Literature update week 03 (2019)

[1] *Huang J, Jiao S, Zhao X et al.* **Characteristics of patients with enhancing intracranial atherosclerosis and association between plaque enhancement and recent cerebrovascular ischemic events: a high-resolution magnetic resonance imaging study**. Acta radiologica (Stockholm, Sweden : 1987) 2019:284185118822645.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30650984
ABSTRACT
BACKGROUND: Atherosclerotic plaque inflammation is a well-known risk factor for the development of ischemic stroke. PURPOSE: To investigate the characteristics of patients with enhancing intracranial atherosclerosis and the relationship between plaque enhancement and recent cerebrovascular ischemic events by using high-resolution magnetic resonance imaging (HR-MRI). MATERIAL AND METHODS: A total of 141 patients (102 men; mean age = 61.1 +/- 11.4 years) with intracranial atherosclerotic plaque who underwent HR-MRI were enrolled in this study. The contrast ratio (CR) and contrast enhancement of the plaques were measured. Binary logistic regression was used to estimate the association between plaque enhancement and clinical and plaque characteristics. The relationship between plaque enhancement and recent ischemic events was evaluated by multivariate logistic regression analysis. RESULTS: Of 141 patients, plaque enhancement was detected in 80 (56.7%). Compared to patients without plaque enhancement, those with plaque enhancement had significantly lower level of high-density lipoprotein cholesterol, greater maximum plaque length, and more severe luminal stenosis. Luminal stenosis was independently associated with plaque enhancement (odds ratio [OR] = 1.026; 95% confidence interval [CI] = 1.014-1.039). Multivariate regression analysis showed that plaque enhancement was an independent indicator for recent ischemic events after adjusting for confounding factors (OR = 9.521; 95% CI = 4.301-19.900) (all P < 0.05). CONCLUSION: Luminal stenosis is independently associated with plaque enhancement. We observed a strong association between plaque enhancement and recent ischemic events, which suggests that plaque enhancement may serve as an indicator of its instability.

[2] *Einarsen E, Saeed S, Cramariuc D et al.* **Impact of Obesity on Persistent Left Ventricular Hypertrophy After Aortic Valve Replacement for Aortic Stenosis**. The American journal of cardiology 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30654925
ABSTRACT
Normalization of left ventricular (LV) hypertrophy is expected after successful aortic valve replacement (AVR) in patients with aortic valve stenosis (AS), but is not always observed. We tested the impact of body mass index (BMI) >/=30 kg/m(2) on persistent post-AVR LV hypertrophy. In the present subanalysis of Simvastatin Ezetimibe in Aortic Stenosis study, clinical and echocardiographic data of 399 patients with severe AS who underwent surgical AVR were analyzed. All patients had a standardized pre- and post-AVR echocardiogram. Patients were grouped by BMI categories into BMI <25 kg/m(2), BMI 25 to 29.9 kg/m(2), and BMI >/=30 kg/m(2). LV hypertrophy was defined as LV mass/height(2.7) >49.2 g/m(2.7) in men and >46.7 g/m(2.7) in women. Predictors of persistent LV hypertrophy after AVR were identified in logistic regression analysis. After a median follow-up of 196 days after AVR, LV hypertrophy was more prevalent in patients with BMI >/=30 kg/m(2) compared with those with BMI 25 to 29.9 kg/m(2) and those patients with BMI <25 kg/m(2) (71% vs 47% and 37%, p <0.01). BMI >/=30 kg/m(2)

patients also remained with lower LV midwall shortening post-AVR compared with patients with normal weight (p <0.01), independent of patient prosthesis mismatch. In multivariable logistic regression analysis, the presence of BMI >/=30 kg/m(2) before AVR was associated with an almost fourfold higher prevalence of post-AVR LV hypertrophy independent of significant associations with higher systolic blood pressure and lower LV midwall shortening preoperatively (odds ratio 3.75 [95% confidence interval 2.04 to 6.91], p <0.001). In conclusion, the presence of BMI >/=30 kg/m(2) before AVR in patients with severe AS was strongly and independently associated with persistent post-AVR LV hypertrophy.

[3] *Xu W, Wang X, Jin J et al.* **Inhibition of GGPPS1 attenuated LPS-induced acute lung injury and was associated with NLRP3 inflammasome suppression**. American journal of physiology. Lung cellular and molecular physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30652497
ABSTRACT
Inhibition of the mevalonate pathway using statins has been shown to be beneficial in the treatment of acute lung injury (ALI). Here, we investigated whether partial inhibition of this pathway by targeting Geranylgeranyl pyrophosphate synthase large subunit 1 (GGPPS1), a catalase downstream of the mevalonate pathway, was effective at treating lung inflammation in ALI. Lipopolysaccharide (LPS) was intra-tracheally instilled to induce ALI in lung specific GGPPS1 knockout and wild-type mice. Expression of GGPPS1 in lung tissues and alveolar epithelial cells was examined. The severity of lung injury and inflammation were determined in lung-specific GGPPS1 knockout and wild-type mice by measuring alveolar exudate, neutrophil infiltration, lung injury and cell death. Change in global gene expression in response to GGPPS1 depletion was measured using mRNA microarray and verified in vivo and in vitro. We found that GGPPS1 levels increased significantly in lung tissues and alveolar epithelial cells in LPS-induced ALI mice. Compared to wildtype and simvastatin treated mice, the specific deletion of pulmonary GGPPS1 attenuated the severity of lung injury by inhibiting apoptosis of AECs. Furthermore, deletion of GGPPS1 inhibited LPS-induced inflammasome activation, in terms of IL-1beta release and pyroptosis, by down-regulating NLRP3 expression. Finally, down-regulation of GGPPS1 reduced the membrane expression of Ras-related protein Rab10 and toll like receptor 4 (TLR4) and inhibited the phosphonation of IkappaB. This effect might be attributed to the downregulation of GGPP levels. Our results suggested that inhibition of pulmonary GGPPS1 attenuated LPS-induced ALI, predominantly by suppressing the NLRP3 inflammasome through Rab10-mediated TLR4 replenishment.

[4] *Nitz K, Lacy M, Atzler D*. **Amino Acids and Their Metabolism in Atherosclerosis**. Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118311572.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30650999
ABSTRACT
As a leading cause of death worldwide, cardiovascular disease is a global health concern. The development and progression of atherosclerosis, which ultimately gives rise to cardiovascular disease, has been causally linked to hypercholesterolemia. Mechanistically, the interplay between lipids and the immune system during plaque progression significantly contributes to the chronic inflammation seen in the arterial wall during atherosclerosis. Localized

inflammation and increased cell-to-cell interactions may influence polarization and proliferation of immune cells via changes in amino acid metabolism. Specifically, the amino acids l-arginine (Arg), l-homoarginine (hArg) and l-tryptophan (Trp) have been widely studied in the context of cardiovascular disease, and their metabolism has been established as key regulators of vascular homeostasis, as well as immune cell function. Cyclic effects between endothelial cells, innate, and adaptive immune cells exist during Arg and hArg, as well as Trp metabolism, that may have distinct effects on the development of atherosclerosis. In this review, we describe the current knowledge surrounding the metabolism, biological function, and clinical perspective of Arg, l-homoarginine, and Trp in the context of atherosclerosis.

[5] *Ackermann K, Bonaterra GA, Kinscherf R, Schwarz A*. **Growth differentiation factor-15 regulates oxLDL-induced lipid homeostasis and autophagy in human macrophages**. Atherosclerosis 2018; 281:128-136.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30658188
ABSTRACT
BACKGROUND AND AIMS: Growth differentiation factor-15 (GDF-15)/macrophage inhibitory cytokine-1 (MIC-1/GDF15) is associated with cardiovascular disease, inflammation and development of atherosclerosis and is highly expressed in macrophages (MPhi) of atherosclerotic lesions. Thus, we were interested in investigating the influence of GDF-15 in lipid homeostasis and autophagy in human MPhi during foam cell formation. METHODS AND RESULTS: Oxidized-low density lipoprotein (50mug/ml oxLDL), recombinant (r)GDF-15, transiently silenced GDF-15 (siGDF-15MPhi), as well as with negative siRNA transfected (nsiGDF-15MPhi) PMA-differentiated human THP-1 MPhi, were used to investigate the effects of GDF-15 on autophagic processes and lipid accumulation. Oil Red O staining revealed that rGDF-15 alone, but also in combination with oxLDL, significantly increased the lipid accumulation in THP-1 MPhi; a reverse effect was detected in siGDF-15MPhi. Western-blot analyses and confocal laser scanning microscopy showed an increase of Atg5, Atg12/Atg5 protein complex and p62 protein in THP-1 MPhi co-incubated with rGDF-15 and oxLDL, as well as an increase of p62 accumulation compared to rGDF-15-treated MPhi. Vice versa, siGDF-15MPhi showed a reduced p62 accumulation compared to nsiGDF-15MPhi. The present study indicates that GDF-15, especially in combination with oxLDL, regulates the expression of autophagy-relevant proteins (p62, Atg5 and Atg12/Atg5 protein complex) and p62 accumulation in human MPhi. CONCLUSIONS: GDF-15, in combination with oxLDL, impairs autophagic processes with consequences for lipid homeostasis in human MPhi, indicating its novel important pathophysiological role in atherosclerotic plaque development and progression.

[6] *Bijnen M, van de Gaar J, Vroomen M et al.* **Adipose tissue macrophages do not affect atherosclerosis development in mice**. Atherosclerosis 2018; 281:31-37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30654169
ABSTRACT
BACKGROUND AND AIMS: Obese individuals have a higher risk of developing atherosclerosis, possibly driven by adipose tissue (AT) inflammation. We recently showed that AT macrophages (ATMs), which accumulate in the expanding obese AT, produce mediators causing immune cell

recruitment from the bone marrow. In the current study, we evaluated whether ATMs are directly involved in atherosclerotic plaque development. METHODS: Lean ldlr(-/-) acceptor mice received visceral AT (vAT) from lean, obese, or ATM-depleted obese ldlr(-/-) mice. Acceptor mice were fed high cholesterol diet (HCD) for 4 weeks before and 8 weeks after AT transplantation to induce atherosclerosis. Atherosclerotic plaque development was studied 8 weeks after transplantation. RESULTS: Transplanting donor vAT from obese mice increased circulating triglycerides and B-cells, but decreased Ly6c(-) monocytes. Plasma cholesterol, Ly6c(+) monocytes, T-cells, NK-cells and eosinophils were unaffected. Depleting ATMs from obese AT using clodronate liposomes prior to vAT transplantation prevented the increase in triglycerides and B-cells and decrease in Ly6c(-) monocytes, but did increase eosinophils. Circulating Cxcl1 was reduced by obese AT transplantation and Ifn-gamma tended to be increased while Tnf and Il-1beta were unaffected. ATM-depleted obese AT transplantation also reduced Cxcl1, but increased circulating Tnf levels. However, obese AT transplantation with or without depletion of ATMs did not influence atherosclerotic plaque size, phenotype, or stability. CONCLUSIONS: ATMs from obese vAT do not affect atherosclerotic plaque development or phenotype.

[7] *Leopold C, Duta-Mare M, Sachdev V et al.* **Hepatocyte-specific lysosomal acid lipase deficiency protects mice from diet-induced obesity but promotes hepatic inflammation**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30639734
ABSTRACT
Lysosomal acid lipase (LAL) hydrolyzes cholesteryl esters (CE) and triglycerides (TG) to generate fatty acids (FA) and cholesterol. LAL deficiency (LAL-D) in both humans and mice leads to hepatomegaly, hypercholesterolemia, and shortened life span. Despite its essential role in lysosomal neutral lipid catabolism, the cell type-specific contribution of LAL to disease progression is still elusive. To investigate the role of LAL in the liver in more detail and to exclude the contribution of LAL in macrophages, we generated hepatocyte-specific LAL-deficient mice (Liv-Lipa(-/-)) and fed them either chow or high fat/high cholesterol diets (HF/HCD). Comparable to systemic LAL-D, Liv-Lipa(-/-) mice were resistant to diet-induced obesity independent of food intake, movement, and energy expenditure. Reduced body weight gain was mainly due to reduced white adipose tissue depots. Furthermore, Liv-Lipa(-/-) mice exhibited improved glucose clearance during glucose and insulin tolerance tests compared to control mice. Analysis of hepatic lipid content revealed a massive reduction of TG, whereas CE concentrations were markedly increased, leading to CE crystal formation in the livers of Liv-Lipa(-/-) mice. Elevated plasma transaminase activities, increased pro-inflammatory cytokines and chemokines as well as hepatic macrophage infiltration indicated liver inflammation. Our data provide evidence that hepatocyte-specific LAL deficiency is sufficient to alter whole-body lipid and energy homeostasis in mice. We conclude that hepatic LAL plays a pivotal role by preventing liver damage and maintaining lipid and energy homeostasis, especially during high lipid availability.

[8] *Takahashi T, Uno Y, Yamazaki H, Kume T*. **Functional characterization for polymorphic organic anion transporting polypeptides (OATP/SLCO1B1, 1B3, 2B1) of monkeys**

recombinantly expressed with various OATP probes. Biopharmaceutics & drug disposition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30652318
ABSTRACT
Hepatic uptake of clinical drugs mediated by human hepatic organic anion transporting polypeptides (OATP/SLCO) has been extensively reported. In this study, hepatic uptake by recombinantly expressed monkey OATP1B1, OATP1B3, and OATP2B1 was investigated using three human OATP1B1 and OATP1B3 substrates (pitavastatin, pravastatin, and rosuvastatin) and one OATP1B3 substrate (telmisartan), of which governmental drug interaction guidelines recommend, and 7 reported clinical drugs. Uptake of known human probes into recombinant OATP-expressing cells was significantly greater than that of mock cells. Consequently, pitavastatin, pravastatin, and rosuvastatin were suggested to be a substrate of recombinant monkey OATP1B1 and OATP1B3, and telmisartan was suggested to be a substrate of recombinant monkey OATP1B3, in a similar manner to human OATPs. In contrast, atorvastatin, bosentan, etoposide, fexofenadine, fluvastatin, glibenclamide, and simeprevir were broadly transported by recombinant monkey OATP1B1, OATP1B3 and OATP2B1. Furthermore, some of the 16 non-synonymous monkey OATP1B1 variants found in 64 cynomolgus and 32 rhesus monkeys mediated up to 1.6-fold [(3) H]pitavastatin uptake (with low Michaelis constant values) in comparison with the wild type under the present conditions. Despite that the sequences of monkey recombinant OATPs are not totally reflexive of those of human OATPs, our results collectively suggested that OATP1B1, OATP1B3 or OATP2B1 in monkeys could mediate roughly similar hepatic uptake of various OATP probes. Recombinant monkey OATPs would be good experimental tools for in vitro hepatic uptake in cell systems.

[9] *Carreras A, Pane LS, Nitsch R et al.* **In vivo genome and base editing of a human PCSK9 knock-in hypercholesterolemic mouse model**. BMC biology 2019; 17:4.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30646909
ABSTRACT
BACKGROUND: Plasma concentration of low-density lipoprotein (LDL) cholesterol is a well-established risk factor for cardiovascular disease. Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), which regulates cholesterol homeostasis, has recently emerged as an approach to reduce cholesterol levels. The development of humanized animal models is an important step to validate and study human drug targets, and use of genome and base editing has been proposed as a mean to target disease alleles. RESULTS: To address the lack of validated models to test the safety and efficacy of techniques to target human PCSK9, we generated a liver-specific human PCSK9 knock-in mouse model (hPCSK9-KI). We showed that plasma concentrations of total cholesterol were higher in hPCSK9-KI than in wildtype mice and increased with age. Treatment with evolocumab, a monoclonal antibody that targets human PCSK9, reduced cholesterol levels in hPCSK9-KI but not in wildtype mice, showing that the hypercholesterolemic phenotype was driven by overexpression of human PCSK9. CRISPR-Cas9-mediated genome editing of human PCSK9 reduced plasma levels of human and not mouse PCSK9, and in parallel reduced plasma concentrations of total cholesterol; genome editing of mouse Pcsk9 did not reduce cholesterol levels. Base editing using a guide RNA that targeted human and mouse PCSK9 reduced plasma levels of human and mouse PCSK9 and total

cholesterol. In our mouse model, base editing was more precise than genome editing, and no off-target editing nor chromosomal translocations were identified. CONCLUSIONS: Here, we describe a humanized mouse model with liver-specific expression of human PCSK9 and a human-like hypercholesterolemia phenotype, and demonstrate that this mouse can be used to evaluate antibody and gene editing-based (genome and base editing) therapies to modulate the expression of human PCSK9 and reduce cholesterol levels. We predict that this mouse model will be used in the future to understand the efficacy and safety of novel therapeutic approaches for hypercholesterolemia.

[10] *Chen Q, Li L, Chen Q et al.* **Critical appraisal of international guidelines for the screening and treatment of asymptomatic peripheral artery disease: a systematic review**. BMC cardiovascular disorders 2019; 19:17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30646843
ABSTRACT
BACKGROUND: Peripheral artery disease (PAD) is often asymptomatic but increases the risk of developing cardiovascular events. Due to the uncertainties regarding the quality of related guidelines and a lack of clear-cut evidence, we performed a systematic review and critical appraisal of these guidelines to evaluate their consistency of the recommendations in asymptomatic PAD population. METHODS: Guidelines in English between January 1st, 2000 to December 31th, 2017 were screened in databases including Medline via PubMed, EMBASE, the G-I-N International Guideline Library, the National Guidelines Clearinghouse, the Canadian Medication Association Infobase and the National Library for Health. Those guidelines containing recommendations on screening and treatment for asymptomatic PAD were included, and three reviewers evaluated the quality of the guidelines using Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. Related recommendations were then fully extracted and compared by two reviewers. RESULTS: Fourteen guidelines were included finally and the AGREE scores ranged from 39 to 73%. Most of included guidelines scored low in Rigor of development and Editorial independence, and only two guidelines (ACCF/AHA, AHA/ACC) reached the standard on Conflict of Interest from Institute of Medicine (IOM). Eight guidelines recommended screening at different strength while the others found insufficient evidence or were against screening. Conflicting recommendations on treatment were found in the target value of the lipid lowering and antiplatelet therapy. The treatment policies in three guidelines (BWG, CEVF, ESC) appeared more aggressive, but they had low transparency between guideline developer and industry or did not reach the standard of IOM. CONCLUSIONS: Current guidelines on asymptomatic PAD varied in the methodological quality and fell short of the standard in the rigor of development and editorial independence. Conflicting recommendations were found both on the screening and treatment. More effort is needed to provide clear-cut evidences with high quality and transparency among guideline developer and industry.

[11] *Creager MD, Hohl T, Hutcheson JD et al.* **(18)F-Fluoride Signal Amplification Identifies Microcalcifications Associated With Atherosclerotic Plaque Instability in Positron Emission Tomography/Computed Tomography Images**. Circulation. Cardiovascular imaging 2019; 12:e007835.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30642216

ABSTRACT

BACKGROUND: Microcalcifications in atherosclerotic plaques are destabilizing, predict adverse cardiovascular events, and are associated with increased morbidity and mortality.(18)F-fluoride positron emission tomography (PET)/computed tomography (CT) imaging has demonstrated promise as a useful clinical diagnostic tool in identifying high-risk plaques; however, there is confusion as to the underlying mechanism of signal amplification seen in PET-positive, CT-negative image regions. This study tested the hypothesis that (18)F-fluoride PET/CT can identify early microcalcifications. METHODS: (18)F-fluoride signal amplification derived from microcalcifications was validated against near-infrared fluorescence molecular imaging and histology using an in vitro 3-dimensional hydrogel collagen platform, ex vivo human specimens, and a mouse model of atherosclerosis. RESULTS: Microcalcification size correlated inversely with collagen concentration. The (18)F-fluoride ligand bound to microcalcifications formed by calcifying vascular smooth muscle cell derived extracellular vesicles in the in vitro 3-dimensional collagen system and exhibited an increasing signal with an increase in collagen concentration (0.25 mg/mL collagen -33.8x10(2)+/-12.4x10(2) counts per minute; 0.5 mg/mL collagen -67.7x10(2)+/-37.4x10(2) counts per minute; P=0.0014), suggesting amplification of the PET signal by smaller microcalcifications. We further incubated human atherosclerotic endarterectomy specimens with clinically relevant concentrations of (18)F-fluoride. The (18)F-fluoride ligand labeled microcalcifications in PET-positive, CT-negative regions of explanted human specimens as evidenced by (18)F-fluoride PET/CT imaging, near-infrared fluorescence, and histological analysis. Additionally, the (18)F-fluoride ligand identified micro and macrocalcifications in atherosclerotic aortas obtained from low-density lipoprotein receptor-deficient mice. CONCLUSIONS: Our results suggest that (18)F-fluoride PET signal in PET-positive, CT-negative regions of human atherosclerotic plaques is the result of developing microcalcifications, and high surface area in regions of small microcalcifications may amplify PET signal.

[12] *Brumpton BM, Fritsche LG, Zheng J et al.* **Variation in Serum PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9), Cardiovascular Disease Risk, and an Investigation of Potential Unanticipated Effects of PCSK9 Inhibition**. Circulation. Genomic and precision medicine 2019; 12:e002335.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30645169

ABSTRACT

[13] *Nelson CP, Lai FY, Nath M et al.* **Genetic Assessment of Potential Long-Term On-Target Side Effects of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibitors**. Circulation. Genomic and precision medicine 2019; 12:e002196.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30645167

ABSTRACT

BACKGROUND: Although short-term trials have suggested that PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors are safe and reduce risk of cardiovascular diseases, their long-term safety is unclear. Genetic variants associated with lower activity of a gene can act as proxies to identify potential long-term side effects of drugs as recently exemplified by

association of LDL (low-density lipoprotein)-lowering variants in the HMGCR (target for statins) and PCSK9 genes with increased risk of type 2 diabetes mellitus (T2DM). However, analyses of the full spectrum of potential side effects of PCSK9 inhibition using a genetic approach have not been undertaken. METHODS: We examined the association of an LDL-lowering variant in the PCSK9 gene (T allele of rs1159147), as well as 2 LDL-lowering HGCMR variants (G allele of rs17238484 and T allele of rs12916) with 80 diseases and traits in up to 479 522 individuals in UK Biobank. RESULTS: The PCSK9 T allele was significantly (Bonferroni P<6.25x10(-4)) associated with risk of T2DM, increased body mass index, waist circumference, waist-hip ratio, diastolic blood pressure, type 1 diabetes mellitus, and insulin use. The HMGCR variants were also associated with risk of T2DM, although their previously reported associations with anthropometric traits were found to be confounded. Mediation analysis suggested that the association of the PCSK9 T allele with risk of T2DM but not diastolic blood pressure was largely independent of its association with body mass index and central obesity. Nominally significant associations of the PCSK9 T allele were also seen with peptic ulcer disease, depression, asthma, chronic kidney disease, and venous thromboembolism. CONCLUSIONS: Our findings support previous genetic analyses suggesting that long-term use of PCSK9 inhibitors, like statins, may be associated with increased risk of T2DM. Some other potential side effects need to be looked for in future studies of PCSK9 inhibitors, although we did not find signals that raise substantial concerns about their long-term safety.

[14] *Ward NC, Watts GF, Eckel RH*. **Statin Toxicity**. Circulation research 2019; 124:328-350.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30653440
ABSTRACT
There is now overwhelming evidence to support lowering LDL-c (low-density lipoprotein cholesterol) to reduce cardiovascular morbidity and mortality. Statins are a class of drugs frequently prescribed to lower cholesterol. However, in spite of their wide-spread use, discontinuation and nonadherence remains a major gap in both the primary and secondary prevention of atherosclerotic cardiovascular disease. The major reason for statin discontinuation is because of the development of statin-associated muscle symptoms, but a range of other statin-induced side effects also exist. Although the mechanisms behind these side effects have not been fully elucidated, there is an urgent need to identify those at increased risk of developing side effects as well as provide alternative treatment strategies. In this article, we review the mechanisms and clinical importance of statin toxicity and focus on the evaluation and management of statin-associated muscle symptoms.

[15] *Cui Y, Li S, Zhang F et al.* **Prevalence of familial hypercholesterolemia in patients with premature myocardial infarction**. Clinical cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30637778
ABSTRACT
BACKGROUND: Familial hypercholesterolemia (FH) is a genetic cause of premature myocardial infarction (PMI). Early diagnosis of FH is critical for prognosis. This study aimed to investigate the prevalence of FH among a cohort of Chinese patients with PMI using genetic testing, and to evaluate different diagnostic criteria. METHODS AND RESULTS: A total of 225 consecutive PMI patients were recruited. LDLR, APOB, PCSK9 and LDLRAP1 genes were detected by Sanger

sequencing. FH was diagnosed using the Dutch Lipid Clinic Network (DLCN) criteria and modified DLCN criteria, respectively. The prevalence and clinical features of FH were analyzed. In all PMI patients, pathogenic mutations of LDLR, APOB, PCSK9 and LDLRAP1 genes were found in 10 of 225 patients. Among all mutations, 4 mutations (LDLR c.129G>C, LDLR c.1867A>T, LDLRAP1 c.65G>C, LDLRAP1 c.274G>A) were newly discovered. The prevalence of FH diagnosed by genetic testing was 4.4%. The prevalence of definite/probable FH diagnosed by DLCN and modified DLCN criteria reached 8.0% and 23.6%, respectively, and the mutation rates were 33.3% and 12.2%, respectively. The low-density lipoprotein cholesterol (LDL-C) levels in PMI patients with FH were far from goal attainment. Only one of the FH patients had LDL-C <2.5 mmol/L, and none of them had LDL-C <1.8 mmol/L. CONCLUSIONS: The prevalence of FH among Chinese patients with PMI appeared relatively common. Underdiagnosis and undertreatment of FH are still a big problem, which should arouse a widespread concern.

[16] *Rodriguez-Perea AL, Rojas M, Velilla-Hernandez PA*. **High concentrations of atorvastatin reduce in vitro function of conventional T and regulatory T cells**. Clinical and experimental immunology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30638266
ABSTRACT
Regulatory T cells (Tregs) modulate the magnitude of immune responses and possess therapeutic potential in an array of immune diseases. Statins reduce the activation and proliferation of conventional T cells (Tcons), and they seem to upregulate the frequency and function of Tregs. However, there is a lack of simultaneous evaluation of the in vitro effect of statins on the functional profile of Tregs vs. Tcons. Herein, magnetically purified Tcons and Tregs were stimulated with CD3/CD28/IL-2 in the presence of atorvastatin (ATV) at 1 or 10 muM. The suppressive function of Tregs, the expression of markers associated with Treg function, activation levels, cytokine production and calcium flux in both subpopulations were assessed by flow cytometry. ATV had no cytotoxic effect on T cells at the concentrations used. Interestingly, 10 muM ATV hampered the suppressive capacity of Tregs. Moreover, this higher concentration reduced the expression of FoxP3, CTLA-4 and PD-1. In Tcons, ATV at 10 muM decreased PD-1 and CD45RO expression. The expression of CD25, CD69, CD95, CD38, CD62L, CCR7 and perforin was not affected in both subpopulations or at any ATV concentrations. Remarkably, 10 muM ATV increased the percentage of TNF-alpha-producing Tregs. Although there was a reduction of calcium flux in Tcons and Tregs, it was only significant in 10 muM ATV-treated Tcons. These results suggested that 10 muM ATV affects the cellular functions of both populations; however, this concentration particularly affected several aspects of Treg biology: its suppressive function, cytokine production and expression of Treg specific markers. This article is protected by copyright. All rights reserved.

[17] *Gopalakrishnan C, Gagne JJ, Sarpatwari A et al.* **Evaluation of Socioeconomic Status Indicators for Confounding Adjustment in Observational Studies of Medication Use**. Clinical pharmacology and therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30659590
ABSTRACT

Methodologic research evaluating confounding due to socioeconomic status (SES) in observational studies of medications is limited. We identified 7,109 patients who initiated brand or generic atorvastatin from Medicare claims (2011-2013) linked to electronic medical records and census data. We created a propensity score (PS) containing only claims-based covariates and augmented it with additional claims-based proxies for SES, ZIP code, and block group level SES. Cox models with PS fine-stratification and weighting were used to compare rates of a cardiovascular endpoint and emergency room visits. Adjustment with only claims-based variables substantially improved balance on all SES variables compared to the unadjusted. Although inclusion of SES in PS models further improved balance on SES variables compared to models with claims-based covariates only, it did not materially change point estimates for either outcome. Inclusion of claims-based proxies may mitigate confounding by SES when aggregate-level SES information is unavailable.

[18] *Preston Mason R*. **New Insights into Mechanisms of Action for Omega-3 Fatty Acids in Atherothrombotic Cardiovascular Disease**. Current atherosclerosis reports 2019; 21:2.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30637567

ABSTRACT

PURPOSE OF REVIEW: Treatment of hypercholesterolemia with statins results in significant reductions in cardiovascular risk; however, individuals with well-controlled low-density lipoprotein cholesterol (LDL-C) levels, but persistent high triglycerides (TG), remain at increased risk. Genetic and epidemiologic studies have shown that elevated fasting TG levels are associated with incident cardiovascular events. At effective doses, omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), lower TG levels but may have additional atheroprotective properties compared to other TG-lowering therapies such as niacin and fibrates. The purpose of this review is to evaluate mechanisms related to the potential benefits of omega-3 fatty acids in atherothrombotic disease. RECENT FINDINGS: Large randomized clinical trials are currently under way to test the cardiovascular benefits of omega-3 fatty acids at a pharmacologic dosage (4 g/day). A large randomized trial with a prescription EPA-only formulation was shown to reduce a composite of cardiovascular events by 25% in statin-treated patients with established cardiovascular disease or diabetes and other CV risk factors. EPA and DHA have distinct tissue distributions as well as disparate effects on membrane structure and lipid dynamics, rates of lipid oxidation, and signal transduction pathways. Compared to other TG-lowering therapies, EPA has been found to inhibit cholesterol crystal formation, inflammation, and oxidative modification of atherogenic lipoprotein particles. The anti-inflammatory and endothelial benefits of EPA are enhanced in combination with a statin. Omega-3 fatty acids like EPA only at a pharmacologic dose reduce fasting TG and interfere with mechanisms of atherosclerosis that results in reduced cardiovascular events. Additional mechanistic trials will provide further insights into their role in reducing cardiovascular risk in subjects with well-managed LDL-C but elevated TG levels.

[19] *Miname MH, Bittencourt MS, Nasir K, Santos RD*. **Subclinical coronary atherosclerosis and cardiovascular risk stratification in heterozygous familial hypercholesterolemia patients undergoing statin treatment**. Current opinion in lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30649025

ABSTRACT

PURPOSE OF REVIEW: To discuss the heterogeneity of atherosclerotic cardiovascular disease (ASCVD) risk in heterozygous familial hypercholesterolemia and evidence and limitations of clinical risk scores and subclinical coronary atherosclerosis (SCA) imaging to evaluate risk. RECENT FINDINGS: Risk evaluation in contemporary familial hypercholesterolemia cohorts needs to consider the cause of the familial hypercholesterolemia phenotype, for example the presence of autosomal molecular defects that impart a greater ASCVD risk than in polygenic hypercholesterolemia, prospective follow-up and the impact of statin treatment. As atherosclerosis is multifactorial, clinical scores like the Montreal familial hypercholesterolemia score and SAFEHEART risk equation have been proposed to stratify ASCVD in statin-treated, molecularly defined familial hypercholesterolemia individuals. However, these scores need further validation. SCA distribution in familial hypercholesterolemia individuals undergoing conventional lipid-lowering treatment is heterogeneous, with 45-50% of individuals not presenting any coronary artery calcification (CAC). One study suggests that the absence of CAC associates with no ASCVD events in asymptomatic familial hypercholesterolemia individuals undergoing statin therapy despite elevated residual LDL-cholesterol levels. In contrast, the presence of CAC was independently associated with ASCVD events. SUMMARY: ASCVD risk is heterogeneous in statin-treated familial hypercholesterolemia individuals. Further studies are necessary to determine how risk stratification, especially with SCA detection, impacts on prescription of proprotein convertase subtilisin kexin type 9 inhibitors within a cost-constrained environment.

[20] *Trinder M, Boyd JH, Brunham LR*. **Molecular regulation of plasma lipid levels during systemic inflammation and sepsis**. Current opinion in lipidology 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30649022

ABSTRACT

PURPOSE OF REVIEW: Sepsis is a common syndrome of multiorgan system dysfunction caused by a dysregulated inflammatory response to an infection and is associated with high rates of mortality. Plasma lipid and lipoprotein levels and composition change profoundly during sepsis and have emerged as both biomarkers and potential therapeutic targets for this condition. The purpose of this article is to review recent progress in the understanding of the molecular regulation of lipid metabolism during sepsis. RECENT FINDINGS: Patients who experience greater declines in high-density lipoprotein during sepsis are at much greater risk of succumbing to organ failure and death. Although the causality of these findings remains unclear, all lipoprotein classes can sequester and prevent the excessive inflammation caused by pathogen-associated lipids during severe infections such as sepsis. This primordial innate immune function has been best characterized for high-density lipoproteins. Most importantly, results from human genetics and preclinical animal studies have suggested that several lipid treatment strategies, initially designed for atherosclerosis, may hold promise as therapies for sepsis. SUMMARY: Lipid and lipoprotein metabolism undergoes significant changes during sepsis. An improved understanding of the molecular regulation of these changes may lead to new opportunities for the treatment of sepsis.

[21] *Cabezas KG, Gomez-Fernandez CR, Vazquez-Padron R*. **A Comprehensive Review of Oxidative Stress as the Underlying Mechanism in Atherosclerosis and the Inefficiency of Antioxidants to Revert this Process**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30652635
ABSTRACT
BACKGROUND: Cardiovascular diseases account for the highest mortality rate in the United States. The major underlying mechanism driving the onset and maintenance of cardiovascular diseases is atherosclerosis. Atherosclerosis is a chronic disease affecting large and medium size arteries; it proceeds through four main stages along the different decades of life, beginning at birth. Atherosclerosis is a consequence of Oxidative stress, where homeostasis between endogenous antioxidants and reactive oxygen species is disrupted. Failure of intrinsic antioxidants and prophylactic antioxidant supplements to prevent atherosclerosis formation is an ongoing area of research on the race to avert, manage and cure atherosclerosis. METHODS: The purpose of this work is to elucidate the actions of reactive oxygen species and oxidative stress on the formation of atherosclerosis as well as the different stages of atherosclerosis and the different mechanisms to prevent it. Through extensive review of scientific literature, this paper correlates cell damage caused by oxidative stress to atheromatous plaque formation, as well as an in-depth analysis of high-density lipoproteins and enzymatic and non-enzymatic antioxidant role on atherosclerosis prevention. Antioxidant mechanism are overwhelmed by atherosclerotic processes and fail to be the ideal treatment of atherosclerosis. There is no scientific data that correlates prophylactic and non-prophylactic antioxidant treatment to a decrease in mortality or comorbidities pertaining to atherosclerosis. This is thought to be due to lack of consensus of optimal therapeutic doses, lack reliable markers indicating which patient is to benefit from therapy and the chemical complexity of antioxidants in vivo. Current treatments for atherosclerosis include HMG-CoA reductase inhibitors which target directly low-density lipoproteins to tackle atherosclerotic plaque formation. CONCLUSION: HMG-CoA reductase inhibitors are not enough for the treatment of atherosclerosis given the complexity of the disease which has immune, musculoskeletal, genetic and hematologic aspects besides the involvement of lipids and lipoproteins. Therefore, other pharmacologic targets such as the PCSK9 enzyme and NFK- beta should be researched in depth as possible treatments for atherosclerosis.

[22] *Doumas M, Imprialos K, Dimakopoulou A et al.* **The role of statins in the management of nonalcoholic fatty liver disease**. Current pharmaceutical design 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30652643
ABSTRACT
BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) and its advanced form non-alcoholic steatohepatitis (NASH) are the most common causes of elevated liver enzymes in the general population. NASH and to a lesser extent NAFLD have been associated with increased liver-related, cardiovascular disease (CVD), and all-cause mortality. No effective treatment is widely acceptable. OBJECTIVE: The purpose of this review is summarize available data on the impact of statins in NAFLD and NASH. METHOD: A comprehensive review of the literature was performed to identify studies assessing the effect of statin use in NAFLD/NASH Results: Recent reports have shown that the use of statins in patients with elevated plasma aminotransferases may be

beneficial. Post hoc data from three large prospective randomized clinical trials (n>11, 000) suggest that specific statins (mainly atorvastatin) ameliorate NAFLD/NASH and reduce CVD events twice as much as in those with normal liver function. Several biopsy studies have found that rosuvastatin use is related with significant histological ameliorating effects in the setting of NASH. Statin treatment may also protect from hepatocellular carcinoma (HCC) related to NAFLD/NASH. CONCLUSION: Since NAFLD/NASH patients have high CVD risk, they will probably require a statin. Thus, why not select a specific statins (atorvastatin or rosuvastatin, both generic now) that offered a substantial liver- and CVD-related adverse event reduction? The administration of statins in these patients is as safe as in the general population.

[23] *Echouffo-Tcheugui JB, Zhao S, Brock G et al.* **Visit-to-Visit Glycemic Variability and Risks of Cardiovascular Events and All-Cause Mortality: The ALLHAT Study**. Diabetes Care 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30659073

ABSTRACT

OBJECTIVE: The prognostic value of long-term glycemic variability is incompletely understood. We evaluated the influence of visit-to-visit variability (VVV) of fasting blood glucose (FBG) on incident cardiovascular disease (CVD) and mortality. RESEARCH DESIGN AND METHODS: We conducted a prospective cohort analysis including 4,982 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) who attended the baseline, 24-month, and 48-month visits. VVV of FBG was defined as the SD or variability independent of the mean (VIM) across FBG measurements obtained at the three visits. Participants free of CVD during the first 48 months of the study were followed for incident CVD (coronary heart disease [CHD], stroke, and heart failure [HF]) and all-cause mortality. RESULTS: Over a median follow-up of 5 years, there were 305 CVD events (189 CHD, 45 stroke, and 81 HF) and 154 deaths. The adjusted hazard ratio (HR) comparing participants in the highest versus lowest quartile of SD of FBG (>/=26.4 vs. <5.5) was 1.43 (95% CI 0.93-2.19) for CVD and 2.22 (95% CI 1.22-4.04) for all-cause mortality. HR for VIM was 1.17 (95% CI 0.84-1.62) for CVD and 1.89 (95% CI 1.21-2.93) for all-cause mortality. Among individuals without diabetes, the highest quartile of SD of FBG (HR 2.67 [95% CI 0.14-6.25]) or VIM (HR 2.50 [95% CI 1.40-4.46]) conferred a higher risk of death. CONCLUSIONS: Greater VVV of FBG is associated with increased mortality risk. Our data highlight the importance of achieving normal and consistent glycemic levels for improving clinical outcomes.

[24] *Belhayara MI, Mellouk Z, Hamdaoui MS et al.* **Relationship between the insulin resistance and circulating predictive biochemical markers in metabolic syndrome among young adults in western Algeria**. Diabetes & metabolic syndrome 2019; 13:504-509.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30641755

ABSTRACT

AIM: The metabolic syndrome (MetS) becomes increasingly obvious from an early age. The current study aimed at exploring the relationship between insulin resistance and the main biomarkers of MetS in young adult algerian patients. METHODS: Glucose, HbA1C, total cholesterol (TC), hjgh bensity lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), insulinemia and C-peptide, adipokins (leptin, adiponectin), inflammatory cytokines (IL-6 and TNF-a), us-CRP and GLP-1 were measured by suitable methods. Homeostasis

model assessment (HOMA) was used to detect the degree of insulin resistance. RESULTS: The MetS patients displayed higher glucose, insulin, HbA1c values and impaired lipid profile as judged by increasing TC, TG, LDL-C levels and lower HDL-C. Furthermore, adipokines, HDL-C and CRP contents were significantly higher whilst TG and LDL-C were much lower in MetS female group as compared to male patients suggesting most pronounced metabolic perturbation in the latter group. The probability of a significant correlation between HOMA and studied variables was often higher in female than male subjects. Such was the case for total cholesterol, HDL-cholesterol, triglycerides, adiponectin, interleukin-6, TNF-alpha and hs-CRP. CONCLUSION: The high rate of metabolic syndrome among young obese adults is alarming, this requiring extensive investigations in prone subjects.

[25] *Fazaeli M, Khoshdel A, Shafiepour M, Rohban M*. **The influence of subclinical hypothyroidism on serum lipid profile, PCSK9 levels and CD36 expression on monocytes**. Diabetes & metabolic syndrome 2019; 13:312-316.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30641718
ABSTRACT
BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease and a secreted protein which increases cholesterol levels in plasma via inducing degradation of low-density lipoprotein receptor (LDLR). Cluster of differentiation 36 (CD36) is a member of a family of cell surface proteins in many cells. CD36 is known as fatty acid translocase (FAT) because it imports fatty acids inside cells and participate in triglyceride storage. It has been suggested that PCSK9 regulates CD36 in some tissues. METHODS: Data and serum levels of TSH, FT4, lipid profile and PCSK9 and the expression of CD36 on monocytes from 40 new untreated patients with subclinical hypothyroidism (SH) and 40 age- sex- and BMI-matched euthyroid controls were analyzed in a cross-sectional study. Then the relationships between these parameters were examined. RESULTS: Patients with SH had higher TSH, FT4, total cholesterol (TC) and triglyceride (TG) Low-density lipoprotein (LDL) and PCSK9 levels than controls. There were significant and positive correlations between serum TSH levels and lipid parameters except HDL-C. PCSK9 had a significant and negative correlation with FT4. No significant correlation could be found in relation to PCSK9 and CD36. CONCLUSIONS: PCSK9 inhibitors are used to reduce blood cholesterol levels as drugs. If it will be proven that PCSK9 can induce CD36 degradation, taking these drugs may have unwanted side effects. This study showed that serum PCSK9 and lipid profile levels increase in patients with subclinical hypothyroidism and there is no relationship between PCSK9 and CD36 in these patients.

[26] *Bjerg L, Hulman A, Carstensen B et al.* **Effect of duration and burden of microvascular complications on mortality rate in type 1 diabetes: an observational clinical cohort study**. Diabetologia 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30649599
ABSTRACT
AIMS/HYPOTHESIS: The role of burden and duration of multiple microvascular complications on mortality rate has not been explored in detail in type 1 diabetes. Taking complication burden and time-updated duration into account we aimed to quantify mortality rate in individuals with and without microvascular complications. METHODS: This observational clinical cohort included

3828 individuals with type 1 diabetes attending the Steno Diabetes Center Copenhagen in 2001-2013. We used information on mortality and detailed clinical measures of microvascular complications from electronic patient records. Poisson models were used to model mortality rates according to complication burden. RESULTS: During 26,665 person-years of follow-up, 503 deaths occurred. Compared with individuals without microvascular complications, the mortality rate ratio was 2.20 (95% CI 1.79, 2.69) for individuals with diabetic kidney disease, 1.72 (95% CI 1.39, 2.12) for individuals with neuropathy and 1.02 (95% CI 0.77, 1.37) for individuals with retinopathy, all adjusted for calendar time (year/month/day), age, duration of diabetes, sex, HbA1c, LDL-cholesterol, BMI, smoking status, systolic blood pressure, use of antihypertensive and lipid-lowering medication, and cardiovascular disease status. In individuals with two complications or more, the risk of mortality did not exceed the combined risk from each individual complication. Mortality rate ratios increased immediately after diagnosis of neuropathy and diabetic kidney disease. Mortality rate ratios were independent of the duration of neuropathy and retinopathy, while the mortality rate associated with diabetic kidney disease reached a stable level after approximately 3 years. CONCLUSIONS/INTERPRETATION: Neuropathy and diabetic kidney disease are strong and independent risk markers of mortality in type 1 diabetes, whereas no evidence of higher mortality rate was found for retinopathy. We found no indication that the mortality risk with multiple complications exceeds the risk conferred by each complication separately. The duration spent with microvascular complications had only a marginal effect on mortality.

[27] *Auti P, Gabhe S, Mahadik K*. **Bioanalytical method development and its application to pharmacokinetics studies on Simvastatin in the presence of Piperine and two of its synthetic derivatives**. Drug development and industrial pharmacy 2019:1-17.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30649976
ABSTRACT
Piperine has been widely used as a bioenhancer. Simvastatin belongs to a group of medicines known as statins. It acts by inhibiting HMG CoA reductase and acts primarily as a hypolipidemic agent. In this study some derivatives of Piperine were synthesized. They were studied for their bioenhencing effect [10mg/kg] and this effect was compared with that of Piperine. The pharmacokinectic profile of Simvastatin alone and in combination with Piperine and Piperine derivatives were investigated by validated HPLC method as per USFDA guidelines. It was seen that the two synthesized derivatives of Piperine significantly improved the bioavailability of Simvastatin in Wistar rats. The 5-(benzo) [1,3]dioxol-5-yl)-N-(pyridin-4-yl)penta-2,4-dienamide was better amongst the synthesized in increasing the bioavailability of Simvastatin in Wistar rat.

[28] *Lamy A, Lonn E, Tong W et al.* **The cost implication of primary prevention in the HOPE 3 trial**. European heart journal. Quality of care & clinical outcomes 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30657891
ABSTRACT
Aims: The Heart Outcomes Prevention Evaluation -3 (HOPE-3) found that rosuvastatin alone or with candesartan and hydrochlorothiazide (HCT) (in a subgroup with hypertension) significantly lowered cardiovascular events compared to placebo in 12,705 individuals from 21 countries at intermediate risk and without cardiovascular disease. We assessed the costs implications of

implementation in primary prevention in countries at different economic levels. Methods and Results: Hospitalizations, procedures, study and non-study medications were documented. We applied country-specific costs to the healthcare resources consumed for each patient. We calculated the average cost per patient in US dollars for the duration of the study (5.6 years). Sensitivity analyses were also performed with cheapest equivalent substitutes. The combination of rosuvastatin with candesartan/HCT reduced total costs and was a cost-saving strategy in United States, Canada, Europe and Australia. By contrast, the treatments were more expensive in developing countries even when cheapest equivalent substitutes were used. After adjustment for gross domestic product (GDP), the costs of cheapest equivalent subsitutes in proportion to the health care costs were higher in developing countries in comparison to developed countries. Conclusion: Rosuvastatin and candesartan/HCT in primary prevention is a cost-saving approach in developed countries, but not in developing countries as both drugs and their cheapest equivalent substitutes are relatively more expensive despite adjustment by GDP. Reductions in costs of these drugs in developing countries is essential to make statins and BP lowering drugs affordable and ensure their use.

[29] *White MN, Shrubsole MJ, Cai Q et al.* **Effects of fish oil supplementation on eicosanoid production in patients at higher risk for colorectal cancer**. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30640206

ABSTRACT

Fish oil supplementation may represent a potential chemopreventive agent for reducing colorectal cancer risk. The mechanism of action of fish oil is unknown but presumed to be related to eicosanoid modification. The purpose of this study was to evaluate the effects of fish oil supplementation on the levels of urinary and rectal eicosanoids. We conducted a randomized, double-blind, controlled trial of 2.5 g of fish oil per day compared with olive oil supplementation over a 6-month period. Study participants had a history of colorectal adenomas. Randomization was stratified based on the gene variant rs174535 in the fatty acid desaturase 1 enzyme (FADS1), which affects tissue levels of arachidonic acid. A total of 141 participants were randomized. Urinary prostaglandin E2 metabolite (PGE-M) was measured at baseline, 3, and 6 months and rectal prostaglandin E2 (PGE2) at baseline and 6 months. Repeated-measures linear regression was used to determine the effect of the intervention on each outcome measure. Overall, fish oil supplementation was found to reduce urinary PGE-M production compared with olive oil (P=0.03). Fish oil did not reduce rectal PGE2 overall; however, it did significantly reduce PGE2 in the subgroup of participants not using aspirin or NSAIDs (P=0.04). FADS1 genotype did not seem to modify effects of fish oil on PGE2 production. We conclude that fish oil supplementation has a modest but beneficial effect on eicosanoids associated with colorectal carcinogenesis, particularly in those not taking aspirin or NSAIDs.

[30] *An L, An S, Jia Z et al.* **Atorvastatin improves left ventricular remodeling and cardiac function in rats with congestive heart failure by inhibiting RhoA/Rho kinase-mediated endothelial nitric oxide synthase**. Experimental and therapeutic medicine 2019; 17:960-966.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30651887

ABSTRACT

The aim of the present study was to investigate the effects and possible mechanisms of atorvastatin (Ato) against chronic heart failure (CHF). A rat model of CHF was established and cardiac functions were assessed using Echocardiography. The expression of RhoA/Rho kinase and endothelial nitric oxide synthase (eNOS) was assessed using western blotting and reverse transcription polymerase chain reaction following 4 weeks of treatment. The three groups assessed in the present study were as follows: The control group (no treatment), the Ato + isopropylnoradrenaline (ISO) group (subcutaneous injections of 340 mg/kg ISO + orally administered 50 mg/kg Ato dissolved in saline; administered once daily) and the ISO group (subcutaneous injections of 340 mg/kg ISO + orally administered with an equal volume of saline; administered once daily). Heart volume and weight in the ISO group were significantly increased compared with the control (C) group ($P<0.01$), whereas contractility was decreased. The results were reverse for the Ato group when compared with the ISO group ($P<0.05$). Levels of RhoA/Rho kinase protein and mRNA were significantly increased in the ISO group ($P<0.01$); however. The mRNA and protein expression of eNOS was significantly decreased ($P<0.05$) when compared with the C group. The mRNA and protein expression of RhoA/Rho kinase was significantly reduced in the Ato+ISO group compared with the ISO group ($P<0.01$), whereas the mRNA and protein expression of eNOS was significantly increased ($P<0.05$). RhoA protein expression was increased in the cytoplasm of the C group and on the cell membrane of the ISO group; however, in the Ato+ISO group, RhoA protein expression on the cell membrane was significantly downregulated when compared with the ISO group ($P<0.05$). The results of the present study suggest that Ato upregulates eNOS by inhibiting RhoA/Rho kinase overexpression in the myocardial tissue of rats with CHF, thus improving left ventricular remodeling and cardiac function.

[31] *Chen X, Jiang D, Xu L et al.* **Elevated methylation of cyclin dependent kinase inhibitor 2B contributes to the risk of coronary heart disease in women**. Experimental and therapeutic medicine 2019; 17:205-213.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30651784
ABSTRACT
Cyclin dependent kinase inhibitor 2B (CDKN2B) encodes a cyclin-dependent kinase inhibitor that may enhance the formation of atherosclerotic plaques. The aim of the present study was to investigate the contribution of CDKN2B promoter methylation on the risk of coronary heart disease (CHD). The present results indicated a significant association between increased CDKN2B methylation and the risk of CHD (adjusted $P=0.043$). A breakdown analysis according to sex demonstrated that CDKN2B methylation was significantly associated with the risk of CHD in women (adjusted $P=0.010$), but not in men. A further breakdown analysis by age indicated a significant association of CHD in the women >60 years ($P=0.024$). Luciferase reporter gene assay results indicated that the CDKN2B promoter fragment significantly enhanced luciferase activity ($P<0.001$). In addition, CDKN2B transcription was significantly enhanced following treatment with 5-aza-2'-deoxycytidine methylation inhibitor in human aortic endothelial cells (HAEC) and human primary coronary artery smooth muscle cells (HPCASMC; $P<0.05$ and $P<0.01$), but not in 293 cells. Notably, estrogen treatment reduced CDKN2B methylation of several CpGs and significantly increased CDKN2B gene expression levels in HAEC, HPCASMC and 293 cells ($P<0.05$ and $P<0.01$). Additionally, treatment of HAEC and HPCASMC with simvastatin and gamma-

carboxy-L-glutamic acid reduced CDKN2B promoter methylation and increased CDKN2B transcription concomitantly. The present study suggests that CDKN2B promoter methylation may be associated with sex dimorphism in the pathogenesis of CHD.

[32] *Ma G, Bi S*. **Effect of rosuvastatin on vascular endothelial functions and inflammatory factors of patients with type 2 diabetes mellitus and coronary heart disease**. Experimental and therapeutic medicine 2019; 17:332-336.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30651799
ABSTRACT
Effects of rosuvastatin on vascular endothelial functions and inflammatory factors of patients with type 2 diabetes mellitus and coronary heart disease were investigated. Eighty patients with type 2 diabetes mellitus and coronary heart disease, who were admitted and treated in Center hospital of Zibo from January 2016 to January 2017, were selected and divided into observation group (n=40) and control group (n=40) by the random number table; symptomatic and supporting therapy, including use of metformin, captopril, asprin and levocarnitine, was used in control group while rosuvastatin was adopted in observation group in addition to the symptomatic and supporting therapy. Patients in both groups were treated for a treatment cycle, namely, 3 consecutive months. After that, indexes related to blood lipid, diabetes mellitus and vascular endothelial activity, as well as variations in inflammation-associated cytokines, before and after intervention were compared; the correlation of changes in total cholesterol (TC) with those in fasting insulin (FINS), high-sensitivity C-reactive protein (hs-CRP) and endothelin-1 (ET-1), respectively, was analyzed. Among the blood lipid indexes of the patients, the levels of TC, triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) after intervention were significantly lower than those before intervention (P<0.05), while the post-intervention level of high-density lipoprotein cholesterol (HDL-C) was higher than that before intervention (P<0.05). Compared with those before intervention, the level of FINS after intervention was remarkably higher (P<0.05), while the homeostasis model assessment of insulin resistance (HOMA-IR) level after intervention was significantly lower (P<0.05). After intervention, the levels of hs-CRP and tumor necrosis factor-alpha (TNF-alpha) in the patients were obviously decreased compared with those before intervention (P<0.05). Compared with that before intervention, the ET-1 level was decreased (P<0.05), while the nitric oxide (NO) level was elevated after intervention (P<0.05). The TC level was negatively correlated with FINS level (P<0.05) but positively correlated with the levels of hs-CRP (P<0.05) and ET-1 (P<0.05). For patients with type 2 diabetes mellitus and coronary heart disease, treatment with rosuvastatin can effectively lower the level of blood lipid and regulate insulin functions; moreover, potent decrease in blood lipid level has great significance in improving the vascular endothelial functions and reducing inflammatory response levels.

[33] *Patti AM, Giglio RV, Papanas N et al.* **Future perspectives of the pharmacological management of diabetic dyslipidemia**. Expert Rev Clin Pharmacol 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30644763
ABSTRACT
INTRODUCTION: Diabetic dyslipidemia is frequent among patients with type 2 diabetes mellitus (T2DM) and is characterized by an increase in triglycerides (TGs), low-density lipoprotein

cholesterol (LDL-C), and small-dense (atherogenic) particles, and by a decrease in low high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) A1 that are strongly related to insulin resistance. The increased flux of free fatty acids from adipose tissue to the liver aggravates hepatic insulin resistance and promotes all of aspects of the dyslipidemic state. Areas covered: Statins are the first-line agents for treatment while other lipid-lowering drugs (ezetimibe, fibrate and proprotein convertase subtilisin/kexin type 9) or novel anti-diabetic agents (dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon like peptide-1 receptor agonist (GLP-1RA), sodium/glucose cotransporter 2 inhibitors (SGLT2is)) or nutraceuticals (berberine, omega 3 fatty acid, red yeast rice) can be used alone or in combination. Expert Opinion: In patients with type 2 diabetes mellitus, lipid abnormalities should be identified and treated as part of the overall diabetic treatment, in order to prevent cardiovascular disease. The choice of drugs to be used is mainly based on the lipid profile and on the characteristic lipoprotein abnormalities; the use of new drugs for the treatment of hyperglycemia and lipids alteration in these patients can improve diabetic dyslipidemia.

[34] *Shamloo A, Amani A, Forouzandehmehr M, Ghoytasi I*. **In Silico study of patient-specific magnetic drug targeting for a coronary LAD atherosclerotic plaque**. Int J Pharm 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30654060

ABSTRACT

Coronary artery disease is the first cause of death across the world. Targeted delivery of therapeutics through controlled release of micro- and nano-particles remains a very capable approach to develop new strategies in treating restenosis and atherosclerotic plaques. In this research, to produce the arterial geometry, an image-processing was done using CT-scan images of a LAD coronary artery. After implementing the finite element mesh, the Fluid-Structure Interaction (FSI) simulation based on physiological boundary conditions was performed. Next, a Lagrangian description of particles dynamics in a non-Newtonian blood flow considering momentum equation of motion for each particle and the imposed external magnetic field was provided. Under the influence of the magnetic field, the optimal particle size scope for which the surface density of particles (SDP) adhered on the plaque lumen reaches its maximum was specified. Also, our results signify that applying a magnetic field can adversely affect the delivery of particles to the targeted site for near micron-size particles. Along with the evaluation of the Brownian and the gravitational forces on nanoparticles, the uniformity of the distribution of particles in the left coronary network with and without the presence of the magnetic field has been studied. In conclusion, the external magnetic field has increased the SDP adhered on the targeted surface by 49.4% and 59.7% for 400 and 600 nm particles, respectively.

[35] *Najafipour M, Zareizadeh M, Khokhi MA, Najafipour F*. **Comparative study of the effect of atorvastatin and fenofibrate on high-density lipoprotein cholesterol levels in patients with type 2 diabetes**. Journal of advanced pharmaceutical technology & research 2018; 9:135-138.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30637231

ABSTRACT

Diabetes is the most common metabolic disease. Type 2 diabetes is a variable combination of insulin resistance and disorder in insulin secretion, leading to disorder of lipids and plasma

lipoproteins. The most common pattern of dyslipidemia in diabetic is high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C). This study was conducted to find a more effective drug to increase HDL-C. In this study, 80 patients (26 males and 54 females) with type 2 diabetes received fenofibrate in cross-sectional way for 2 months, and they did not take antilipid drugs for 2 month. Then, they underwent atorvastatin for 2 months and HDL-C was measured before and after taking drugs. Patients did not change their diet during this study. Effect of atorvastatin and fenofibrate on HDL-C levels in patients with type 2 diabetes was evaluated. The mean HDL-C and total cholesterol (TC) before and after taking drugs were 36.5 mg/dL and 174.56 mg/dL, respectively. After atorvastatin, the mean HDL-C and TC were 43.30 and 150.144 mg/dL, respectively, and after fenofibrate, 43.40 were mg/dL and 146.36 mg/dL, respectively. Atorvastatin caused increase in HDL-C by 18.44% and reduction in TC by 13.82% and fenofibrate increase in HDL-C by18.62% and reduction in TC by 16.05%. No difference was seen between atorvastatin and fenofibrate in terms of effect on the HDL-C excess (P = 0.449). In addition, no difference was seen between atorvastatin and fenofibrate in terms of effect on TC reduction (P = 0.992). In conclusion various factors are involved in increasing the HDL, such as race, sex, nutrition, physical activity and, of course, medications. The effect of medications is also different on races and genetics. The value of increase in HDL-C after Fenofibrate and Atorvastatin was associated with gender so that it caused more increase of HDL-C in females.

[36] *Apaijai N, Moisescu DM, Palee S et al.* **Pretreatment With PCSK9 Inhibitor Protects the Brain Against Cardiac Ischemia/Reperfusion Injury Through a Reduction of Neuronal Inflammation and Amyloid Beta Aggregation**. Journal of the American Heart Association 2019; 8:e010838.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30636486
ABSTRACT
Background Cardiac ischemic/reperfusion (I/R) injury leads to brain damage. A new antihyperlipidemic drug is aimed at inhibiting PCSK 9 (proprotein convertase subtilisin/kexin type 9), a molecule first identified in a neuronal apoptosis paradigm. Thus, the PCSK 9 inhibitor (PCSK 9i) may play a role in neuronal recovery following cardiac I/R insults. We hypothesize that PCSK 9i attenuates brain damage caused by cardiac I/R via diminishing microglial/astrocytic hyperactivation, beta-amyloid aggregation, and loss of dendritic spine. Methods and Results Adult male rats were divided into 7 groups: (1) control (n=4); (2) PCSK 9i without cardiac I/R (n=4); (3) sham (n=4); and cardiac I/R (n=40). Cardiac I/R rats were divided into 4 subgroups (n=10/subgroup): (1) vehicle; (2) PCSK 9i (10 mug/kg, IV) before ischemia; (3) PCSK 9i during ischemia; and (4) PCSK 9i at the onset of reperfusion. At the end of cardiac I/R protocol, brains were removed to determine microglial and astrocytic activities, beta-amyloid aggravation, and dendritic spine density. The cardiac I/R led to the activation of the brain's innate immunity resulting in increasing Iba1(+) microglia, GFAP (+) astrocytes, and CD 11b(+)/ CD 45(+high) cell numbers. However, CD 11b(+)/ CD 45(+low) cell numbers were decreased following cardiac I/R. In addition, cardiac I/R led to reduced dendritic spine density, and increased beta-amyloid aggregation. Only the administration of PCSK 9i before ischemia effectively attenuated these deleterious effects on the brain following cardiac I/R. PCSK 9i administration under the physiologic condition did not affect the aforementioned parameters. Conclusions Cardiac I/R injury activated microglial activity in the brain, leading to brain damage. Only the pretreatment

with PCSK 9i prevented dendritic spine loss via reduction of microglial activation and Abeta aggregation.

[37] *Numaguchi R, Furuhashi M, Matsumoto M et al.* **Differential Phenotypes in Perivascular Adipose Tissue Surrounding the Internal Thoracic Artery and Diseased Coronary Artery**. Journal of the American Heart Association 2019; 8:e011147.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30638109
ABSTRACT
Background Perivascular adipose tissue (PVAT) is causally associated with vascular function and the pathogenesis of vascular disease in association with metabolically driven chronic inflammation called metaflammation. However, the difference in PVAT surrounding the coronary artery (CA - PVAT) and that surrounding the internal thoracic artery (ITA-PVAT), a vessel resistant to atherosclerosis, remains unclear. Herein, we investigated whether CA - PVAT , ITA - PVAT , and subcutaneous adipose tissue (SCAT) have distinct phenotypes. Methods and Results Fat pads were sampled from 44 patients (men/women, 36:8; age, 67+/-13 years) with CA disease who underwent elective CA bypass grafting. Adipocyte size in ITA - PVAT and that in CA - PVAT were significantly smaller than that in SCAT . A greater extent of fibrosis and increased gene expression levels of fibrosis-related molecules were observed in CA - PVAT than those in SCAT and those in ITA - PVAT . CA - PVAT exhibited more pronounced metaflammation, as indicated by a significantly larger extent of CD 68-positive and CD 11c-positive M1 macrophages, a lower ratio of CD 206-positive M2 to CD 11c-positive M1 macrophages, a lower gene expression level of adiponectin, and higher gene expression levels of inflammatory cytokines and inflammasome- and endoplasmic reticulum stress-related molecules, than did ITA - PVAT and SCAT . Expression patterns of adipocyte developmental and pattern-forming genes were totally different among SCAT , ITA - PVAT, and CA - PVAT . Conclusions The phenotype of ITA - PVAT is closer to that of SCAT than that of CA - PVAT , which may result from inherent differences in adipocytes. ITA - PVAT appears to be protected from metaflammation and consecutive adipose tissue remodeling, which may contribute to the decreased atherosclerotic plaque burden in the ITA.

[38] *Wang H, Liu D, Zhang H*. **Investigation of the Underlying Genes and Mechanism of Macrophage-Enriched Ruptured Atherosclerotic Plaques Using Bioinformatics Method**. Journal of atherosclerosis and thrombosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30643084
ABSTRACT
AIM: The study aimed to identify the underlying differentially expressed genes (DEGs) and mechanism of macrophage-enriched rupture atherosclerotic plaque using bioinformatics methods. METHODS: GSE41571, which includes six stable samples and five ruptured atherosclerotic samples, was downloaded from the GEO database. After preprocessing, DEGs between ruptured and stable atherosclerotic samples were identified using LIMMA. Gene Ontology biological process (GO_BP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of DEGs were performed using the Database for Annotation, Visualization, and Integration Discovery (DAVID) online tool. Based on the STRING database, protein-protein interactions (PPIs) network among DEGs were constructed. Regulatory relationships between

miRNAs/transcriptional factors (TFs) and target genes were predicted using Enrichr, and regulatory networks were visualized using Cytoscape. RESULTS: A total of 268 DEGs (64 up-regulated and 204 down-regulated DEGs) were identified between ruptured and stable samples. In the PPI network, collagen type III alpha 1 chain (COL3A1), collagen type I alpha 2 chain (COL1A2), and asporin (ASPN) were more than 15 interaction degrees. In the miRNA-target network, miR21 was highlighted with highest degrees and ASPN could be targeted by miR21. Functional enrichment analysis showed that COL3A1 and COL1A2 were significantly enriched in extracellular matrix organization and cell adhesion GO_BP terms. Pre-platelet basic protein (PPBP) was the most significantly up-regulated gene in ruptured atherosclerotic samples and enriched in immune response and inflammatory response GO_BP terms. CONCLUSIONS: Down-regulated COL3A1, COL1A2 and ASPN, and up-regulated PPBP might perform critical promotional roles in atherosclerotic plaque rupture. Furthermore, miR21 might be potential target to prevent atherosclerotic rupture.

[39] *Aktay G, Gursoy SO, Uyumlu U et al.* **Protective effect of atorvastatin on oxidative stress in streptozotocin-induced diabetic rats independently their lipid-lowering effects**. Journal of biochemical and molecular toxicology 2019:e22295.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30657622
ABSTRACT
In the present study, we investigate the effects of atorvastatin on the lipid profile, oxidative stress, and liver enzyme markers, and its protective activity against diabetic complications, in streptozotocin (STZ)-induced diabetic rats. Fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), and high-density lipoprotein (HDL) levels, as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzyme activities, were measured 7 weeks after the administration of STZ and atorvastatin. Thiobarbituric acid reactive substances (TBARS), non-protein associated sulfhydryl (NP-SH), total sulfhydryl (T-SH), and nitric oxide (NO) levels were measured to evaluate oxidative stress. Atorvastatin was found to inhibit ALT and AST activities and to reduce FBG levels in rats with STZ-induced diabetes. Moreover, atorvastatin treatment significantly reduced lipid peroxidation in kidney, heart, and eye tissues ($P < 0.001$, for all), and resulted in a significant increase in NP-SH levels in brain tissues ($P < 0.001$). Total NO and nitrate levels increased significantly after atorvastatin treatment ($P < 0.01$). Our results revealed that atorvastatin has a protective effect against STZ-induced oxidative damage by reducing TBARS levels and increasing NP-SH levels, has a hepatoprotective effect by decreasing ALT and AST activities. It also shows the antihyperglycemic activity by lowering FBG levels.

[40] *Encarnacao IC, Sordi MB, Aragones A et al.* **Release of simvastatin from scaffolds of poly(lactic-co-glycolic) acid and biphasic ceramic designed for bone tissue regeneration**. Journal of biomedical materials research. Part B, Applied biomaterials 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30653823
ABSTRACT
The aim of this study was to evaluate the release of simvastatin from scaffolds composed of poly(lactic-co-glycolic) acid (PLGA) and biphasic ceramic designed for bone engineering and to assess the physico-chemical and mechanical properties of the scaffolds. Samples with 30% and 70% porosity were obtained with 0, 2, 5, and 8 wt %. of simvastatin through the solvent

evaporation technique and leaching of sucrose particles. Scaffold degradation and simvastatin release were evaluated in phosphate-buffered saline. Scaffolds were analyzed by scanning electron microscopy and microtomography for two-dimensional and three-dimensional morphological characterization of the porosity, connectivity, and intrinsic permeability. The mechanical characterization was conducted based on the compressive strength and the chemical characterization by differential scanning calorimetry and energy dispersive X-ray spectroscopy. Gradual and prolonged simvastatin release from the scaffolds was observed. The release followed the Korsmeyer kinetics model with the predominance of case II transport for 30% porosity scaffolds, and anomalous behavior for the 70% porosity samples. Simvastatin release was also influenced by the slow scaffold degradation due to the strong chemical interaction between simvastatin and PLGA, as observed by differential scanning calorimetry. The scaffolds presented spherical and sucrose crystal-shaped pores that resulted in a homogenous porosity, with a predominance of open pores, ensuring interconnectivity. Simvastatin incorporation into the scaffolds and increased porosity did not influence the mechanical properties. The scaffolds presented gradual and prolonged simvastatin release, with satisfactory physico-chemical and mechanical properties. The scaffolds presented gradual and prolonged simvastatin release, with satisfactory physico-chemical and mechanical properties, a promise for applications in bone regeneration. (c) 2019 Wiley Periodicals, Inc. J Biomed Mater Res B Part B, 2019.

[41] *Momtazi-Borojeni AA, Katsiki N, Pirro M et al.* **Dietary natural products as emerging lipoprotein(a)-lowering agents**. Journal of cellular physiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30637725
ABSTRACT
Elevated plasma lipoprotein(a) (Lp(a)) levels are associated with an increased risk of cardiovascular disease (CVD). Hitherto, niacin has been the drug of choice to reduce elevated Lp(a) levels in hyperlipidemic patients but its efficacy in reducing CVD outcomes has been seriously questioned by recent clinical trials. Additional drugs may reduce to some extent plasma Lp(a) levels but the lack of a specific therapeutic indication for Lp(a)-lowering limits profoundly reduce their use. An attractive therapeutic option is natural products. In several preclinical and clinical studies as well as meta-analyses, natural products, including l-carnitine, coenzyme Q 10 , and xuezhikang were shown to significantly decrease Lp(a) levels in patients with Lp(a) hyperlipoproteinemia. Other natural products, such as pectin, Ginkgo biloba, flaxseed, red wine, resveratrol and curcuminoids can also reduce elevated Lp(a) concentrations but to a lesser degree. In conclusion, aforementioned natural products may represent promising therapeutic agents for Lp(a) lowering.

[42] *Chung TH, Shim JY, Kwon YJ, Lee YJ*. **High triglyceride to high-density lipoprotein cholesterol ratio and arterial stiffness in postmenopausal Korean women**. Journal of clinical hypertension (Greenwich, Conn.) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30657241
ABSTRACT
The ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL) is positively linked to insulin resistance, and it has emerged as an independent predictor of cardiovascular disease.

Menopause is characterized by various detrimental metabolic and vascular changes that may lead to high TG with low HDL cholesterol and arterial stiffness. Several epidemiological studies have reported that high TG/HDL ratio has a positive association with arterial stiffness in both adult and adolescent populations; it is not known whether TG/HDL ratio is related to brachial-ankle PWV (baPWV) in postmenopausal women. Thus, the authors aimed to investigate the association between TG/HDL ratio and arterial stiffness as measured by baPWV in 434 postmenopausal women. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for high baPWV were calculated after adjusting for confounding variables across TG/HDL ratio quartiles using multiple logistic regression analysis. The mean values of meaningful cardiometabolic variables increased with TG/HDL ratio quartiles. The adjusted baPWV (SEs) significantly increased with TG/HDL quartiles: Q1 = 1412 (22.1), Q2 = 1469 (21.4), Q3 = 1482 (21.0), and Q4 = 1505 (21.6) cm/s after adjusting for age, body mass index (BMI), and systolic blood pressure. The OR (95% CI) of the highest TG/HDL ratio quartile as compared to the lowest TG/HDL ratio quartile for high PWV was 2.77 (1.16-6.63) after adjusting for age, BMI, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, total cholesterol level, hypertension, log-transformed C-reactive protein, and the use of antihypertensive and lipid-lowering drugs. The TG/HDL ratio was positively and independently associated with arterial stiffness in postmenopausal Korean women.

[43] *Barahman M, Zhang W, Yaffe Harris H et al.* **Radiation-primed hepatocyte transplantation in murine monogeneic dyslipidemia normalizes cholesterol and prevents atherosclerosis**. Journal of hepatology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30654068

ABSTRACT

BACKGROUND & AIMS: Binding of the apolipoprotein E (ApoE)-containing lipoprotein complex to the low-density lipoprotein receptor (LDLR) is essential for cholesterol and lipid homeostasis. Inherited abnormalities in ApoE or LDLR function result in early onset cardiovascular disease and death, and lipid-lowering therapeutics, e.g statins or PCSK9 inhibitors are ineffective in the absence of LDLR or ApoE function. Liver transplantation corrects these metabolic disorders as hepatocytes are central to lipid homeostasis. Hepatic cell transplantation is a potential alternative to liver transplantation for many inherited liver-based disorders. However, physiological levels of hepatocyte engraftment and repopulation requires a competitive proliferative advantage of transplanted cells over host hepatocytes, as we have demonstrated previously by preparative open hepatic irradiation (HIR) of the recipient liver and expression of hepatic growth factor via an adenoviral vector (AdenoHGF). METHODS: Here we report a well-tolerated regimen of image guided conformal external-beam hepatic irradiation method targeting the median and right lobes that enhance cell transplant engraftment and repopulation of the liver in ApoE-deficient mice when combined with administration of the hepatic mitogen GC-1, a thyroid hormone receptor-beta agonist mimetic. RESULTS: The preparative regimen leads to robust liver repopulation by transplanted hepatocytes, with associated normalization of serum cholesterol and prevention of atherosclerosis in recipient mice CONCLUSIONS: Significant hepatic repopulation and the cure of dyslipidemia in this model using a novel and well-tolerated preparative regimen suggest a clinical potential for the application of this method in the treatment of inherited metabolic diseases of the liver. Lay

Summary Hepatocyte transplantation is a promising alternative to liver transplantation for the treatment of liver diseases but is inefficient as growth of transplanted cells in the liver is restricted, limiting therapeutic benefits. Preparative treatments improve the efficiency of this procedure but so far, no clinically-feasible options are available. In this study we develop a novel well-tolerated preparative treatment to improve growth of cells in the liver and then demonstrate that this treatment completely cures an inherited lipid disorder in a mouse model.

[44] *Seidah NG*. **The Elusive Inhibitory Function of the Acidic N-Terminal Segment of the Prodomain of PCSK9: The Plot Thickens**. Journal of molecular biology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30658056
ABSTRACT

[45] *Ultsch M, Li W, Eigenbrot C et al.* **Identification of a Helical Segment within the Intrinsically Disordered Region of the PCSK9 Prodomain**. Journal of molecular biology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30653992
ABSTRACT
Proprotein convertase subtilisin/kexin 9 (PCSK9) is a key regulator of lipid metabolism by degrading liver LDL receptors. Structural studies have provided molecular details of PCSK9 function. However, the N-terminal acidic stretch of the PCSK9 prodomain (Q31-T60) has eluded structural investigation, since it is in a disordered state. The interest in this region is intensified by the presence of human missense mutations associated with low and high LDL-c levels (E32K, D35Y and R46L, respectively), as well as two posttranslationally modified sites, sulfated Y38 and phosphorylated S47. Herein we show that a segment within this region undergoes disorder-to-order transition. Experiments with acidic-stretch derived peptides demonstrated that the folding is centered at the segment Y38-L45, which adopts an alpha-helix as determined by nuclear magnetic resonance analysis of free peptides and by X-ray crystallography of peptides in complex with antibody 6E2 (Ab6E2). In the Fab6E2-peptide complexes, the structured region features a central 2 1/4-turn alpha-helix and encompasses up to 2/3 of the length of the acidic stretch, including the missense mutations and posttranslationally modified sites. Experiments with helix-breaking proline substitutions in peptides and in PCSK9 protein indicated that Ab6E2 specifically recognizes the helical conformation of the acidic stretch. Therefore, the observed quantitative binding of Ab6E2 to native PCSK9 from various cell lines suggests that the disorder-to-order transition is a true feature of PCSK9 and not limited to peptides. Because the helix provides a constrained spatial orientation of the missense mutations and the posttranslationally modified residues, it is probable that their biological functions take place in the context of an ordered conformational state.

[46] *Yang R, Hu Z, Zhang P et al.* **Probucol ameliorates hepatic stellate cell activation and autophagy is associated with farnesoid X receptor**. Journal of pharmacological sciences 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30638990
ABSTRACT
Probucol has antioxidant effects and inhibits inflammation. Farnesoid X receptor (FXR) is a nuclear receptor that regulates autophagy, which is regarded as the key cause of the activation of hepatic stellate cell (HSC). In this study, the effects of probucol on HSC activation and

autophagy in vitro and vivo and the role of FXR in this progress were investigated. Results showed that probucol ameliorated hepatic fibrosis and autophagy, and increased the expression of FXR in liver in a mouse model of fibrosis induced by CCl4. And probucol could alleviate lipopolysaccharide-induced autophagy and HSC activation in vitro. In addition, probucol increased FXR expression, and the Z-guggulsterone, an antagonist of FXR, could block the effects of probucol on HSC activation and autophagy. Additionally, agonists of FXR could suppress LPS-induced autophagy and activation. These results suggest that probucol could ameliorate hepatic fibrosis, and inhibit HSC autophagy and activation, and these effects are associated with FXR.

[47] *Lung YJ, Weng WC, Wu CL, Huang WY*. **Association Between Total Cholesterol and 5 year Mortality in Patients with Carotid Artery Stenosis and Poststroke Functional Dependence**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30642665
ABSTRACT
BACKGROUND: Aggressive lipid-lowering treatment reduces the risk of cardiovascular events, but remains controversial in stroke patients. We investigate the influence of total cholesterol level on 5-year outcomes of ischemic stroke patients with high-grade internal carotid artery (ICA) stenosis and poststroke functional dependence. METHODS: One-hundred and ninety-six acute ischemic stroke patients with high-grade ICA stenosis and modified Rankin Scale score >/= 3 upon discharge were enrolled and prospectively observed for 5 years. Patients were divided into 2 groups according to total cholesterol level at admission: >/=200 mg/dL or <200 mg/dL. Demographic features, vascular risk factors, co-morbidities, and outcomes were compared between the 2 groups. RESULTS: 117 (59.7%) patients had higher and 79 (40.3%) patients had lower total cholesterol levels. The prevalence of older age and atrial fibrillation was significantly higher in patients with lower total cholesterol; the prevalence of diabetes mellitus was higher in patients with higher total cholesterol. After adjusting for the established clinical predictors of adverse outcomes, the multivariate Cox regression revealed that lower total cholesterol level is a significant predictor of 5-year mortality (HR (hazard ratio)=1.88, 95% CI (confidence interval)=1.09-3.23, P=.023). CONCLUSIONS: Lower total cholesterol level is associated with increased risk of 5-year mortality in ischemic stroke patients with high-grade ICA stenosis and post-stroke functional dependence. Aggressive treatment of hyperlipidemia should be carefully considered in these patients although it could reduce the risk of atherosclerotic cardiovascular diseases and stroke recurrence in some stroke patients.

[48] *Zhang H, Zhao X, Wang C et al.* **A Preliminary Study of the Association between Apolipoprotein E Promoter Methylation and Atherosclerotic Cerebral Infarction**. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30658954
ABSTRACT
AIM: To investigate association of Apolipoprotein E (ApoE) gene promoter methylation with atherosclerotic cerebral infarction (ACI) in the Han Chinese population. METHODS: Twenty-six ACI patients (the case group) and 26 healthy (the control group) were recruited randomly from

Henan Han nationality population, from April 2016 to August 2016. Bisulfite pyrosequencing technology was used to examine the role of the aberrant gene promoter methylation in ACI in Han Chinese population. Especially, we used the odds ratio and 95% confidence interval (95% CI) method to elevate the correlation between ApoE Promoter Methylation and ACI. RESULTS: The case group was significantly more likely to have hypertension and carotid atherosclerotic plaques (Table 1). The case group had significantly lower levels of high-density lipoprotein cholesterol (HDL-C), folate, and higher levels of homocysteine (Table 2). We observed that ACI patients (n=26) had significantly higher methylation levels at cytosine-phosphate-guanine (CpG) 14 and CpG16 compared with controls (n=26) (Table 3). Importantly, our results indicated a significant association between ApoE promoter methylation and ACI (OR=16.146; 95% CI, 1.154-225.832; P* < .05; P*: adjusted for age, gender, carotid atherosclerotic plaque, hypertension, HDL-C, homocysteine, and folate) (Table 4). CONCLUSIONS: Our study indicates that ApoE promoter methylation may be associated with ACI in Han Chinese people.

[49] *Ahmad S, Moorthy MV, Demler OV et al.* **Assessment of Risk Factors and Biomarkers Associated With Risk of Cardiovascular Disease Among Women Consuming a Mediterranean Diet**. JAMA network open 2018; 1:e185708.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30646282

ABSTRACT

Importance: Higher Mediterranean diet (MED) intake has been associated with lower risk of cardiovascular disease (CVD), but limited data are available about the underlying molecular mechanisms of this inverse disease association in human populations. Objective: To better characterize the relative contribution of traditional and novel factors to the MED-related risk reduction in CVD events in a US population. Design, Setting, and Participants: Using a prospective cohort design, baseline MED intake was assessed in 25994 initially healthy US women in the Women's Health Study who were followed up to 12 years. Potential mediating effects of a panel of 40 biomarkers were evaluated, including lipids, lipoproteins, apolipoproteins, inflammation, glucose metabolism and insulin resistance, branched-chain amino acids, small-molecule metabolites, and clinical factors. Baseline study information and samples were collected between April 30, 1993, and January 24, 1996. Analyses were conducted between August 1, 2017, and October 30, 2018. Exposures: Intake of MED is a 9-category measure of adherence to a Mediterranean dietary pattern. Participants were categorized into 3 levels based on their adherence to the MED. Main Outcomes and Measures: Incident CVD confirmed through medical records and the proportion of CVD risk reduction explained by mediators. Results: Among 25994 women (mean [SD] age, 54.7 [7.1] years), those with low, middle, and upper MED intakes composed 39.0%, 36.2%, and 24.8% of the study population and experienced 428 (4.2%), 356 (3.8%), and 246 (3.8%) incident CVD events, respectively. Compared with the reference group who had low MED intake, CVD risk reductions were observed for the middle and upper groups, with respective HRs of 0.77 (95% CI, 0.67-0.90) and 0.72 (95% CI, 0.61-0.86) (P for trend < .001). The largest mediators of the CVD risk reduction of MED intake were biomarkers of inflammation (accounting for 29.2% of the MED-CVD association), glucose metabolism and insulin resistance (27.9%), and body mass index (27.3%), followed by blood pressure (26.6%), traditional lipids (26.0%), high-density lipoprotein measures (24.0%) or very low-density lipoprotein measures (20.8%), with lesser contributions

from low-density lipoproteins (13.0%), branched-chain amino acids (13.6%), apolipoproteins (6.5%), or other small-molecule metabolites (5.8%). Conclusions and Relevance: In this study, higher MED intake was associated with approximately one-fourth relative risk reduction in CVD events, which could be explained in part by known risk factors, both traditional and novel.

[50] *Khunti K, Danese MD, Kutikova L et al.* **Association of a Combined Measure of Adherence and Treatment Intensity With Cardiovascular Outcomes in Patients With Atherosclerosis or Other Cardiovascular Risk Factors Treated With Statins and/or Ezetimibe**. JAMA network open 2018; 1:e185554.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30646277
ABSTRACT
Importance: Both adherence and treatment intensity can alter the effectiveness of lipid-lowering therapy in routine clinical practice. Objective: To evaluate the association of adherence and treatment intensity with cardiovascular outcomes in patients with documented cardiovascular disease (CVD), type 2 diabetes without CVD or chronic kidney disease (CKD), and CKD without CVD. Design, Setting, and Participants: Retrospective cohort study using the Clinical Practice Research Datalink from January 2010 through February 2016. United Kingdom primary care was the setting. Participants were newly treated patients who received their first statin and/or ezetimibe prescription between January 1, 2010, and December 31, 2013, plus an additional prescription for statins and/or ezetimibe during the following year. Exposures: Adherence was assessed annually using the proportion of days covered, with adherent defined as a proportion of days covered of 80% or higher. Treatment intensity was classified according to guidelines based on the expected percentage of low-density lipoprotein cholesterol (LDL-C) reduction as low (<30% reduction), moderate (30% to <50% reduction), or high (>/=50% reduction). Adherence and treatment intensity were multiplied to create a combined measure, reflecting treatment intensity after accounting for adherence. Main Outcomes and Measures: Composite end point of cardiovascular death or hospitalization for myocardial infarction, unstable angina, ischemic stroke, heart failure, or revascularization. Hazard ratios (HRs) were estimated against patients not treated for 1 year or longer. Results: Among a total of 29797 newly treated patients, there were 16701, 12422, and 674 patients with documented CVD, type 2 diabetes without CVD or CKD, and CKD without CVD, respectively; mean (SD) ages were 68.3 (13.2), 59.3 (12.4), and 67.3 (15.1) years, and male proportions were 60.6%, 55.0%, and 47.0%. In the documented CVD cohort, patients receiving high-intensity therapy were more likely to be adherent over time (84.1% in year 1 and 72.3% in year 6) than patients receiving low-intensity therapy (57.4% in year 1 and 48.4% in year 6). Using a combined measure of adherence and treatment intensity, a graded association was observed with both LDL-C reduction and CVD outcomes: each 10% increase in the combined measure was associated with a 10% lower risk (HR, 0.90; 95% CI, 0.86-0.94). Adherent patients receiving a high-intensity regimen had the lowest risk (HR, 0.60; 95% CI, 0.54-0.68) vs patients untreated for 1 year or longer. Findings in the other 2 cohorts were similar. Conclusions and Relevance: Results of this study demonstrate that the lowest cardiovascular risk was observed among adherent patients receiving high-intensity therapy, and the highest cardiovascular risk was observed among nonadherent patients receiving low-intensity therapy. Strategies that improve adherence and greater use of intensive therapies could substantially improve cardiovascular risk.

[51] *Patel MS, Kurtzman GW, Kannan S et al.* **Effect of an Automated Patient Dashboard Using Active Choice and Peer Comparison Performance Feedback to Physicians on Statin Prescribing: The PRESCRIBE Cluster Randomized Clinical Trial**. JAMA network open 2018; 1:e180818.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30646039
ABSTRACT
Importance: Statins are not prescribed to approximately 50% of patients who could benefit from them. Objective: To evaluate the effectiveness of an automated patient dashboard using active choice framing with and without peer comparison feedback on performance to nudge primary care physicians (PCPs) to increase guideline-concordant statin prescribing. Design, Setting, and Participants: This 3-arm cluster randomized clinical trial was conducted from February 21, 2017, to April 21, 2017, at 32 practice sites in Pennsylvania and New Jersey. Participants included 96 PCPs and 4774 patients not previously receiving statin therapy. Data were analyzed from April 25, 2017, to June 16, 2017. Interventions: Primary care physicians in the 2 intervention arms were emailed a link to an automated online dashboard listing their patients who met national guidelines for statin therapy but had not been prescribed this medication. The dashboard included relevant patient information, and for each patient, PCPs were asked to make an active choice to prescribe atorvastatin, 20 mg, once daily, atorvastatin at another dose, or another statin or not prescribe a statin and select a reason. The dashboard was available for 2 months. In 1 intervention arm, the email to PCPs also included feedback on their statin prescribing rate compared with their peers. Primary care physicians in the usual care group received no interventions. Main Outcomes and Measures: Statin prescription rates. Results: Patients had a mean (SD) age of 62.4 (8.3) years and a mean (SD) 10-year atherosclerotic cardiovascular disease risk score of 13.6 (8.2); 2625 (55.0%) were male, 3040 (63.7%) were white, and 1318 (27.6%) were black. In the active choice arm, 16 of 32 PCPs (50.0%) accessed the patient dashboard, but only 2 of 32 (6.3%) signed statin prescription orders. In the active choice with peer comparison arm, 12 of 32 PCPs (37.5%) accessed the patient dashboard and 8 of 32 (25.0%) signed statin prescription orders. Statins were prescribed in 40 of 1566 patients (2.6%) in the usual care arm, 116 of 1743 (6.7%) in the active choice arm, and 117 of 1465 (8.0%) in the active choice with peer comparison arm. In the main adjusted model, compared with usual care, there was a significant increase in statin prescribing in the active choice with peer comparison arm (adjusted difference in percentage points, 5.8; 95% CI, 0.9-13.5; P = .008), but not in the active choice arm (adjusted difference in percentage points, 4.1; 95% CI, -0.8 to 13.1; P = .11). Conclusions and Relevance: An automated patient dashboard using both active choice framing and peer comparison feedback led to a modest but significant increase in guideline-concordant statin prescribing rates. Trial Registration: ClinicalTrials.gov Identifier: NCT03021759.

[52] *Worm D, Madsbad S, Hansen DL*. **Metabolic Health in Severely Obese Subjects: A Descriptive Study**. Metab Syndr Relat Disord 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30649996
ABSTRACT

BACKGROUND: The prevalence of metabolically healthy obese (MHO) subjects among morbidly obese subjects is poorly described. AIM: To describe the prevalence of metabolically healthy subjects in a group of morbidly obese referred for bariatric surgery. METHODS: Descriptive cross-sectional study, 1209 subjects (825 women/384 men) mean body mass index (BMI) of 45.6 (range: 35-72.6) kg/m(2) and mean age of 42.9 (range: 18-72) years were included. Metabolically unhealthy obese subjects had at least two metabolic risk factors: systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or use of antihypertensive medication, diagnosed diabetes with a HbA1c >6.5% (>48 mmol/mol) or use of antidiabetic medication, high plasma triglycerides or low plasma high-density lipoprotein, or use of lipid-lowering medication. MHO subjects had one or no metabolic risk factors. RESULTS: Thirty-four percent (413/1209) were characterized as MHO subjects. The MHO stage was characterized by female sex, younger age, and lower neck and waist circumferences. The odds ratio of metabolic unhealthy was 1.12 (1.07-1.17, P < 0.001) and 1.02 (1.01-1.04, P < 0002) for every 1 cm increase in neck and waist circumferences, respectively, and 0.94 (0.91-0.97, P < 0.001) for every 1 U increase in BMI and 1.04 (1.03-1.05, P < 0.001) for every 1 year increase in age. CONCLUSIONS: Among severely obese subjects, 34% were classified as having a metabolically healthy state, which was more likely to occur in females, younger individuals and was associated with a lower neck and waist circumferences, younger age, and higher BMI. Whether a group of MHO subjects will remain healthy lifelong is unknown.

[53] *Omori M, Okuma Y, Hakozaki T, Hosomi Y*. **Statins improve survival in patients previously treated with nivolumab for advanced non-small cell lung cancer: An observational study**. Molecular and clinical oncology 2019; 10:137-143.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30655989
ABSTRACT
There are a number of suggested predictive factors of nivolumab for non-small cell lung cancer (NSCLC), however, there is not enough evidence to determine a single factor that can predict the efficacy of nivolumab. As the progress of biomarkers for cancer treatment is improving, it has been speculated that certain clinical factors serve an important role when predicting the outcome of chemotherapy. A total of 67 patients treated with nivolumab for NSCLC from 2016-2017 were prospectively investigated. Age, sex, the Eastern Cooperative Oncology Group Performance Status, histology, epidermal growth factor receptor (EGFR) mutation, history of chemotherapy, smoking status, use of statins, use of fibrates, use of dipeptidyl peptidase-4 (DPP-4) inhibitors, and use of metformin were examined as clinical factors. Statistical analyses were performed using the Kaplan-Meier method and Cox regression adjusted for risk factors and the tumor response of 67 patients was assessed. The patients had a median age of 67 years (range, 36-87 years), and 46 males and 21 females were enrolled; performance status 0/1 was 59. Cases were categorized as adenocarcinoma (n=41), squamous cell carcinoma (n=17) and other (n=9). A total of 13 patients (19.4%) had EGFR mutations. These clinical factors were not statistically significant in overall survival (OS). Clinical laboratory findings, complications and use of medical agents including antidiabetes mellitus or lipidemia were also analyzed. Statins exhibited statistical significance for response (P=0.02). Time-to-treatment failure (TTF) in statin-use group was not reached [95% confidence interval (CI): 1.9-not reached] and was 4.0 months (95% CI: 2.0-5.4) in the non-statin group (P=0.039). The median OS in statin-use group was not

reached (95% CI: 8.7-not reached) and was 16.5 months (95% CI: 7.5-not reached) in the non-statin group (P=0.058). NSCLC patients previously treated with nivolumab who were administered statins exhibited an increased response rate and longer TTF. This response was not statistically significant in OS.

[54] *Springer M, Moco S*. **Resveratrol and Its Human Metabolites-Effects on Metabolic Health and Obesity**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30641865
ABSTRACT
Resveratrol is one of the most widely studied polyphenols and it has been assigned a plethora of metabolic effects with potential health benefits. Given its low bioavailability and extensive metabolism, clinical studies using resveratrol have not always replicated in vitro observations. In this review, we discuss human metabolism and biotransformation of resveratrol, and reported molecular mechanisms of action, within the context of metabolic health and obesity. Resveratrol has been described as mimicking caloric restriction, leading to improved exercise performance and insulin sensitivity (increasing energy expenditure), as well as having a body fat-lowering effect by inhibiting adipogenesis, and increasing lipid mobilization in adipose tissue. These multi-organ effects place resveratrol as an anti-obesity bioactive of potential therapeutic use.

[55] *Thompson M, Hein N, Hanson C et al.* **Omega-3 Fatty Acid Intake by Age, Gender, and Pregnancy Status in the United States: National Health and Nutrition Examination Survey 2003(-)2014**. Nutrients 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30650613
ABSTRACT
Despite the importance of n-3 fatty acids for health, intakes remain below recommended levels. The objective of this study was to provide an updated assessment of fish and n-3 fatty acid intake (i.e., eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and EPA+DHA) in the United States using the 2003(-)2014 National Health and Nutrition Examination Survey (NHANES) data (n = 45,347)). Over this survey period, toddlers, children, and adolescents (aged 1(-)19) had significantly lower n-3 fatty acid intake ($p < 0.001$) compared to adults and seniors, which remained significant after adjusting for caloric intake. Females demonstrated lower n-3 fatty acid intake than males ($p < 0.001$), with adult and senior women having significantly lower intakes compared to men in the same age categories ($p < 0.001$) after adjustment for energy intake. Women also consumed less fish than men (5.8 versus 6.1 servings/month, $p < 0.001$). The estimated intakes of n-3 fatty acids in pregnant women did not differ from non-pregnant women ($p = 0.6$ for EPA+DHA), although pregnant women reported consuming less high n-3 fatty acid-containing fish than non-pregnant women (1.8 versus 2.6 servings/month, $p < 0.001$). Our findings indicate that subgroups of the population may be at higher risk of n-3 fatty acid intakes below recommended levels.

[56] *Malinowski SS, Barber KE, Kishk OA et al.* **Effect of fish oil supplement administration method on tolerability and adherence: a randomized pilot clinical trial**. Pilot and feasibility studies 2019; 5:3.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30637118

ABSTRACT

Objectives: Anecdotally, several strategies have been suggested in order to improve tolerability of fish oil supplements, but there is little evidence supporting any of these strategies. The aim of this study was to determine if there is a difference among four methods of oral administration of fish oil supplementation in terms of tolerability and adherence. Methods: A randomized, prospective, open-label, four-arm pilot study was conducted on 60 healthy adult subjects randomized to different fish oil supplement administration methods with (1) milk, (2) food, (3) an empty stomach, and (4) frozen capsules prior to ingestion. Each subject was instructed to take two capsules three times daily for 30 consecutive days. Adherence was assessed by pill counts. Adverse effects were assessed by survey and patient exit interview. Results: No apparent differences were demonstrated among the four administration groups in terms of adherence, reasons for non-adherence, or self-reported adverse effects. Conclusions: Method of administration did not affect rates of adherence or incidence of adverse effects in a small cohort of healthy adults taking fish oil supplement capsules for 30 days. Trial registration: ClinicalTrials.gov NCT01471366. Registered November 16, 2011.

[57] *Diamond DM, de Lorgeril M, Kendrick M et al.* **Formal comment on "Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease"**. PloS one 2019; 14:e0205138.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30653537

ABSTRACT

Statins have been prescribed for primary prevention of cardiovascular disease (CVD) for nearly 3 decades. Throughout this period key opinion leaders in the field have been dismayed by the high rate of non-adherence of patients to follow their statin regimen. Hope et al., [1] have addressed this issue by providing a systematic review of research on predictors of statin adherence for primary prevention of CVD. However, their review does not address the ongoing debate as to whether statin treatment is warranted for primary prevention of CVD, nor does it adequately address concerns regarding adverse effects of statins. We have therefore written a commentary which provides a broader perspective on the benefits versus harms of statin therapy. Our perspective of the literature is that non-adherence to statin treatment for primary prevention of CVD is justified because the meager benefits are more than offset by the extensive harms.

[58] *Hope HF, Binkley GM, Fenton S et al.* **Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease**. PloS one 2019; 14:e0201196.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30653535

ABSTRACT

INTRODUCTION: Previous research has shown that statin adherence for the primary prevention of CVD is lower compared to secondary prevention populations. Therefore the aim of this systematic review was to review predictors of statin adherence for the primary prevention of CVD. METHODS: A systematic search of papers published between Jan 1984 and May 2017 was conducted in PubMed, PsycINFO, EMbase and CINAHL databases. A study was eligible for inclusion if; 1) it was a study of the general population or of patients with familial

hypercholesterolemia, hypertension, diabetes or arthritis; 2) statins were prescribed; 3) adherence was defined and measured as the extent to which patients followed their statin regimen during the period of prescription, and 4) it was an original trial or observational study (excluding case reports). A study was subsequently excluded if 1) results were not presented separately for primary prevention; 2) it was a trial of an intervention (for example patient education). Papers were reviewed by two researchers and consensus agreed with a third. A quality assessment (QA) tool was used to formally assess each included article. To evaluate the effect of predictors, data were quantitatively and qualitatively synthesised. RESULTS: In total 19 studies met the inclusion criteria and nine were evaluated as high quality using the QA tool. The proportion of patients classed as "adherent" ranged from 17.8% to 79.2%. Potential predictors of statin adherence included traditional risk factors for CVD such as age, being male, diabetes and hypertension. Income associated with adherence more strongly in men than women, and highly educated men were more likely and highly educated women less likely to be adherent. Alcohol misuse and high BMI associated with non-adherence. There was no association between polypharmacy and statin adherence. The evidence base for the effect of other lifestyle factors and health beliefs on statin adherence was limited. CONCLUSION: Current evidence suggests that patients with more traditional risk factors for CVD are more likely to be adherent to statins. The implications for future research are discussed.

[59] *Kuhl M, Binner C, Jozwiak J et al.* **Treatment of hypercholesterolaemia with PCSK9 inhibitors in patients after cardiac transplantation**. PloS one 2019; 14:e0210373.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30650126

ABSTRACT

BACKGROUND: Hypercholesterolaemia is common in patients after cardiac transplantation. Monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) reduce low-density lipoprotein (LDL) cholesterol levels and subsequently the risk of cardiovascular events in patients with dyslipidaemia. There are no published data on the effect of this medication class on cholesterol levels in patients after cardiac transplantation. METHODS: In this retrospective study we investigated patients who were treated with PCSK9 inhibitors either because of intolerance of statins or residual hypercholesterolaemia with evidence of cardiac allograft vasculopathy. We compared the data of patients prior to the start with these medications with their most recent dataset. RESULTS: Ten patients (nine men; mean age 58+/-6 years) underwent cardiac transplantation 8.3+/-4.5 (range 3-15) years ago. The treatment duration of Evolocumab or Alirocumab was on average 296+/-125 days and lead to a reduction of total Cholesterol (281+/-52 mg/dl to 197+/-36 mg/dl; p = 0.002) and LDL Cholesterol (170+/-22 mg/dl to 101+/-39 mg/dl; p = 0.001). No significant effects on HDL Cholesterol, BNP, Creatin Kinase or hepatic enzymes were noticed. There were no unplanned hospitalisations, episodes of rejections, change of ejection fraction or opportunistic infections. Both patients on Alirocumab developed liver pathologies: One patient died of hepatocellular carcinoma and the other developed hepatitis E. CONCLUSIONS: Our study demonstrates that the PCSK9 inhibitors Evolocumab and Alirocumab lead to a significant reduction of LDL Cholesterol in heart transplantation recipients. No effect on cardiac function or episodes of rejections were noticed. Larger and long-term studies are needed to establish safety and efficacy of PCSK9 inhibitors after cardiac transplantation.

[60] *Kwiatkowska K, Ciesielska A*. **Lipid-mediated regulation of pro-inflammatory responses induced by lipopolysaccharide**. Postepy biochemii 2018; 64:175-182.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30656902
ABSTRACT
Lipopolysaccharide (LPS, endotoxin) is the component of the outer membrane of Gramnegative bacteria which upon infection induces the body's inflammatory reaction facilitating eradication of pathogens. However, exaggerated reactions to LPS can lead to potentially deadly sepsis while chronic, low-grade inflammation is linked with the development of several metabolic diseases, like type 2 diabetes. These processes are initiated by the binding of LPS to CD14 protein and the TLR4/MD2 receptor complex located in the plasma membrane of immune cells and also by the activation of a cytoplasmic multi-protein complex called the inflammasome. Recent studies have shown that lipids of the plasma membrane and endomembranes are important regulators of LPS-triggered signaling pathways. In this review we summarize those data emphasizing the role of phosphatidylinositols and modification of proteins by palmitoylation. Dysregulation of the lipid-dependent steps of the LPS-induced signaling can lead to excessive production of cytokines during sepsis and metabolic diseases linked with endotoxemia.

[61] **Ezetimibe + statin: insufficient benefit**. Prescrire international 2016; 25:245-246.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30645833
ABSTRACT
After an acute coronary syndrome, the 6-year results of the "IMPROVE-IT" randomized trial showed a 1.6% reduction in the number of nonfatal myocardial infarctions with the ezetimibe + simvastatin combination compared with simvastatin alone, but no reduction in mortality.

[62] *Joentausta RM, Rannikko A, Murtola TJ*. **Prostate cancer survival among statin users after prostatectomy in a Finnish nationwide cohort**. Prostate 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30652328
ABSTRACT
BACKGROUND: Improved prostate cancer (PCa) survival by statin use has been reported among PCa patients managed with radiation or androgen deprivation therapy (ADT), while results are controversial for men managed surgically. We evaluate the association between cholesterol-lowering medication with initiation of ADT and disease-specific death among PCa cases who underwent radical prostatectomy in Finland between 1995 and 2013. METHODS: The study cohort included 14 424 men with PCa who underwent radical prostatectomy in Finland between 1995 and 2013. Cases were identified from national hospital discharge registry. Clinical data were amended from patient files of the treating hospitals. Information on co-morbidities, additional radiation- or chemotherapy, and causes of deaths were collected from national registries. Personal-level data on medication use during 1995-2014 were gathered from national prescription database. Registry linkages were carried out using personal identification number. Lipid-lowering drugs were categorized into statins and non-statin drugs. Risk of PCa death and initiation of ADT was analyzed using Cox-regression model with adjustment for age, radiation therapy, chemotherapy, co-morbidities and other drug use. Statin use was analyzed as time-dependent variable. Delayed risk associations were evaluated in lag-

time analysis. RESULTS: Compared to non-users the risk of PCa death was significantly lower among statin users before PCa diagnosis (HR 0.70, 95%CIs 0.52-0.95). For statin use after PCa diagnosis the risk was lowered in age-adjusted analysis (HR 0.76 95%CIs 0.62-0.93) but not after multivariable-adjustment. Post-diagnostic statin use was associated with improved PCa-specific survival in 1, 3 and 5 years lag-time analyses. The risk reduction was clearest for statin use initiated 5 years earlier (HR 0.71 95%CIs 0.55-0.92). Use of statins both before and after PCa diagnosis was associated with reduced risk of ADT use (HR 0.72 95%CIs 0.65-0.80 and HR 0.73, 95%CI 0.67-0.80, respectively). The risk of ADT decreased by increasing intensity of statin use before diagnosis. CONCLUSION: Statin use among surgically treated PCa patients has significant association with decreased risk of starting ADT and PCa death. The risk is lowered especially among men with statin use before PCa diagnosis and in men who used statins at high-dose. Our results are hypothesis generating due to retrospective study design.

[63] *Kraege V, Aebischer O, Chocron Y et al.* **[The internal medicine articles that struck us the most in 2018]**. Revue medicale suisse 2019; 15:146-148.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30657265
ABSTRACT
2018 has continued to bring important progress in all areas of internal medicine, impacting our daily practice. From bezafibrate in primary biliary cholangitis to the new Clostridioides difficile guidelines, passing by use of procalcitonine, cristalloids, copeptin and how to administer furosemide, internal medicine journals are full of novelties. Every year, the chief residents of the CHUV internal medicine ward meet up to share their readings : here is their selection of 12 articles, chosen, summarized and commented for you.

[64] *Beverly BEJ, Furr JR, Lambright CS et al.* **In utero exposure to simvastatin reduces postnatal survival and permanently alters reproductive tract development in the Crl:CD(SD) male rat**. Toxicology and applied pharmacology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30639414
ABSTRACT
We showed previously that in utero exposure to the cholesterol-lowering drug simvastatin (SMV) during sex differentiation lowers fetal lipids and testicular testosterone production (T Prod) in Hsd:SD rats. Here, the effects of SMV on fetal lipids and T Prod in Crl:CD(SD) rats were correlated with postnatal alterations in F1 males. The current study was conducted in two parts: 1) a prenatal assessment to confirm and further characterize the dose response relationship among previously reported alterations of SMV on fetal T Prod and the fetal lipid profile and 2) a postnatal assessment to determine the effects of SMV exposure during the periods of major organogenesis and/or sexual differentiation on F1 offspring growth and development. We hypothesized that SMV would have adverse effects on postnatal development and sexual differentiation as a consequence of the disruptions of fetal lipid levels and testicular T Prod since fetal cholesterol is essential for normal intrauterine growth and development and steroid synthesis. In the prenatal assessment, SMV was administered orally at 0, 15.6, 31.25, 62.5, 80, 90, 100, and 110mg SMV/kg/d from GD 14-18, the period that cover the critical window of sex differentiation in the male rat fetus. T Prod was maximally reduced by ~40% at 62.5mg/kg/d, and higher doses induced overt maternal and toxicity. In the postnatal

assessment, SMV was administered at 0, 15.6, 31.25, and 62.5mg/kg/d from GD 8-18 to determine if it altered postnatal development. We found that exposure during this time frame to 62.5mg SMV/kg/d reduced pup viability by 92%, decreased neonatal anogenital distance, and altered testis histology and morphology in 17% of the F1 males. In another group, SMV was administered only during the masculinizing window (GD14-18) at 62.5mg/kg/d to determine if male rat sexual differentiation and postnatal reproductive development were altered. SMV-exposed F1 males displayed female-like areolae/nipples, delayed puberty, and reduced seminal vesicle and levator ani-bulbocavernosus weights. Together, these results demonstrate that in utero exposure to SMV reduces offspring viability and permanently disrupts reproductive tract development in the male offspring. While the effects of high dose, short term in utero exposure to SMV in the adult male are likely androgen-dependent and consistent with the 40% reduction in T Prod in the fetal testes, long-term, lower dose administration induced some effects that were likely not mediated by decreased T Prod.

[65] *Almeida SO, Budoff M*. **Effect of statins on atherosclerotic plaque**. Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30642643
ABSTRACT
Lipid lowering therapy has been the mainstay of cardiovascular risk reduction and prevention. Statin drugs have been shown to reduce serum cholesterol along with significant reduction in morbidity and mortality of cardiovascular disease. Whether these benefits are purely through lipid lowering or pleiotropic (cholesterol independent) effects has yet to be fully understood. Advances in cardiac imaging, from intravascular ultrasound to multi-detector coronary computed tomography angiography, have furthered our understanding of statin's effect on atherosclerotic plaque. Notably, statins play a role in plaque regression with reduction in lipid content. These drugs further stabilize atherosclerotic plaque with thickened fibrous caps and macrocalcification that serves to stabilize atheromas.

[66] *Kubekina MV, Myasoedova VA, Karagodin VP, Orekhov AN*. **[Dietary phospholipids: lipid metabolism and risk factors for cardiovascular diseases]**. Voprosy pitaniia 2017; 86:6-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30645858
ABSTRACT
Eggs are a major source of phospholipids (PL) in the Western diet. Dietary PL have emerged as a potential source of bioactive lipids that may have widespread effects on pathways related to inflammation, cholesterol metabolism, and high-density lipoprotein (HDL) function. Based on pre-clinical studies, egg phosphatidylcholine (PC) and sphingomyelin appeared to regulate cholesterol absorption and inflammation. In clinical studies, egg PL intake is associated with beneficial changes in biomarkers related to HDL reverse cholesterol transport. Recently, egg PC was shown to be a substrate for the generation of trimethylamine N-oxide (TMAO), a gut microbe-dependent metabolite associated with increased cardiovascular disease (CVD) risk. More researches are warranted to examine potential serum TMAO responses to chronic egg ingestion and in different populations, such as diabetics. In this review, the recent basic science, clinical, and epidemiological findings examining egg PL intake and risk of CVD are summarized.

[67] *Li XT, Yuan JL, Hu WL*. **Vertebrobasilar artery dissection manifesting as Millard-Gubler syndrome in a young ischemic stroke patient: A case report**. World journal of clinical cases 2019; 7:73-78.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30637255

ABSTRACT
BACKGROUND: Millard-Gubler syndrome (MGS) is caused by a lesion in the brainstem at the level of the facial nerve nucleus, and it is also a rare ventral pontine syndrome. Vertebrobasilar artery dissection (VAD) is an uncommon cause of ischemic stroke. To the best of our knowledge, this is the first case report on the coexistence of MGS and VAD in a young acute ischemic stroke patient. CASE SUMMARY: We herein describe an unusual case of young acute ischemic stroke patient, presenting with acute right peripheral facial palsy, right abducens palsy, and contralateral hemihypesthesia, manifesting as MGS. After receiving dual antiplatelet therapy with aspirin and clopidogrel, as well as rosuvastatin, the patient recovered significantly. The high-resolution magnetic resonance imaging (MRI) indicated a diagnosis of VAD. CONCLUSION: Our finding further demonstrated that high-resolution MRI is a useful technique to early detect underlying dissection in posterior circulation ischemic stroke.