018; 10:281-289.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29511415>

ABSTRACT

An epidemiological survey in the Northwest Greenland reported that the Greenlanders have a lower frequency of acute myocardial infarction and diabetes mellitus. The very low incidence of ischemic heart disease in the Greenlanders was explained by consumption of a diet rich in

Literature update week 10 (2018)

omega-3 polyunsaturated fatty acids (PUFAs). Possible anti-atherothrombotic effects of omega-3 PUFA include an improvement of lipid metabolism such as a reduction of triglyceride and an increase of high-density lipoprotein-cholesterol (HDL-C), and glucose metabolism, anti-platelet activity, anti-inflammatory effects, an improvement of endothelial function and stabilization of atherosclerotic plaque. The present study reviews an improvement of cardiovascular risk factors such as dyslipidemia and diabetes due to consumption of omega-3 PUFA. A sufficient number of studies suggest that omega-3 PUFA supplementation reduces serum triglyceride and increases HDL-cholesterol. The mechanisms for omega-3 PUFA-mediated improvements of lipid metabolism have been partially elucidated. The studies using experimental animals, part of trials in humans, have shown the beneficial effects of omega-3 PUFA on glucose metabolism and insulin sensitivity. The meta-analysis showed that omega-3 PUFA might prevent development of diabetes in part of population. Further studies should be performed to elucidate the association of omega-3 PUFA supplementation with diabetes, in the future.

[36] *Mutemberezi V, Buisseret B, Masquelier J et al. Oxysterol levels and metabolism in the course of neuroinflammation: insights from in vitro and in vivo models. Journal of neuroinflammation* 2018; 15:74.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29523207>

ABSTRACT

BACKGROUND: Oxysterols are cholesterol derivatives that have been suggested to play a role in inflammatory diseases such as obesity, atherosclerosis, or neuroinflammatory diseases. However, the effect of neuroinflammation on oxysterol levels has only been partially studied so far. **METHODS:** We used an HPLC-MS method to quantify over ten oxysterols both in in vitro and in vivo models of neuroinflammation. In the same models, we used RT-qPCR to analyze the expression of the enzymes responsible for oxysterol metabolism. Using the BV2 microglial cell line, we explored the effect of lipopolysaccharide (LPS)-induced (M1-type) and IL-4-induced (M2-type) cell activation on oxysterol levels. We also used LPS-activated co-cultures of mouse primary microglia and astrocytes. In vivo, we induced a neuroinflammation by administering LPS to mice. Finally, we used a mouse model of multiple sclerosis, namely the experimental autoimmune encephalomyelitis (EAE) model, that is characterized by demyelination and neuroinflammation. **RESULTS:** In vitro, we found that LPS activation induces profound alterations in oxysterol levels. Interestingly, we could discriminate between control and LPS-activated cells based on the changes in oxysterol levels both in BV2 cells and in the primary co-culture of glial cells. In vivo, the changes in oxysterol levels were less marked than in vitro. However, we found in both models increased levels of the GPR183 agonist 7 α ,25-dihydroxycholesterol. Furthermore, we studied in vitro the effect of 14 oxysterols on the mRNA expression of inflammatory markers in LPS-activated co-culture of microglia and astrocytes. We found that several oxysterols decreased the LPS-induced expression of pro-inflammatory markers. **CONCLUSIONS:** These data demonstrate that inflammation profoundly affects oxysterol levels and that oxysterols can modulate glial cell activation. This further supports the interest of a large screening of oxysterol levels when studying the interplay between neuroinflammation and bioactive lipids.

Literature update week 10 (2018)

[37] *Tabeta K, Hosojima M, Nakajima M et al. Increased serum PCSK9, a potential biomarker to screen for periodontitis, and decreased total bilirubin associated with probing depth in a Japanese community survey. Journal of periodontal research* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29516504>

ABSTRACT

BACKGROUND AND OBJECTIVES: Previous reports suggest that several serum biomarkers play roles in the pathogenesis, inflammatory response, and oxidative stress in periodontitis caused by bacterial infections, linking chronic periodontitis to atherosclerotic vascular disease (ASVD). The aim of this preliminary study was to investigate, in a Japanese cross-sectional community survey, potential serum biomarkers of periodontitis that are associated with ASVD and chronic periodontitis. **MATERIAL AND METHODS:** The study cohort included a total of 108 male subjects who underwent annual health examinations. Serum biomarkers (high-sensitivity C-reactive protein [hs-CRP], proprotein convertase subtilisin/kexin type 9 [PCSK9], interleukin-6, tumor necrosis factor- α , soluble CD14, myeloperoxidase, matrix metalloproteinase-3, adiponectin, total bilirubin [TBIL], and serum lipids) were analyzed to determine their association (if any) with periodontal parameters. Aortic stiffness was evaluated using the brachial-ankle aortic pulse wave velocity (PWV) index and the cardio-ankle vascular index (CAVI). **RESULTS:** The concentrations of PCSK9 and hs-CRP were increased ($P = .001$ and $.042$, respectively), and the concentration of TBIL was decreased ($P = .046$), in subjects with periodontal disease (determined as a probing depth of ≥ 4 mm in at least one site) compared with periodontally healthy subjects. The ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol and the concentrations of triglycerides, remnant-like particles-cholesterol, and oxidized LDL were elevated in subjects with periodontal disease compared with periodontally healthy subjects ($P = .038$, $.007$, $.002$, and $.049$, respectively). Multivariate regression analyses indicated that the number of sites with a pocket depth of ≥ 4 mm was associated with the concentration of PCSK9 and inversely associated with the concentration of TBIL independently (standardized beta = $.243$, $P = .040$; standardized beta = $-.443$, $P = .0002$; respectively). Analysis of receiver operating characteristic curves of PCSK9 indicated moderate accuracy for predicting the presence of disease sites (probing depth ≥ 4 mm) (area under the curve = 0.740). No significance in the values of PWV and CAVI was observed between subjects with periodontal disease and periodontally healthy subjects. **CONCLUSION:** In Japanese male subjects, the concentrations of serum PCSK9 and TBIL were correlated with periodontal parameters. Moreover, PCSK9 could be a candidate biomarker for diagnosing chronic periodontitis, and may also have potential to evaluate the risk for periodontitis to cause ASVD. Longitudinal studies of larger populations are necessary to confirm the exact association of periodontitis with increased serum PCSK9 and decreased TBIL.

[38] *Shen Z, Li S, Sheng B et al. The role of atorvastatin in suppressing tumor growth of uterine fibroids. Journal of translational medicine* 2018; 16:53.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29523174>

ABSTRACT

BACKGROUND: Medical therapeutic options remain quite limited for uterine fibroids treatment. Statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, have anti-tumoral effects on multiple cancer types, however, little is known about their effects on uterine

Literature update week 10 (2018)

fibroids. **METHODS:** Initially, we conducted a retrospective study of 120 patients with uterine fibroids and hyperlipidemia from the Second Affiliated Hospital of Wenzhou Medical University. Then, we evaluated the effect of atorvastatin on proliferation and apoptosis both in immortalized uterine fibroids cells and primary uterine fibroids cells. Furthermore, the molecular mechanism by which atorvastatin suppressed uterine fibroids cell growth was explored. **RESULTS:** Our results showed that atorvastatin use for 1 or 2 years significantly suppressed growth of uterine fibroids. Atorvastatin inhibited the proliferation of immortalized and primary uterine fibroids cells in a dose and time-dependent manner and stimulated apoptosis of uterine fibroids cells by inducing caspase-3 activation, up-regulating Bim and down-regulating Bcl-2. Additionally, atorvastatin treatment suppressed phosphorylation of ERK1/2 and JNK. Furthermore, GGPP, a downstream lipid isoprenoid intermediate, significantly rescued the effect of atorvastatin. **CONCLUSIONS:** These results suggest that atorvastatin exerts anti-tumoral effects on uterine fibroids through inhibition of cell proliferation and induction of apoptosis in HMG-CoA-dependent pathway. Our results provide the first clinical and preclinical data on the use of atorvastatin as a promising nonsurgical treatment option for uterine fibroids.

[39] *Hwang AR, Nam JO, Kang YJ. Fluvastatin inhibits advanced glycation end products-induced proliferation, migration, and extracellular matrix accumulation in vascular smooth muscle cells by targeting connective tissue growth factor. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology* 2018; 22:193-201.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29520172>

ABSTRACT

Connective tissue growth factor (CTGF) is a novel fibrotic mediator, which is considered to mediate fibrosis through extracellular matrix (ECM) synthesis in diabetic cardiovascular complications. Statins have significant immunomodulatory effects and reduce vascular injury. We therefore examined whether fluvastatin has anti-fibrotic effects in vascular smooth muscle cells (VSMCs) and elucidated its putative transduction signals. We show that advanced glycation end products (AGEs) stimulated CTGF mRNA and protein expression in a time-dependent manner. AGE-induced CTGF expression was mediated via ERK1/2, JNK, and Egr-1 pathways, but not p38; consequently, cell proliferation and migration and ECM accumulation were regulated by CTGF signaling pathway. AGE-stimulated VSMC proliferation, migration, and ECM accumulation were blocked by fluvastatin. However, the inhibitory effect of fluvastatin was restored by administration of CTGF recombinant protein. AGE-induced VSMC proliferation was dependent on cell cycle arrest, thereby increasing G1/G0 phase. Fluvastatin repressed cell cycle regulatory genes cyclin D1 and Cdk4 and augmented cyclin-dependent kinase inhibitors p27 and p21 in AGE-induced VSMCs. Taken together, fluvastatin suppressed AGE-induced VSMC proliferation, migration, and ECM accumulation by targeting CTGF signaling mechanism. These findings might be evidence for CTGF as a potential therapeutic target in diabetic vasculature complication.

[40] *Agus A, Phair G, Page VJ, McAuley DF. Simvastatin for the prevention and treatment of delirium in critically ill, mechanically ventilated patients (MoDUS): a cost-effectiveness analysis. The lancet. Respiratory medicine* 2018; 6:e9-e10.

Literature update week 10 (2018)

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29508709>

ABSTRACT

[41] *Affane F, Louala S, El Imane Harrat N et al. Hypolipidemic, antioxidant and antiatherogenic property of sardine by-products proteins in high-fat diet induced obese rats. Life sciences 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29505784>

ABSTRACT

AIMS: Fish by-products valorization on account of their richness in bioactive compounds may represent a better alternative to marine products with a view to economic profitability and sustainable development. In this study, we compared the effect of sardine by-product proteins (SBy-P), with those of the fillets (SF-P) or casein (Cas), on growth parameters, serum leptin level, lipids disorders, lipid peroxidation and reverse cholesterol transport, in diet-induced obese rats. MAIN METHODS: Obesity was induced by feeding rats a high-fat diet (20% sheep fat), during 12 weeks. At body weight (BW) of 400±20g, eighteen obese rats were divided into three homogenous groups and continue to consume the high-fat diet for 4 weeks containing either, 20% SBy-P, SF-P or Cas. KEY FINDINGS: The results showed that SBy-P, compared to SF-P and Cas, efficiently reduced food intake (FI), BW gain and serum leptin level, and improved blood lipids levels and reverse cholesterol transport by reducing total cholesterol (TC), triacylglycerols (TG) and low-density lipoprotein cholesterol (LDL-HDL1-C) serum levels, increasing the level of high-density lipoprotein cholesterol (HDL2-C and HDL3-C), and enhancing lecithin: cholesterol acyltransferase (LCAT) activity. Furthermore, they attenuated lipid peroxidation by increasing atheroprotective activity of the paraoxonase-1 (PON-1). SIGNIFICANCE: Sardine by-product proteins due to their richness in certain essential amino acids, highlight weight-loss, lipid-lowering, antioxidant and anti-atherogenic potentials, contributing to the improvement of the complications associated with obesity.

[42] *Patel RV, Mistry BM, Syed R et al. Quercetin: A plant-derived polyphenol with tremendous cardioprotective effects. Mini reviews in medicinal chemistry 2018.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29512459>

ABSTRACT

Flavonoids are allocated among various vegetations and in foodstuffs; consequently, they represent an inevitable part of the diet. Historical and epidemiological proof recommend that diet plans loaded with flavonoids such as quercetin have positive health benefits, especially on the heart. Flavonoids have been proven to have potential action towards hypertension, inflammation, diabetes and vascular disease. Their results on LDL lowering, platelet aggregation and vasodilatation recommend an ability to expel the pathophysiology of atherosclerotic plaque formation. Searching for experimental evidence to validate the cardio protective effects of quercetin, we review here the detailed in vivo facts performed in recent years. Quercetin and its derivatives led to an enhancement in heart features, indicating the prospective for quercetin to be used therapeutically in the treatment of cardiac diseases. Several evidence-based studies suggest mechanisms to observe cardiovascular diseases such as aging effects, hypertension, angiotensin-converting enzyme activity and endothelial-dependent and independent functions. Different animal models involving human are used to elucidate the role of quercetin in

Literature update week 10 (2018)

cardiovascular diseases in vivo. The role of quercetin and its derivatives may go beyond their existence in food and has potential a lead molecule in drug development programs.

[43] Jin H, Yan C, Xiao T et al. **High fish oil diet promotes liver inflammation and activates the complement system.** Molecular medicine reports 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29512716>

ABSTRACT

Diets rich in n-3 polyunsaturated fatty acid (n-3 PUFA) fish oil (FO) have beneficial effects in obesity-associated metabolic disease. However, contradictory roles in inflammatory disease intervention have been reported. Our previous work revealed that a highFO diet promoted myeloid cell differentiation by modifying the bone marrow microenvironment; however, its effects on liver inflammation and complement system activation remain unknown. By performing ELISA, reverse transcription quantitative polymerase chain reaction, flow cytometry and histology on mice fed with highFO and lowfat diets, the present study demonstrated that a 4week highFO diet promoted liver inflammation in mice without affecting body or liver weight. The livers of highFO diet mice exhibited increased infiltration of T cells and CD11b⁺ Gr1⁺ myeloid cells. Additionally, a higher level of IL1 β and MCP1 mRNA expression was detected, suggesting that the highFO diet promoted liver inflammation. Further experiments indicated that the highFO diet increased the total hemolytic complement activity (CH50), promoted the production of the membrane attack complex and increased the levels of various complement proteins in vivo, including complement components C3, C4b, C1qb and factor B. Furthermore, higher concentrations of triglyceride were detected in the peripheral blood of highFO diet mice, indicating the potential protective roles of n3 PUFAs in FO against lipotoxicity in hyperlipidemia. Collectively, the present study demonstrated that high FO intake induced inflammation and activated the complement system in the liver. However, further study is required to determine the exact mechanisms.

[44] Scolaro B, Nogueira MS, Paiva A et al. **Statin dose reduction with complementary diet therapy: A pilot study of personalized medicine.** Molecular metabolism 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29503145>

ABSTRACT

OBJECTIVE: Statin intolerance, whether real or perceived, is a growing issue in clinical practice. Our aim was to evaluate the effects of reduced-dose statin therapy complemented with nutraceuticals. METHODS: First phase: Initially, 53 type 2 diabetic statin-treated patients received a supplementation with fish oil (1.7 g EPA + DHA/day), chocolate containing plant sterols (2.2 g/day), and green tea (two sachets/day) for 6 weeks. Second phase: "Good responders" to supplementation were identified after multivariate analysis (n = 10), and recruited for a pilot protocol of statin dose reduction. "Good responders" were then provided with supplementation for 12 weeks: standard statin therapy was kept during the first 6 weeks and reduced by 50% from weeks 6-12. RESULTS: First phase: After 6 weeks of supplementation, plasma LDL-C (-13.7% +/- 3.7, P = .002) and C-reactive protein (-35.5% +/- 5.9, P = .03) were reduced. Analysis of lathosterol and campesterol in plasma suggested that intensity of LDL-C reduction was influenced by cholesterol absorption rate rather than its synthesis. Second phase: no difference was observed for plasma lipids, inflammation, cholesterol efflux capacity,

Literature update week 10 (2018)

or HDL particles after statin dose reduction when compared to standard therapy.

CONCLUSIONS: Although limited by the small sample size, our study demonstrates the potential for a new therapeutic approach combining lower statin dose and specific dietary compounds. Further studies should elucidate "good responders" profile as a tool for personalized medicine. This may be particularly helpful in the many patients with or at risk for CVD who cannot tolerate high dose statin therapy. **TRIAL REGISTRATION:** ClinicalTrials.gov, NCT02732223.

[45] *Hoffmann TJ, Theusch E, Haldar T et al. A large electronic-health-record-based genome-wide study of serum lipids. Nature genetics* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29507422>

ABSTRACT

A genome-wide association study (GWAS) of 94,674 ancestrally diverse Kaiser Permanente members using 478,866 longitudinal electronic health record (EHR)-derived measurements for untreated serum lipid levels empowered multiple new findings: 121 new SNP associations (46 primary, 15 conditional, and 60 in meta-analysis with Global Lipids Genetic Consortium data); an increase of 33-42% in variance explained with multiple measurements; sex differences in genetic impact (greater impact in females for LDL, HDL, and total cholesterol and the opposite for triglycerides); differences in variance explained among non-Hispanic whites, Latinos, African Americans, and East Asians; genetic dominance and epistatic interaction, with strong evidence for both at the ABO and FUT2 genes for LDL; and tissue-specific enrichment of GWAS-associated SNPs among liver, adipose, and pancreas eQTLs. Using EHR pharmacy data, both LDL and triglyceride genetic risk scores (477 SNPs) were strongly predictive of age at initiation of lipid-lowering treatment. These findings highlight the value of longitudinal EHRs for identifying new genetic features of cholesterol and lipoprotein metabolism with implications for lipid treatment and risk of coronary heart disease.

[46] *Tachtsis B, Camera D, Lacham-Kaplan O. Potential Roles of n-3 PUFAs during Skeletal Muscle Growth and Regeneration. Nutrients* 2018; 10.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29510597>

ABSTRACT

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), which are commonly found in fish oil supplements, are known to possess anti-inflammatory properties and more recently alter skeletal muscle function. In this review, we discuss novel findings related to how n-3 PUFAs modulate molecular signaling responsible for growth and hypertrophy as well as the activity of muscle stem cells. Muscle stem cells commonly known as satellite cells, are primarily responsible for driving the skeletal muscle repair process to potentially damaging stimuli, such as mechanical stress elicited by exercise contraction. To date, there is a paucity of human investigations related to the effects of n-3 PUFAs on satellite cell content and activity. Based on current in vitro investigations, this review focuses on novel mechanisms linking n-3 PUFA's to satellite cell activity and how they may improve muscle repair. Understanding the role of n-3 PUFAs during muscle growth and regeneration in association with exercise could lead to the development of novel supplementation strategies that increase muscle mass and strength, therefore possibly reducing the burden of muscle wasting with age.

Literature update week 10 (2018)

[47] Wang H, Zhu C, Ying Y *et al.* **Metformin and berberine, two versatile drugs in treatment of common metabolic diseases.** *Oncotarget* 2018; 9:10135-10146.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29515798>

ABSTRACT

Metformin has been used as a glucose lowering drug for several centuries and is now a first-line drug for type 2 diabetes mellitus (T2DM). Since the discovery that it activates AMP-activated protein kinase (AMPK) and reduces risk of cancer, metformin has drawn great attentions. Another drug, berberine, extracted from berberis vulgaris L. (root), was an ancient herbal medicine in treating diarrhea. Ongoing experimental and clinical studies have illuminated great potential of berberine in regulation of glucose and lipid homeostasis, cancer growth and inflammation. Furthermore, the lipid lowering effect of berberine is comparable to those conventional lipid drugs but with low toxicity. Therefore, it is right time to transform beneficial effects of berberine into therapeutic practice. Metformin and berberine share many features in actions despite different structure and both could be excellent drugs in treating T2DM, obesity, cardiac diseases, tumour, as well as inflammation. Since these disorders are often connected and comprise common pathogenic factors that could be targeted by the two drugs, understanding their actions can give us rationale for expansion of their clinical uses.

[48] Xu D, Hu J, Wu Q *et al.* **Efficacy and safety of Zhibitai in combination with atorvastatin for lipid lowering in patients with coronary heart disease.** *Oncotarget* 2018; 9:9489-9497.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29507705>

ABSTRACT

Background: Zhibitai, a natural lipid-lowering Chinese medicine, is well tolerated in patients and has low incidence of adverse events. In this study, we evaluated the efficacy, safety, and side effects of Zhibitai in combination with low dose Atorvastatin compared to high dose Atorvastatin in patients with coronary heart disease or at high risk of coronary heart disease. **Methods:** This was a randomized, double-blind, multi-center clinical trial on 720 patients with coronary heart disease or at high risk of coronary heart disease. The patients were randomly assigned to a Zhibitai-Atorvastatin group (480 mg Zhibitai twice daily plus 10 mg atorvastatin once daily) or Monotherapy group (40 mg Atorvastatin once daily). Blood samples were obtained at baseline, week 4, and week 8 after a minimum 8-hour fast. Efficacy was evaluated in terms of the changes in the following parameters: lipoprotein profiles [total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)]. Safety was assessed throughout the study by clinical laboratory tests including liver function [alanine transaminase, aspartate transaminase] and renal function [blood urea nitrogen], and creatine kinase; physical examination; and adverse events monitoring. **Results:** TC, TG, LDL-C levels were significantly decreased and HDL-C levels were significantly increased at week 4 and week 8 (all $P < 0.05$) in both groups but had no significant differences between the two groups ($P > 0.05$). In subgroup analyses, Zhibitai-Atorvastatin Group produced significantly greater reduction in TG compared with Monotherapy Group at week 8 in patients with $TG > 203.72\text{mg/dL}$ ($P < 0.01$). Among patients with $LDL-C$ levels $> 131.48\text{mg/dL}$, Zhibitai-Atorvastatin Group produced a greater reduction of LDL-C levels compared with the Monotherapy Group at week 4 ($P < 0.05$). The incidence of liver dysfunction, headache, or gastrointestinal intolerance was significantly lower in the Zhibitai-Atorvastatin Group compared

Literature update week 10 (2018)

with Monotherapy Group during the 8-week study period ($P < 0.001$). There were no significant differences in renal function, myopathy, and other adverse events between the groups. Conclusion: Overall the two groups have similar lipid regulation efficacy. Zhibitai plus low dose Atorvastatin is more efficacious in lowering TG in patients with TG > 203.72 mg/dL at week 8. There are fewer side effects in Zhibitai plus low dose Atorvastatin group. Long term follow up is required to evaluate cardiovascular outcomes.

[49] Klaus G, Taylan C, Buscher R et al. **Multimodal lipid-lowering treatment in pediatric patients with homozygous familial hypercholesterolemia-target attainment requires further increase of intensity.** *Pediatric nephrology (Berlin, Germany)* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29502162>

ABSTRACT

BACKGROUND: Familial hypercholesterolemia (FH) causes premature cardiovascular disease (CVD). Lipoprotein apheresis (LA) is recommended as first-line lipid-lowering treatment (LLT) for homozygous (ho) FH. **METHODS:** Efficacy of multimodal LLT including lifestyle counseling, drug treatment, and LA was analyzed in 17 pediatric hoFH or compound heterozygous (c-het) FH patients, who commenced chronic LA in Germany before the age of 18. **RESULTS:** At time of diagnosis, mean low-density lipoprotein cholesterol (LDL-C) concentration was 19.6 mmol/l (756 mg/dl). Multimodal LLT resulted in 73% reduction of mean LDL-C concentration including a 62% contribution of LA. Only three children (18%) achieved mean LDL-C concentrations below the recommended pediatric target of 3.5 mmol/l (135 mg/dl). In 13 patients (76%) during chronic LA, neither cardiovascular events occurred nor was CVD progression detected clinically or by routine imaging techniques. In four patients (24%), cardiovascular events documented progression of CVD despite weekly LA, including one death due to coronary and cerebrovascular CVD which was not stabilized after commencing LA. Based on the mutational status, only 6 out of the 17 children were candidates for proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibition. Two already responded with further LDL-C decrease by 40%. **CONCLUSIONS:** Next to drug therapy, regular LA is an essential component of LLT for approaching LDL-C targets in children with hoFH or c-hetFH, which was successful only in a minority of children. Progression of CVD morbidity and resulting mortality remain unresolved issues. Early and intensified multimodal LLT guided by risk factors beyond LDL-C concentration is needed to improve outcome.

[50] Mercado CI, Gregg E, Gillespie C, Loustalot F. **Trends in lipid profiles and descriptive characteristics of U.S. adults with and without diabetes and cholesterol-lowering medication use-National Health and Nutrition Examination Survey, 2003-2012, United States.** *PLoS one* 2018; 13:e0193756.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29509776>

ABSTRACT

BACKGROUND: With a cholesterol-lowering focus for diabetic adults and in the age of polypharmacy, it is important to understand how lipid profile levels differ among those with and without diabetes. **OBJECTIVE:** Investigate the means, differences, and trends in lipid profile measures [TC, total cholesterol; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; and TG, triglycerides] among US adults by diabetes status and cholesterol-lowering medication.

Literature update week 10 (2018)

METHODS: Population number and proportion of adults aged ≥ 21 years with diabetes and taking cholesterol-lowering medication were estimated using data on 10,384 participants from NHANES 2003-2012. Age-standardized means, trends, and differences in lipid profile measures were estimated by diabetes status and cholesterol medication use. For trends and differences, linear regression analysis were used adjusted for age, gender, and race/ethnicity. **RESULTS:** Among diabetic adults, 52% were taking cholesterol-lowering medication compared to the 14% taking cholesterol-lowering medication without diabetes. Although diabetic adults had significantly lower TC and LDL-c levels than non-diabetic adults [% difference (95% confidence interval): TC = -5.2% (-6.8 --3.5), LDL-c = -8.0% (-10.4 --5.5)], the percent difference was greater among adults taking cholesterol medication [TC = -8.0% (-10.3 --5.7); LDL-c = -13.7% (-17.1 --10.2)] than adults not taking cholesterol medication [TC = -3.5% (-5.2 --1.6); LDL-c = -4.3% (-7.1 --1.5)] (interaction p-value: TC = <0.001 ; LDL-c = <0.001). From 2003-2012, mean TC and HDL-c significantly decreased among diabetic adults taking cholesterol medication [% difference per survey cycle (p-value for linear trend): TC = -2.3% (0.003) and HDL-c = -2.3% (0.033)]. Mean TC, HDL-c, and LDL-c levels did not significantly change from 2003 to 2012 in non-diabetic adults taking cholesterol medication or for adults not taking cholesterol medications. **CONCLUSIONS:** Diabetic adults were more likely to have lower lipid levels, except for triglyceride levels, than non-diabetic adults with profound differences when considering cholesterol medication use, possibly due to the positive effects from clinical diabetes management.

[51] *Kotlega D, Stolarczyk J, Karpowicz A et al. Protective properties of HDL cholesterol and atherosclerotic plaque calcifications in advanced atherosclerosis in ischaemic stroke patients. Pomeranian journal of life sciences 2015; 61:378-382.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29522305>

ABSTRACT

Introduction: Atherosclerotic changes in carotid arteries play an important role in the pathogenesis of ischaemic stroke. To a high extent there is evident asymmetry within the development of these changes, affecting just one artery. The aim of the study was to determine the impact of the cardiovascular risk factors on the presence of haemodynamically significant atherosclerotic changes or occlusion only in one compared to both of the carotid arteries in patients with ischaemic stroke. **Material and methods:** Patients diagnosed with ischaemic stroke were retrospectively assessed towards stenosis of $\geq 70\%$ or occlusion in at least one of the internal or common carotid arteries. There were 104 patients enrolled in the study. Group I consisted of individuals with haemodynamically significant ($\geq 70\%$) stenosis or occlusion in one carotid artery (n = 48). Group II consisted of patients with bilateral significant ($\geq 70\%$) stenosis or occlusion in carotid arteries (n = 56). **Results:** There were no changes found in the presence of non-modifiable stroke risk factors between the groups. In group I higher HDL level (45.7 vs 38.9 mg/dL, p = 0.038) and significantly more frequent calcifications in the atherosclerotic plaques of carotid arteries were found (p = 0.03). There were no differences in other tested factors between groups. **Conclusions:** The protective properties of HDL cholesterol and the slow formation of more stable, calcified plaques play an important role only in the development of unilateral advanced atherosclerosis in carotid arteries. The role of HDL cholesterol in stroke pathomechanism needs further studies.

Literature update week 10 (2018)

[52] *Mendes de Cordova CM, de Santa Helena ET, Galgowski C et al. Evaluation of a new equation for LDL-c estimation and prediction of death by cardiovascular related events in a German population-based study cohort. Scandinavian journal of clinical and laboratory investigation* 2018:1-10.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29517392>

ABSTRACT

A simple equation established by Cordova & Cordova (LDL-COR) was developed to provide an improved estimation of LDL-cholesterol in a large Brazilian laboratory database. We evaluated this new equation in a general population cohort in Pomerania, north-eastern Germany (SHIP Study) compared to other existing formulas (Anandaraja, Teerakanchana, Chen, Hattori, Martin, Friedewald and Ahmadi), and its power in the prediction of death by atherosclerosis related events as the primary outcome. Analysis was conducted on a cohort of 4075 individuals considering age, gender, use of lipid lowering therapy and associated co-morbidities such as diabetes, hepatic, kidney and thyroid disease. LDL-COR values had a lower standard deviation compared to the previously published equations: 0.92 versus 1.02, 1.02, 1.03, 1.04, 1.09, 1.10 and 1.74 mmol/L, respectively. All of the factors known to affect the results obtained by the Friedewald's equation (LDL-FW), except fibrate use, were associated with the difference between LDL-COR and LDL-FW ($p < .01$), with TSH being borderline ($p = .06$). LDL-COR determined a higher hazard ratio (1.23 versus 1.12, 1.19, 1.21, 1.19, 1.21 and 1.19) for cardiovascular disease related mortality, incident stroke or myocardial infarction compared to the other evaluated formulas, except for Ahmadi's (1.24), and the same adjusted predictive power considering all confounding factors. The proposed simple equation was demonstrated to be suitable for a more precise LDL-c estimation in the studied population. Since LDL-c is a parameter frequently requested by medical laboratories in clinical routine, and will probably remain so, precise methods for its estimation are needed when direct measurement is not available.

[53] *Kundel V, Trivieri MG, Karakatsanis NA et al. Assessment of atherosclerotic plaque activity in patients with sleep apnea using hybrid positron emission tomography/magnetic resonance imaging (PET/MRI): a feasibility study. Sleep & breathing = Schlaf & Atmung* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29508121>

ABSTRACT

PURPOSE: Evidence suggests that the inflammatory state of an atherosclerotic plaque is important in predicting future risk of plaque rupture. This study aims to investigate the feasibility of measuring plaque inflammation in patients with obstructive sleep apnea (OSA) utilizing advanced vascular imaging - hybrid positron-emission tomography/magnetic resonance imaging (PET/MRI) with fluorodeoxyglucose (FDG) tracer-before and after continuous positive airway pressure (CPAP). **METHODS:** Patients with newly diagnosed moderate to severe OSA underwent baseline PET/MRI for assessment of vascular inflammation of the carotid arteries and thoracic aorta prior to initiation of CPAP. Those adherent to CPAP returned for repeat imaging after 3-6 months of CPAP use. Atherosclerotic plaque activity, as measured by arterial wall FDG uptake, was calculated using target-to-background ratios (TBR) before and after CPAP. **RESULTS:** Five patients were recruited as part of a focused project. Mean age was 52 years (80% male), and mean apnea-hypopnea index (AHI) was 33. Three patients were objectively adherent

Literature update week 10 (2018)

with CPAP. In the pre-CPAP phase, all patients had focal FDG uptake in the carotid arteries and aorta. After CPAP, there was an average reduction in TBR of 5.5% (TBRmean) and 6.2% (TBRmax) in carotid and aortic plaque inflammation, similar in magnitude to the reduction observed with statin therapy alone in non-OSA patients (previously reported by others). CONCLUSIONS: We demonstrate the feasibility of using hybrid PET/MRI to assess atherosclerotic plaque inflammation in patients with OSA before and after CPAP. Use of the vascular PET/MRI platform in patients with OSA may provide better insight into the role of OSA and its treatment in reducing atherosclerotic inflammation.

[54] *Hosomi N, Kitagawa K, Nagai Y et al. Desirable Low-Density Lipoprotein Cholesterol Levels for Preventing Stroke Recurrence: A Post Hoc Analysis of J-STARS Study (Japan Statin Treatment Against Recurrent Stroke). Stroke* 2018.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29511130>

ABSTRACT

BACKGROUND AND PURPOSE: To define desirable target low-density lipoprotein (LDL) cholesterol levels for the prevention of stroke recurrence, a post hoc analysis was performed in the J-STARS study (Japan Statin Treatment Against Recurrent Stroke). METHODS: Subjects (n=1578) were divided into groups based on mean value of postrandomized LDL cholesterol levels until the last observation in 20 mg/dL increments. Adjusted hazard ratios (HRs) and 95% confidence intervals were analyzed for each group, with adjustments for baseline LDL cholesterol, baseline body mass index, hypertension, diabetes mellitus, and statin usage. RESULTS: The postrandomized LDL cholesterol level until the last observation were 104.1+/-19.3 mg/dL in the pravastatin group and 126.1+/-20.6 mg/dL in the control group. The adjusted HRs for stroke and transient ischemic attack and all vascular events decreased in the postrandomized LDL cholesterol level of 80 to 100 mg/dL (P=0.23 and 0.25 for the trend, respectively). The adjusted HR for atherothrombotic infarction significantly reduced with the usage of statin after adjusting baseline LDL cholesterol levels (HR, 0.39; 95% confidence intervals, 0.19-0.83). The adjusted HR for atherothrombotic infarction and intracranial hemorrhage were similar among the postrandomized LDL-cholesterol-level subgroups (P=0.50 and 0.37 for the trend, respectively). The adjusted HR for lacunar infarction decreased in the postrandomized LDL cholesterol level of 100 to 120 mg/dL (HR, 0.45; 95% confidence intervals, 0.20-0.99; P=0.41 for the trend). CONCLUSIONS: The composite risk of stroke and transient ischemic attack reduced in the postrandomized LDL cholesterol level of 80 to 100 mg/dL after adjusting for statin usage. CLINICAL TRIAL REGISTRATION: URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00221104.

[55] *Wangqin R, Wang X, Wang Y et al. Risk factors associated with 90-day recurrent stroke in patients on dual antiplatelet therapy for minor stroke or high-risk TIA: a subgroup analysis of the CHANCE trial. Stroke and vascular neurology* 2017; 2:176-183.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=29507777>

ABSTRACT

Objective: Many patients receiving dual antiplatelet therapy still had recurrent strokes. We aimed to identify factors associated with recurrent stroke at 90 days in patients receiving dual antiplatelet therapy in Clopidogrel in High-risk patients with Acute Non-disabling

Literature update week 10 (2018)

Cerebrovascular Events trial. Methods: Patients with transient ischaemic attack or minor stroke receiving clopidogrel and aspirin in the trial were analysed in the study. The primary outcome was recurrent stroke within 90 days after the index event. Cox proportional hazard model with backward selection was used to identify factors associated with stroke. Results: Among 2584 patients, 212 (8.2%) had a recurrent stroke, 216 (8.4%) had a composite of stroke, myocardial infarction, or vascular death and 204 (7.9%) had ischaemic stroke within 90 days. Multivariate analysis identified the following factors associated with stroke: history of hypertension with poor blood pressure control (HR, 1.92; 95% CI 1.22 to 3.03), the high baseline National Institute of Health Stroke Scale (NIHSS) score of 2 and 3 (2.12 (1.07 to 4.21) and 4.11 (2.05 to 8.22), respectively), time from onset to randomisation of <12 hours (1.47 (1.12 to 1.94)), the lipid-lowering therapy (0.61 (0.47 to 0.83)), the open-label aspirin dose at day 1 of ≥ 300 mg (1.98 (1.45 to 2.69)). Intracranial arterial stenosis (ICAS) was significantly associated with stroke in the sensitivity analysis (2.17 (1.16 to 4.04)). Conclusions: The high baseline NIHSS score, hypertension with poor blood pressure control, ICAS, time from onset to randomisation of less than 12 hours and no lipid-lowering therapy were associated with stroke, suggesting that patients with identified predictors still remain to be at high risk of recurrent stroke although being under the dual antiplatelet therapy. Trial registration number: <http://clinicaltrials.gov/show/NCT00979589>. ClinicalTrials.gov number: NCT00979589.