

Literature update week 04 (2019)

[1] Li X, Dardik A, Guo R et al. **Atorvastatin regulates pericardial patch healing via the microRNA140-ADAM10-ephrinB2 pathway.** American journal of translational research 2018; 10:4054-4064.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30662650>

ABSTRACT

Background: Pericardial patches are frequently used in vascular surgery to close arteriotomies. The early healing of these patches is mediated by attraction of CD34 and ephrinB2-positive cells. Atorvastatin is a commonly used statin drug that promotes healing of cardiovascular injury. We hypothesized that atorvastatin attracts ephrinB2-positive cells by regulating the microRNA140-ADAM10-ephrinB2 pathway during patch healing in the arterial environment. Methods: Pericardial patches were used to close an infra-renal aortic arteriotomy in Wistar rats (male, 200-400 g). Atorvastatin was given to rats at a daily dose of 0 mg, 2.5 mg, 5 mg or 10 mg. Patches were harvested at 1 or 4 weeks and analyzed by histology, immunohistochemistry, immunofluorescence, western blot and qPCR. Result: Animals treated with atorvastatin showed a higher number of infiltrating cells and a thicker patch neointima than the control animals. Furthermore, ADAM10 protein expression decreased ($P<0.01$) and ephrinB2 expression increased ($P<0.01$) in time- and atorvastatin dose-dependent manner. Similarly, ADAM10 mRNA expression decreased ($P<0.01$), while the expression of ephrinB2 mRNA and miR-140 mRNA expression increased ($P<0.01$; $P<0.01$) in a time- and dose-dependent manner. Conclusion: Atorvastatin regulates neointimal growth after pericardial patch angioplasty; atorvastatin is associated with infiltration of ephrinB2-positive cells, diminished ADAM10 expression, and increased ephrinB2 and miR-140 expression. These results suggest new mechanisms for regulating neointimal formation after vascular procedures. Clinical relevance: This study may help physicians to know more healing mechanism after pericardial patch angioplasty. Further, it may reveal some mechanism that how atorvastatin play roles in endothelium repair of the cardiovascular system.

[2] Larsen LE, Stoekenbroek RM, Kastelein JJP, Holleboom AG. **Moving Targets.** Arteriosclerosis, thrombosis, and vascular biology 2019:Atvbaha118312028.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30676072>

ABSTRACT

Statin therapy has delivered tremendous value to society by improving the burden of atherosclerotic cardiovascular disease. Nonetheless, atherosclerotic cardiovascular disease remains the leading cause of death globally. Technological advances such as in the field of genomics have revolutionized drug discovery and development and have revealed novel therapeutic targets to lower low-density lipoprotein cholesterol (LDL-C), as well as other detrimental lipids and lipoproteins. Therapeutic LDL-C lowering prevents atherosclerotic cardiovascular disease with an effect size proportional to absolute LDL-C reductions and time of exposure. This understanding supports the notion that reducing cumulative LDL-C exposure should be a key therapeutic target. PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibiting monoclonal antibodies provides the possibility of reducing LDL-C to very low levels. Novel therapeutic platforms such as RNA inhibition present opportunities to combine robust lipid lowering with infrequent dosing regimens, introducing therapies with vaccine-like properties. The position of lipid-lowering therapies with targets other than LDL-C, such as Lp(a)

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[lipoprotein(a)], TRL (triglyceride-rich lipoproteins), and remnant cholesterol, will likely be determined by the results of ongoing clinical trials. Current evidence suggests that reducing Lp(a) or TRLs could attenuate atherosclerotic cardiovascular disease risk in specific categories of patients. This review provides an overview of the latest therapeutic developments, focusing on their mechanisms, efficacy, and safety.

[3] *Wake M, Oh A, Onishi Y et al. Adherence and persistence to hyperlipidemia medications in patients with atherosclerotic cardiovascular disease and those with diabetes mellitus based on administrative claims data in Japan. Atherosclerosis 2018; 282:19-28.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30669019>

ABSTRACT

BACKGROUND AND AIMS: Real-world data on treatment patterns in Japanese hyperlipidemia patients with diabetes mellitus (DM) or prior atherosclerotic cardiovascular diseases (ASCVD) are lacking. **METHODS:** This is a retrospective, longitudinal cohort analysis of administrative claims data (Japan Medical Data Center [JMDC] and Medical Data Vision [MDV] databases) for patients prescribed a new hyperlipidemia medication between 2014 and 2015. Patients were followed for ≥ 12 months. Outcomes included prescribing patterns, persistence (discontinuations), and adherence (proportion of days covered). **RESULTS:** Data were analyzed for 11,718 and 27,746 DM, and 4101 and 14,356 ASCVD patients from the JMDC and MDV databases, respectively. Among previously-untreated patients, index prescriptions were primarily for moderate statins in the DM (JMDC: 74.7%, MDV: 77.5%) and ASCVD (JMDC: 75.4%, MDV: 78.5%) sub-cohorts. Combinations were rarely prescribed ($\leq 2.5\%$). Previously-treated patients were most frequently prescribed combinations in the DM (JMDC: 46.7%, MDV: 53.6%) and ASCVD (JMDC: 49.3%, MDV: 53.3%) sub-cohorts. Intensive statins were rarely used by previously-untreated ($\leq 1\%$) or previously-treated ($\leq 8\%$) patients in either sub-cohort. Approximately half of previously-untreated patients discontinued hyperlipidemia therapy within 12 months. Adherence was $\geq 80\%$ across most drug classes. **CONCLUSIONS:** Many Japanese hyperlipidemia patients with DM or ASCVD are prescribed single-agent lipid-lowering therapy. Use of intensive therapy is lower than expected, and is suggestive of under-treatment. The low persistence rates are concerning, and warrant further study.

[4] *Gilroy DW, Bishop-Bailey D. LIPID MEDIATORS IN IMMUNE REGULATION AND RESOLUTION. Br J Pharmacol 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30674066>

ABSTRACT

We are all too familiar with the events that follow a bee sting - heat, redness, swelling and pain. These are Celsus' four cardinal signs of inflammation that are driven by very well defined signals and hormones; in fact targeting the factors that drive this onset phase is the basis upon which most current anti-inflammatory therapies were developed. We are also very well aware that within a few hours these cardinal signs normally disappear. In other words, inflammation resolves. When it does not, inflammation persists resulting in damaging chronic conditions. While inflammatory onset is actively driven so also is its resolution - years of research has identified novel internal counter-regulatory signals that work together to switch off inflammation. Among these signals, lipids are potent signaling molecules that regulate an array

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of immune responses including vascular hyper reactivity and pain as well as leukocyte trafficking and clearance, so-called resolution. Here, we collate bioactive lipid research to date and summarise the major pathways involved in their biosynthesis and their role in inflammation as well as resolution.

[5] *Shirouchi B, Furukawa Y, Nakamura Y et al. Inhibition of Niemann-Pick C1-Like 1 by Ezetimibe Reduces Dietary 5beta,6beta-Epoxycholesterol Absorption in Rats. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30671747>

ABSTRACT

PURPOSE: Oxysterols (OCs) are produced from cholesterol by oxidation of the steroidal backbone and side-chain. OCs are present in blood and evidence suggests their involvement in disease development and progression. However, limited information is available regarding the absorption mechanisms and relative absorption rates of dietary OCs. Although ezetimibe is known to inhibit intestinal cholesterol absorption via Niemann-Pick C1-Like 1 (NPC1L1), whether it also inhibits dietary OC absorption is unclear. **METHODS:** We investigated the effects of ezetimibe on OC absorption in rats fed an OC-rich diet containing 10 different OCs. We collected lymphatic fluid using permanent cannulation of the thoracic duct and quantified OC levels. **RESULTS:** Ezetimibe treatment significantly reduced the apparent absorption of 5beta,6beta-epoxycholesterol (5,6beta-epoxy) and its levels in the proximal intestinal mucosa in OC-fed rats. Using *in silico* analyses, the binding energy of NPC1L1 N-terminal domain (NPC1L1-NTD) and 5,6beta-epoxy was found to be similar to that of NPC1L1-NTD and cholesterol, suggesting that polar uncharged amino acids located in the steroidal part of 5,6beta-epoxy were involved. **CONCLUSION:** Our results indicate that ezetimibe-mediated inhibition of dietary OC absorption varies depending on the specific OC, and only the absorption of 5,6beta-epoxy is significantly reduced.

[6] *Becares N, Gage MC, Voisin M et al. Impaired LXRalpha Phosphorylation Attenuates Progression of Fatty Liver Disease. Cell Rep 2019; 26:984-995.e986.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30673619>

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a very common indication for liver transplantation. How fat-rich diets promote progression from fatty liver to more damaging inflammatory and fibrotic stages is poorly understood. Here, we show that disrupting phosphorylation at Ser196 (S196A) in the liver X receptor alpha (LXRalpha, NR1H3) retards NAFLD progression in mice on a high-fat-high-cholesterol diet. Mechanistically, this is explained by key histone acetylation (H3K27) and transcriptional changes in pro-fibrotic and pro-inflammatory genes. Furthermore, S196A-LXRalpha expression reveals the regulation of novel diet-specific LXRalpha-responsive genes, including the induction of *Ces1f*, implicated in the breakdown of hepatic lipids. This involves induced H3K27 acetylation and altered LXR and TBLR1 cofactor occupancy at the *Ces1f* gene in S196A fatty livers. Overall, impaired Ser196-LXRalpha phosphorylation acts as a novel nutritional molecular sensor that profoundly alters the hepatic H3K27 acetylome and

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transcriptome during NAFLD progression placing LXRA phosphorylation as an alternative anti-inflammatory or anti-fibrotic therapeutic target.

[7] Nakada TA, Takahashi W, Nakada E et al. **Genetic polymorphisms in sepsis and cardiovascular disease Do similar risk genes suggest similar drug targets?** *Chest* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30660782>

ABSTRACT

Genetic variants are associated with altered clinical outcome of patients with sepsis and cardiovascular diseases. Common gene signaling pathways may be involved in the pathophysiology of these diseases. A better understanding of genetic commonality among these diseases may enable the discovery of important genes, signaling pathways and therapeutic targets for these diseases. We investigated the common genetic factors by a systematic search of the literature. 24 genes (ADRB2, CD14, FGB, FV, HMOX1, IL1B, IL1RN, IL6, IL10, IL17A, IRAK1, MASP2, MBL, MIR608, MIF, NOD2, PCSK9, PPARG, PROC, SERPINE1, SOD2, SVEP1, TF, TIRAP, TLR1) were extracted as reported genetic variations associated with altered outcome of both sepsis and cardiovascular diseases. Of the 24 genes, the adverse allele (or combinations) was same in 9 genes (ADRB2, FV, HMOX1, IL6, MBL, MIF, NOD2, PCSK9, SERPINE1), and the effect appears to be in the same direction in both sepsis and cardiovascular disease. Shared gene signaling pathways suggest that these are true biological results and could point to overlapping drug targets in sepsis and cardiovascular disease.

[8] Tang SL, Zhao ZW, Liu SM et al. **Pregnancy-Associated Plasma Protein-A Accelerates Atherosclerosis by Regulating Reverse Cholesterol Transport and Inflammation.** *Circulation journal : official journal of the Japanese Circulation Society* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30662023>

ABSTRACT

BACKGROUND: Recent studies have suggested that pregnancy-associated plasma protein-A (PAPP-A) is involved in the pathogenesis of atherosclerosis. This study aim is to investigate the role and mechanisms of PAPP-A in reverse cholesterol transport (RCT) and inflammation during the development of atherosclerosis. Methods and Results: PAPP-A was silenced in apolipoprotein E (apoE(-/-)) mice with administration of PAPP-A shRNA. Oil Red O staining of the whole aorta root revealed that PAPP-A knockdown reduced lipid accumulation in aortas. Oil Red O, hematoxylin and eosin (HE) and Masson staining of aortic sinus further showed that PAPP-A knockdown alleviated the formation of atherosclerotic lesions. It was found that PAPP-A knockdown reduced the insulin-like growth factor 1 (IGF-1) levels and repressed the PI3K/Akt pathway in both aorta and peritoneal macrophages. The expression levels of LXRA, ABCA1, ABCG1, and SR-B1 were increased in the aorta and peritoneal macrophages from apoE(-/-) mice administered with PAPP-A shRNA. Furthermore, PAPP-A knockdown promoted RCT from macrophages to plasma, the liver, and feces in apoE(-/-) mice. In addition, PAPP-A knockdown elevated the expression and secretion of monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), tumor necrosis factor-alpha, and interleukin-1beta through the nuclear factor kappa-B (NF-kappaB) pathway. CONCLUSIONS: The present study results suggest that PAPP-A promotes the development of atherosclerosis in apoE(-/-) mice through reducing RCT capacity and activating an inflammatory response.

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[9] Xu H, Wang T, Liu S et al. **Extreme Levels of Air Pollution Associated with Changes in Biomarkers of Atherosclerotic Plaque Vulnerability and Thrombogenicity in Healthy Adults: The Beijing AIRCHD Study.** *Circulation research* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30661461>

ABSTRACT

RATIONALE: The pathophysiologic mechanisms of air pollution associated exacerbation of cardiovascular events remain incompletely understood. **OBJECTIVE:** To assess whether ambient air pollution can be a trigger of the vulnerable plaque and heightened thrombogenicity through systemic inflammatory pathways. **METHODS AND RESULTS:** In Beijing AIRCHD study, seventy-three healthy adults (mean {plus minus} standard deviation, 23.3 {plus minus} 5.4 years) were followed up in 2014-2016. We estimated associations between air pollutants and biomarkers relevant to atherosclerotic plaque vulnerability, thrombogenicity and inflammation using linear mixed-effects models, and elucidated the biological pathways involved using mediation analyses. Receiver operating characteristic (ROC) analyses were conducted to assess the ability of each biomarker to predict ambient air pollution exposures. High average concentrations of particulate matter in diameter less than 2.5 μm (PM_{2.5}) (91.8 {plus minus} 63.8 $\mu\text{g}/\text{m}^3$) were observed during the study period. Significant increases in circulating biomarkers of plaque vulnerability, namely matrix metalloproteinases (MMP-1, 2, 3, 7, 8 and 9), of 8.6% (95% confidence interval [CI]: 0.1, 17.8) to 141.4% (95% CI: 111.8, 171.0) were associated with interquartile range (IQR) increases in moving averages of PM_{2.5}, number concentrations of particles in sizes of 5-560 nm and black carbon (BC), over the last 1 to 7 days prior to each participant's clinic visit. Higher air pollutant levels were also significantly associated with decreases in tissue inhibitors of MMPs (TIMP-1 and 2), heightened thrombogenicity (shortened prothrombin time [PT] and increases in soluble CD40 ligand [sCD40L], soluble P-selectin [sCD62P], fibrinogen/fibrin degradation products [FDPs]), and elevations in systemic inflammation (interleukin-1 β [IL-1 β], C-reactive protein [CRP], macrophage inflammatory protein-1 α/β [MIP-1 α/β], soluble receptor for advanced glycation end products [sRAGE], insulin-like growth factor-binding protein [IGFBP]-1 and 3). ROC curves showed that several biomarkers can serve as robust pollutant-specific predictors with high versus low BC exposure (area under the ROC curve [AUC] of 0.974 [95% CI: 0.955, 0.992] for MMP-8, AUC of 0.962 [95% CI: 0.935, 0.988] for sRAGE). Mediation analysis further showed that systemic inflammation can mediate up to 46% of the changes in MMPs and thrombogenicity associated with IQR increases in air pollutants. **CONCLUSIONS:** Our results suggest that air pollution may prompt cardiovascular events by triggering vulnerable plaque along with heightened thrombogenicity possibly through systemic inflammatory pathways.

[10] Rossato LT, Schoenfeld BJ, de Oliveira EP. **Is there sufficient evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults?** *Clinical nutrition (Edinburgh, Scotland)* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30661906>

ABSTRACT

Omega-3 (omega-3) is a polyunsaturated fatty acid with anti-inflammatory properties that presents three main forms: alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic

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acid. Recently, studies performed in both young and older adults suggest that omega-3 may improve gains in muscle mass and/or enhance physical function. Thus, the aim of this narrative review was to evaluate the current evidence of omega-3 intake/supplementation on muscle/lean mass (LM) and physical function in young and older adults, and draw research-based conclusions as to the practical implications of findings. We first assessed whether omega-3 intake is associated with muscle mass and strength (observational studies), and then sought to determine whether evidence shows that supplementation of omega-3 increases muscle protein synthesis, LM and strength in adults and older adults (interventional studies). The search was carried out in PubMed and Scopus databases for the periods between 1997 and November 2018. The following keywords were used alone and in combination: omega-3, fish oil, muscle protein synthesis, muscle mass, lean mass, body composition, and physical function. In general, the evidence is mixed as to the effects of omega-3 supplementation on muscle mass in sedentary young and older adults; the hypertrophic effects of supplementation when combined with resistance training remain equivocal. Moreover, there is conflicting evidence as to whether supplementation confers a beneficial effect on muscle function in older adults. Importantly, this conclusion is based on limited data and more studies are needed before omega-3 supplementation can be recommended as a viable strategy for such purposes in clinical practice.

[11] Ashton L, Williams R, Wood L *et al.* **The comparative validity of a brief diet screening tool for adults: The Fruit And Vegetable VAriety index (FAVVA).** *Clinical nutrition ESPEN* 2019; 29:189-197.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30661686>

ABSTRACT

BACKGROUND & AIMS: A brief assessment tool on frequency and variety of fruit and vegetable intake could provide a cost-effective and sustainable approach to improving diet. The primary aim was to evaluate the comparative validity of a brief index of Fruit And Vegetable VAriety (FAVVA) relative to food and nutrient intakes derived from a comprehensive food frequency questionnaire (FFQ). The secondary aim was to evaluate the FAVVA index in relation to fasting plasma carotenoid concentrations. **METHODS:** Dietary intakes and fasting plasma carotenoid concentrations of 99 overweight and obese adults (49.5% female; 44.6 +/- 9.9 years) were assessed at baseline and 3-months. Food and nutrient intakes were assessed using the Australian Eating Survey (AES) FFQ. The FAVVA index was derived from a sub-set of 35 AES questions related to fruit and vegetable intake frequency and variety. Associations were assessed using Spearman's correlation coefficients and linear regression analysis, and agreement using weighted kappa (Kw). **RESULTS:** Total FAVVA score demonstrated moderate to strong, significant (all $p < 0.01$) correlations with total daily intakes of vegetables ($r = 0.75$), vitamin C ($r = 0.71$), fruit ($r = 0.66$), vitamin A ($r = 0.49$), fibre ($r = 0.49$), potassium ($r = 0.46$), magnesium ($r = 0.39$), iron ($r = 0.26$), riboflavin ($r = 0.24$), calcium ($r = 0.23$), zinc ($r = 0.20$) and niacin equivalent ($r = 0.20$). These associations remained significant in the adjusted regression analyses and agreement testing. Total FAVVA was significantly correlated with plasma carotenoid concentrations ($\mu\text{g/dL}$) of alpha-carotene ($r = 0.22$, $p < 0.01$), beta-carotene ($r = 0.26$, $p < 0.001$), beta-cryptoxanthin ($r = 0.22$, $p < 0.01$) and total carotenoids ($r = 0.18$, $p < 0.05$). The associations with alpha-carotene (beta = 0.09, $p < 0.001$), beta-carotene (beta = 0.42,

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$p < 0.05$) and total plasma carotenoids ($\beta = 0.85$, $p < 0.05$) remained significant in the adjusted regression analyses and for agreement testing. CONCLUSIONS: FAVVA is suitable as a brief tool to rank frequency and variety of fruit and vegetable intake.

[12] *Sohrab G, Roshan H, Ebrahimof S et al. Effects of pomegranate juice consumption on blood pressure and lipid profile in patients with type 2 diabetes: A single-blind randomized clinical trial. Clinical nutrition ESPEN* 2019; 29:30-35.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30661697>

ABSTRACT

Pomegranate juice (PJ) has abundant anti-oxidative polyphenolic compounds which are assumed to have cardioprotective effects such as hypotensive properties. This study aimed to investigate the effects of PJ consumption on blood pressure and lipid profile variables in patients with type 2 diabetes. Sixty subjects (30 in intervention group and 30 in control group) were recruited in this single-blind placebo-controlled randomized clinical trial. The volunteers were randomly assigned to one of two groups. Treatment group consumed 200 ml/day PJ for 6 weeks, while control group received no intervention. Systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations were measured following 12-14 h of fasting at baseline and at the end of the study. After 6 weeks of intervention, SBP (13.5 ± 1.5 mmHg vs. 12.3 ± 2.5 , $P < 0.001$) and DBP (7.7 ± 1.6 vs. 7.2 ± 1.6 mmHg, $P < 0.05$) significantly decreased in the intervention group. Similarly, SBP and DBP in the intervention group were significantly lower than the control group after intervention ($P < 0.02$ and $P < 0.03$, respectively). At the end of the intervention, TC, TG, LDL-C and HDL-C did not significantly differ between the intervention group and the control group however, TC and LDL-C decreased significantly compared to pre-trial values within the intervention group. It is concluded that PJ consumption could decrease systolic and diastolic blood pressure in patients with diabetes while having no effect on lipid profile. A more definitive result will be obtained if future studies could be conducted in hyperlipidemic individuals who might be more prone to respond to the lipid-lowering effects.

[13] *Lee E, Gibbs JP, Emery MG et al. Influence of Renal Function on Evolocumab Exposure, Pharmacodynamics, and Safety. Clinical pharmacology in drug development* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30676701>

ABSTRACT

We evaluated the pharmacokinetics, pharmacodynamics, and safety of evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin kexin type 9 (PCSK9), in an open-label, parallel-design study in participants with normal renal function ($n = 6$), severe renal impairment (RI; $n = 6$), or end-stage renal disease (ESRD) receiving hemodialysis ($n = 6$) who received a single 140-mg dose of evolocumab. The effects of evolocumab treatment on low-density lipoprotein cholesterol (LDL-C) lowering and unbound PCSK9 concentrations were similar in the normal renal function group and the renally impaired groups. Geometric mean C_{max} and AUC_{last} values in the severe RI and ESRD hemodialysis groups compared with the normal renal function group were lower but within 37% of the normal renal function group (Jonckheere-Terpstra trend test; C_{max} , $P = .23$; AUC_{last} , $P = .22$) and within 26% after

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adjusting for body weight (mean body weight was approximately 9% higher in the renally impaired groups compared with the normal renal function group). No correlations were observed between exposure and baseline creatinine clearance. No adverse event was determined by the investigators to be related to evolocumab, and there were no trends indicative of clinically important effects on laboratory variables or vital signs. Overall, there were no meaningful differences in evolocumab exposure, as assessed by C_{max} and AUC_{last}, in patients with severe RI and ESRD hemodialysis compared with patients with normal renal function, and LDL-C-lowering effects were similar across groups. These results support the use of evolocumab without dose adjustment in patients who have severe RI or ESRD.

[14] *Ward NC, Page MM, Watts GF. PCSK9 inhibition 2018: riding a new wave of coronary prevention. Clinical science (London, England : 1979) 2019; 133:205-224.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30670671>

ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a hepatic enzyme that regulates the low-density lipoprotein cholesterol (LDL-c) receptor and thus circulating LDL-c levels. With overwhelming evidence now supporting the reduction in LDL-c to lower the risk of cardiovascular disease, PCSK9 inhibitors represent an important therapeutic target, particularly in high-risk populations. Here, we summarise and update the science of PCSK9, including its discovery and the development of various inhibitors, including the now approved monoclonal antibodies. In addition, we summarise the clinical applications of PCSK9 inhibitors in a range of patient populations, as well as the major randomised controlled trials investigating their use in coronary prevention.

[15] *Hong SJ, Jeong HS, Cho JM et al. Efficacy and Safety of Triple Therapy With Telmisartan, Amlodipine, and Rosuvastatin in Patients With Dyslipidemia and Hypertension: The Jeil Telmisartan, Amlodipine, and Rosuvastatin Randomized Clinical Trial. Clinical therapeutics 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30665829>

ABSTRACT

PURPOSE: Fixed-dose combination therapy with telmisartan, amlodipine, and rosuvastatin is needed in patients with hypertension and dyslipidemia for better adherence and cost-effectiveness than free-equivalent combination therapies. This study aimed to compare the efficacy and safety of combination therapy with telmisartan, amlodipine, and rosuvastatin versus telmisartan plus amlodipine or telmisartan plus rosuvastatin in patients with hypertension and dyslipidemia. **METHODS:** The Jeil Telmisartan, Amlodipine, and Rosuvastatin Randomized Clinical Trial (J-TAROS-RCT) was an 8-week, multicenter, randomized, double-blind, parallel, Phase III clinical trial conducted at 9 hospitals in Korea. After a run-in period of >4 weeks, patients who fulfilled the criteria of the National Cholesterol Education Program Adult Treatment Panel III guidelines were eligible for randomization to receive 1 of 3 treatments for 8 weeks: (1) telmisartan/amlodipine 80 mg/10 mg plus rosuvastatin 20 mg, (2) telmisartan/amlodipine 80 mg/10 mg, or (3) telmisartan 80 mg plus rosuvastatin 20 mg. The primary end point was efficacy evaluation of combination therapy with telmisartan/amlodipine/rosuvastatin by comparing the change in mean sitting systolic blood

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pressure (msSBP) and mean percentage change in LDL-C from baseline after 8 weeks of treatment. Adverse events (AEs), clinical laboratory data, and vital signs were assessed in all patients. FINDINGS: Among 148 patients, the changes in msSBP from baseline after 8 weeks of treatment were a mean (SD) of -24.41 (2.38) versus -9.31 (2.36) mm Hg in the telmisartan/amlodipine/rosuvastatin and telmisartan/rosuvastatin groups, respectively. Significantly more participants achieved the target BP at week 8 in the telmisartan/amlodipine/rosuvastatin group (41 patients [87.2%]) than in the telmisartan/rosuvastatin group (24 [50.0%], $P < 0.001$). The changes in mean (SD) LDL-C at 8 weeks compared with baseline values were -57.59% (11.59%) versus 6.08% (20.98%) in the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine groups, respectively. The percentages of patients who achieved the target LDL-C according to their risk factors after 8 weeks of treatment were 97.87% vs 6.12% in the telmisartan/amlodipine/rosuvastatin and the telmisartan/amlodipine groups ($P < 0.0001$), respectively. No significant differences were found in the incidence of overall AEs and adverse drug reactions, and serious AEs were comparable among 3 groups. IMPLICATIONS: Fixed-dose combinations of telmisartan, amlodipine, and rosuvastatin decreased BP and LDL-C in patients with hypertension and dyslipidemia. The safety and tolerability profiles of fixed-dose telmisartan, amlodipine, and rosuvastatin combination therapy were comparable with those of telmisartan plus amlodipine or telmisartan plus rosuvastatin. ClinicalTrials.gov identifier: NCT03088254.

[16] Tao C, Shkumatov AA, Alexander ST et al. **Stigmasterol accumulation causes cardiac injury and promotes mortality.** *Communications biology* 2019; 2:20.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30675518>

ABSTRACT

Cardiovascular disease is expected to remain the leading cause of death worldwide despite the introduction of proprotein convertase subtilisin/kexin type 9 inhibitors that effectively control cholesterol. Identifying residual risk factors for cardiovascular disease remains an important step for preventing and clinically managing the disease. Here we report cardiac injury and increased mortality occurring despite a 50% reduction in plasma cholesterol in a mouse model of phytosterolemia, a disease characterized by elevated levels of dietary plant sterols in the blood. Our studies show accumulation of stigmasterol, one of phytosterol species, leads to left ventricle dysfunction, cardiac interstitial fibrosis and macrophage infiltration without atherosclerosis, and increased mortality. A pharmacological inhibitor of sterol absorption prevents cardiac fibrogenesis. We propose that the pathological mechanism linking clinical sitosterolemia to the cardiovascular outcomes primarily involves phytosterols-induced cardiac fibrosis rather than cholesterol-driven atherosclerosis. Our studies suggest stigmasterol is a potent and independent risk factor for cardiovascular disease.

[17] Zibaenezhad MJ, Ostovan P, Mosavat SH et al. **Almond oil for patients with hyperlipidemia: A randomized open-label controlled clinical trial.** *Complementary therapies in medicine* 2019; 42:33-36.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30670262>

ABSTRACT

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BACKGROUND: Cardiovascular diseases currently account for nearly half of non-communicable diseases. It was shown that enjoying a handful of nuts every day can significantly reduce the risk of developing heart diseases as they contain a variety of nutrients and other bioactive substances contributing to lowering the risk of heart diseases and controlling the cholesterol. The aim of this study was to determine the effect of almond oil on the lipid profile of patients with hyperlipidemia. **METHODS:** Ninety-seven patients were divided into the intervention (n = 49) and control (n = 48) groups. The intervention group received 10 ml of almond oil two times daily for 30 days. There was no intervention for the control group. The serum lipoproteins were measured before and after the study. **RESULTS:** The total cholesterol and LDL levels decreased significantly in the intervention group (treatment difference = -16.12 +/- 26.16, P = 0.009; treatment difference = -20.88 +/- 18.4, p < 0.001 respectively). But regular almond oil consumption did not significantly affect the triglyceride and HDL in this sample of hyperlipidemic patients. **CONCLUSION:** Consumption of almond could reduce the total cholesterol and LDL in dyslipidemic patients.

[18] *Tentolouris A, Eleftheriadou I, Tzeravini E et al. Endothelium as a Therapeutic Target in Diabetes Mellitus: From Basic Mechanisms to Clinical Practice. Curr Med Chem* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30663560>

ABSTRACT

Endothelium plays an essential role in human homeostasis by regulating arterial blood pressure, distributing nutrients and hormones as well as providing a smooth surface that modulates coagulation, fibrinolysis and inflammation. Endothelial dysfunction is present in diabetes mellitus (DM) and contributes to the development and progression of macrovascular disease, while it is also associated with most of the microvascular complications such as diabetic retinopathy, nephropathy and neuropathy. Hyperglycemia, insulin resistance, hyperinsulinemia and dyslipidemia are the main factors involved. Regarding antidiabetic medication, metformin, gliclazide, pioglitazone, exenatide and dapagliflozin exert a beneficial effect on endothelial function (EF); the other sulfonylureas, dipeptidyl peptidase-4 inhibitors and liraglutide have neutral effect, while studies examining the effect of insulin analogues, empagliflozin and canagliflozin on EF are limited. In terms of lipid-lower medication, statins improve EF in subjects with DM, whereas data from short-term trials suggest that fenofibrate improves EF; ezetimibe also improves EF but further studies are required in people with DM. The effect of acetylsalicylic acid on EF is dose-dependent and lower doses improve EF while higher ones do not. Clopidogrel, improves EF, but more studies in subjects with DM are required. Furthermore, angiotensin- converting-enzyme inhibitors /angiotensin II receptor blockers improve EF. Phosphodiesterase type 5 inhibitors improve endothelial function locally in the corpus cavernosum. Finally, cilostazol exerts favorable effect on EF, nevertheless, more data in people with DM are required.

[19] *Iacocca MA, Dron JS, Hegele RA. Progress in finding pathogenic DNA copy number variations in dyslipidemia. Current opinion in lipidology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30664016>

ABSTRACT

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PURPOSE OF REVIEW: DNA copy number variations (CNVs) are large-scale mutations that include deletions and duplications larger than 50 bp in size. In the era when single-nucleotide variations were the major focus of genetic technology and research, CNVs were largely overlooked. However, CNVs clearly underlie a substantial proportion of clinical disorders. Here, we update recent progress in identifying CNVs in dyslipidemias. **RECENT FINDINGS:** Until last year, only the LDLR and LPA genes were appreciated as loci within which clinically relevant CNVs contributed to familial hypercholesterolemia and variation in Lp(a) levels, respectively. Since 2017, next-generation sequencing panels have identified pathogenic CNVs in at least five more genes underlying dyslipidemias, including a PCSK9 whole-gene duplication in familial hypercholesterolemia; LPL, GPIHBP1, and APOC2 deletions in hypertriglyceridemia; and ABCA1 deletions in hypoalphalipoproteinemia. **SUMMARY:** CNVs are an important class of mutation that contribute to the molecular genetic heterogeneity underlying dyslipidemias. Clinical applications of next-generation sequencing technologies need to consider CNVs concurrently with familiar small-scale genetic variation, given the likely implications for improved diagnosis and treatment.

[20] *Reklou A, Katsiki N, Karagiannis A, Athyros V. Effects of lipid lowering drugs on arterial stiffness. One more way to reduce cardiovascular risk? Current vascular pharmacology 2019.*
PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30663570>

ABSTRACT

Arterial stiffness (AS) is considered an independent predictor of cardiovascular disease (CVD) events. Among lipid lowering drugs, statins have a beneficial effect on AS, independent of their hypolipidaemic effect. Based on 3 meta-analyses and other studies, this effect is compound- and dose-related. Potent statins at high doses are more effective than less powerful statins. Ezetimibe (+/- statin) also seems to decrease AS in patients with dyslipidaemia. Fibrates have no effect on AS. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have data that beneficially affect all AS risk factors, suggesting a beneficial effect on artery compliance. However, there is no direct measurement of their effect on AS indices. In patients with dyslipidaemia, prescribing high dose statins (+/- ezetimibe) will not only decrease low-density lipoprotein cholesterol levels but also improve AS (in addition to other effects). This effect on AS may contribute to the observed reduction in vascular events.

[21] *Arnaud M. Risk of diabetes with fibrates and statins: a pharmacoepidemiological study in Vigibase((R)). Fundamental & clinical pharmacology 2019; 33:107.*
PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30663142>

ABSTRACT

[22] *Momtazi-Borojeni AA, Abdollahi E, Nikfar B et al. Curcumin as a potential modulator of M1 and M2 macrophages: new insights in atherosclerosis therapy. Heart failure reviews 2019.*
PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30673930>

ABSTRACT

Accumulation of macrophages within the artery wall is an eminent feature of atherosclerotic plaques. Macrophages are influenced by various plaque microenvironmental stimuli, such as oxidized lipids, cytokines, and senescent erythrocytes, and thereby polarize into two main

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phenotypes called proinflammatory M1 and anti-inflammatory M2 macrophages. In the hemorrhagic zones of atheroma, upon exposure to iron, sequestration of iron by M1 macrophages results in an uncontrolled proinflammatory phenotype impairing wound healing, while M2 macrophages phagocytose both apoptotic cells and senescent erythrocytes. M1 macrophages are prominent phenotype in the unstable plaques, in which plaque shoulder contains macrophages mainly present markers of M1 phenotype, whereas the fibrous cap encompassing the necrotic lipid core content macrophages expressed markers of both M1 and M2 subtypes. The abovementioned findings suggest macrophage modulation as a potent approach for atherosclerosis therapy. Curcumin is a polyphenol dietary derived from turmeric with numerous pharmacological activities. Recent in vitro and in vivo studies have indicated that curcumin exerted lipid-lowering effects, and also can modulate function of different macrophage subsets in various macrophage-involved diseases. The current review aimed to present role of macrophage subtypes in atherosclerosis development and progression, and to understand effect of curcumin on macrophage polarization and foam cell formation in the atherosclerosis lesions. Overall, we would address important targets for macrophage modulation in atherosclerotic plaques.

[23] Pratt DS. **Hepatology Elsewhere**. Hepatology 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30672600>

ABSTRACT

The recently published BEZURSO trial (Corpechot C, Chazouilleres A, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *NEJM* 2018;378:2171-2181.) studied the role of bezafibrate, a peroxisome proliferator-activated receptor alpha (PPARalpha) agonist, in patients with primary biliary cholangitis (PBC) who failed to achieve a biochemical response with ursodeoxycholic acid (UDCA).(1) The BEZURSO trial, a phase 3, double blind, placebo-controlled trial, randomized patients to receive 24 months of either bezafibrate, 400 mg a day, or placebo. All patients continued UDCA. This article is protected by copyright. All rights reserved.

[24] Lutski M, Weinstein G, Goldbourt U, Tanne D. **Plasma Lipids, Apolipoproteins, and Subsequent Cognitive Decline in Men with Coronary Heart Disease**. Journal of Alzheimer's disease : JAD 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30664505>

ABSTRACT

BACKGROUND: Lipid levels are associated with an increased risk of cardiovascular disease. OBJECTIVE: We investigated the association between plasma lipids, apolipoproteins levels, apolipoprotein B/low-density lipoprotein cholesterol (Apo-B/LDL-C), and Apo-B/Apo-A ratios and rate of cognitive decline two decades later in men with coronary heart disease (CHD). METHODS: A subset of 337 men (mean age at baseline 56.6+/-6.4 years) who previously participated in the Bezafibrate Infarction Prevention (BIP) trial (1990-1997) underwent cognitive evaluations 15+/-3 years (T1) and 19.9+/-1 years after baseline (T2) as part of the BIP Neurocognitive study. Lipid and apolipoprotein fractions were measured at baseline. Cognitive function for memory, executive function, visual spatial, attention domains, and composite score were assessed using the NeuroTrax Computerized Battery at T1 and T2 evaluations. Linear

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mixed models were used to assess change in cognitive function between the two cognitive evaluations. RESULTS: Controlling for confounders, the decline in composite cognitive score (beta= -0.161+/-0.06; p = 0.013) as well as in memory (beta= -0.269+/-0.10; p = 0.009) and visual spatial function (beta= -0.304+/-0.12; p = 0.010) was greater among patients in the upper (≥ 105 mg/dL) Apo-B tertile as compared to counterparts with < 105 mg/dL. The decline in the composite cognitive score (beta= -0.124+/-0.06; p = 0.043) was also greater among patients in the estimated LDL-C ≥ 160 mg/dL group compared to counterparts with LDL-C < 160 mg/dL. Upper tertile of Apo-B/LDL-C ratio (≥ 0.75) compared to the lower tertiles was significantly associated with change in memory score (beta= -0.210+/-0.10; p = 0.041). CONCLUSION: Our findings suggest that the plasma concentrations of Apo-B, LDL-C, and Apo-B/LDL-C ratio are potential predictors of accelerated late-life cognitive decline among men with CHD.

[25] Lee R, Ahn HR, Shin MH et al. **Association of Plasma Pentraxin-3 Level with Lipid Levels and Cardiovascular Risk Factors in People with No History of Lipid-Lowering Medication: the Dong-gu Study.** *Journal of atherosclerosis and thrombosis* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30674758>

ABSTRACT

AIM: To elucidate the role of pentraxin-3 (PTX3) in atherosclerosis, we evaluated lipid and cardiovascular risk profiles according to the plasma PTX3 levels in subjects from the general population. METHODS: A sub-cohort of 2,000 subjects was randomly sampled from a Korean community-based cohort study. After excluding those with a medication history for dyslipidemia, 1,747 subjects (902 men and 845 women) were included in the final analyses. Linear and logistic regressions with adjustment for appropriate variables were performed. RESULTS: The PTX3 level was positively associated with the high-density lipoprotein cholesterol (HDL-C) level and negatively associated with the log-transformed triglyceride (TG) level, total cholesterol/HDL-C ratio, and low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio (p < 0.05). Subjects with the highest PTX3 levels (≥ 1.17 ng/dl) exhibited a lower risk of metabolic syndrome (odds ratio [OR] 0.73, 95% confidence interval [CI] 0.57-0.94), overweight/obesity (OR 0.65, 95% CI 0.50-0.83), increased TG level (OR 0.66, 95% CI 0.51-0.86), and increased HDL-C level (OR 0.67, 95% CI 0.51-0.88) compared to those with the lowest PTX3 level (0.7 ng/dl). CONCLUSION: The circulating PTX3 level was inversely associated with metabolic syndrome, overweight/obesity, and parameters of dyslipidemia, suggesting a cardioprotective role of PTX3 in atherosclerosis.

[26] Pirro M, Simental-Mendia LE, Bianconi V et al. **Effect of Statin Therapy on Arterial Wall Inflammation Based on 18F-FDG PET/CT: A Systematic Review and Meta-Analysis of Interventional Studies.** *Journal of clinical medicine* 2019; 8.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30669380>

ABSTRACT

Aim. To evaluate by meta-analysis of interventional studies the effect of statin therapy on arterial wall inflammation. Background. Arterial exposure to low-density lipoprotein (LDL) cholesterol levels is responsible for initiation and progression of atherosclerosis and arterial wall inflammation. 18F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (18F-FDG PET/CT) has been used to detect arterial wall inflammation and monitor

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the vascular anti-inflammatory effects of lipid-lowering therapy. Despite a number of statin-based interventional studies exploring 18F-FDG uptake, these trials have produced inconsistent results. Methods. Trials with at least one statin treatment arm were searched in PubMed-Medline, SCOPUS, ISI Web of Knowledge, and Google Scholar databases. Target-to-background ratio (TBR), an indicator of blood-corrected 18F-FDG uptake, was used as the target variable of the statin anti-inflammatory activity. Evaluation of studies biases, a random-effects model with generic inverse variance weighting, and sensitivity analysis were performed for qualitative and quantitative data assessment and synthesis. Subgroup and meta-regression analyses were also performed. Results. Meta-analysis of seven eligible studies, comprising 10 treatment arms with 287 subjects showed a significant reduction of TBR following statin treatment (Weighted Mean Difference (WMD): -0.104, $p = 0.002$), which was consistent both in high-intensity (WMD: -0.132, $p = 0.019$) and low-to-moderate intensity statin trials (WMD: -0.069, $p = 0.037$). Statin dose/duration, plasma cholesterol and C-reactive protein level changes, and baseline TBR did not affect the TBR treatment response to statins. Conclusions. Statins were effective in reducing arterial wall inflammation, as assessed by 18F-FDG PET/CT imaging. Larger clinical trials should clarify whether either cholesterol-lowering or other pleiotropic mechanisms were responsible for this effect.

[27] Hilleman DE, Teply R, Packard KA. **Knowledge, Perceptions, and Patterns of Fish Oil Use in Cardiac Patients.** *Journal of pharmacy practice* 2019;897190018824485.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30669926>

ABSTRACT

BACKGROUND:: Fish oils are the most widely used nonvitamin, nonmineral dietary supplements in the United States. They are not over-the-counter medications and are neither approved nor indicated for treating disease. Patient knowledge and patterns of fish oil use are not well defined. OBJECTIVE:: To determine cardiac patients' knowledge and patterns of fish oil use. METHODS:: One thousand consecutive patients admitted to an in-patient cardiology service (2015-2017) taking fish oil dietary supplements or prescription omega-3 fatty acids were asked to complete an anonymous questionnaire concerning product knowledge and use. RESULTS:: A total of 711 (71%) patients completed the questionnaire. Primary reasons for use included general health (34%), heart health (28%), arthritis (9%), and lipid disorders (8%). Few patients (14%) were advised to take fish oil products by a health-care provider. Only 2.5% were taking prescription omega-3 fatty acids. Only 26% knew the active ingredient in their fish oil product. Supplements were purchased through a nonpharmacy retail seller by 81% of respondents. CONCLUSIONS:: Most cardiac patients consuming fish oil dietary supplements do so without medical supervision and without knowledge of the active ingredients. As most patients obtain supplements outside of a pharmacy, opportunities to monitor and educate patients remain a major challenge.

[28] Adela R, Reddy PNC, Ghosh TS et al. **Serum protein signature of coronary artery disease in type 2 diabetes mellitus.** *Journal of translational medicine* 2019; 17:17.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30674322>

ABSTRACT

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BACKGROUND: Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The purpose of the present study was to discriminate the Indian CAD patients with or without T2DM by using multiple pathophysiological biomarkers. **METHODS:** Using sensitive multiplex protein assays, we assessed 46 protein markers including cytokines/chemokines, metabolic hormones, adipokines and apolipoproteins for evaluating different pathophysiological conditions of control, T2DM, CAD and T2DM with CAD patients (T2DM_CAD). Network analysis was performed to create protein-protein interaction networks by using significantly ($p < 0.05$) altered protein markers in each disease using STRING 10.5 database. We used two supervised analysis methods i.e., between class analysis (BCA) and principal component analysis (PCA) to reveals distinct biomarkers profiles. Further, random forest classification (RF) was used to classify the diseases by the panel of markers. **RESULTS:** Our two supervised analysis methods BCA and PCA revealed a distinct biomarker profiles and high degree of variability in the marker profiles for T2DM_CAD and CAD. Thereafter, the present study identified multiple potential biomarkers to differentiate T2DM, CAD, and T2DM_CAD patients based on their relative abundance in serum. RF classified T2DM based on the abundance patterns of nine markers i.e., IL-1beta, GM-CSF, glucagon, PAI-I, rantes, IP-10, resistin, GIP and Apo-B; CAD by 14 markers i.e., resistin, PDGF-BB, PAI-1, lipocalin-2, leptin, IL-13, eotaxin, GM-CSF, Apo-E, ghrelin, adipsin, GIP, Apo-CII and IP-10; and T2DM_CAD by 12 markers i.e., insulin, resistin, PAI-1, adiponectin, lipocalin-2, GM-CSF, adipsin, leptin, Apo-AII, rantes, IL-6 and ghrelin with respect to the control subjects. Using network analysis, we have identified several cellular network proteins like PTPN1, AKT1, INSR, LEPR, IRS1, IRS2, IL1R2, IL6R, PCSK9 and MYD88, which are responsible for regulating inflammation, insulin resistance, and atherosclerosis. **CONCLUSION:** We have identified three distinct sets of serum markers for diabetes, CAD and diabetes associated with CAD in Indian patients using nonparametric-based machine learning approach. These multiple marker classifiers may be useful for monitoring progression from a healthy person to T2DM and T2DM to T2DM_CAD. However, these findings need to be further confirmed in the future studies with large number of samples.

[29] *Thassakorn P, Patchanee P, Pongkan W et al. Effect of atorvastatin on oxidative stress and inflammation markers in myxomatous mitral valve disease in dogs: A comparison of subclinical and clinical stages. Journal of veterinary pharmacology and therapeutics 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30666669>

ABSTRACT

Myxomatous mitral valve disease (MMVD) is the most common acquired cardiac disorder found in dogs. The disease process can lead to heart failure (HF) and has been found to be associated with oxidative stress and inflammation. Statins exert antioxidant and anti-inflammatory effects in human HF patients. However, the beneficial effects of statins in MMVD dogs are still unclear. Thirty MMVD dogs were enrolled in the study and were divided into two groups: MMVD without HF dogs (n = 15) and MMVD with HF dogs (n = 15). Atorvastatin (8 mg kg⁻¹ day⁻¹) was administered orally to all dogs for 4 weeks. All dogs underwent physical examination and cardiac examination at the beginning and end of the experiment, including baseline values for hematology, blood chemistry profile, lipid profile, N-terminal pro B-type natriuretic peptide, oxidative stress marker (8-isoprostane), and inflammatory marker (tumor necrosis factor

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alpha). The results showed that atorvastatin reduced plasma cholesterol levels in both groups. In addition, plasma concentrations of 8-isoprostane, tumor necrosis factor alpha, and N-terminal pro B-type natriuretic peptide were significantly lower after atorvastatin administration, but only in MMVD dogs in the HF group. Atorvastatin found to be associated with possible antioxidant and inflammatory effects in dogs with HF secondary to MMVD. The potential benefits of statins in dogs with HF merits further investigation in larger, placebo-controlled studies.

[30] *Maurovich-Horvat P. 2 Steps Forward, 1 Step Back. JACC. Cardiovascular imaging 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30660528>

ABSTRACT

[31] *van Rosendaal AR, Shaw LJ, Xie JX et al. Superior Risk Stratification With Coronary Computed Tomography Angiography Using a Comprehensive Atherosclerotic Risk Score. JACC. Cardiovascular imaging 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30660516>

ABSTRACT

OBJECTIVES: This study was designed to assess the prognostic value of a new comprehensive coronary computed tomography angiography (CTA) score compared with the stenosis severity component of the Coronary Artery Disease-Reporting and Data System (CAD-RADS).

BACKGROUND: Current risk assessment with coronary CTA is mainly focused on maximal stenosis severity. Integration of plaque extent, location, and composition in a comprehensive model may improve risk stratification. **METHODS:** A total of 2,134 patients with suspected but without known CAD were included. The predictive value of the comprehensive CTA score

(ranging from 0 to 42 and divided into 3 groups: 0 to 5, 6 to 20, and >20) was compared with the CAD-RADS combined into 3 groups (0% to 30%, 30% to 70% and >=70% stenosis). Its predictive performance was internally and externally validated (using the 5-year follow-up dataset of the CONFIRM [Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry] registry, n = 1,971).

RESULTS: Patients mean age was 55 +/- 13 years, mean follow-up 3.6 +/- 2.8 years, and 130 events (myocardial infarction or death) occurred. The new, comprehensive CTA score showed strong and independent predictive value using the Cox proportional hazard analysis. A model including clinical variables plus comprehensive CTA score showed better discrimination of events compared with a model consisting of clinical variables plus CAD-RADS (0.768 vs. 0.742, p = 0.001). Also, the comprehensive CTA score correctly reclassified a significant proportion of patients compared with the CAD-RADS (net reclassification improvement 12.4%, p < 0.001). Good predictive accuracy was reproduced in the external validation cohort.

CONCLUSIONS: The new comprehensive CTA score provides better discrimination and reclassification of events compared with the CAD-RADS score based on stenosis severity only. The score retained similar prognostic accuracy when externally validated. Anatomic risk scores can be improved with the addition of extent, location, and compositional measures of atherosclerotic plaque.

Comprehensive CTA risk score calculator is available at: <http://18.224.14.19/calApp/>.

[32] Lv G, Wang GQ, Xia ZX et al. **Influences of blood lipids on the occurrence and prognosis of hemorrhagic transformation after acute cerebral infarction: a case-control study of 732 patients.** *Military Medical Research* 2019; 6:2.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30665465>

ABSTRACT

BACKGROUND: To study the influence of blood lipid levels on hemorrhagic transformation (HT) and prognosis after acute cerebral infarction (ACI). METHODS: Patients with ACI within 72 h of symptoms onset between January 1st, 2015, and December 31st, 2016, were retrospectively analyzed. Patients were divided into group A (without HT) and group B (HT). The outcomes were assessed after 3 months of disease onset using the modified Rankin Scale (mRS). An mRS score of 0-2 points indicated excellent prognosis, and an mRS score of 3-6 points indicated poor prognosis. RESULTS: A total of 732 patients conformed to the inclusion criteria, including 628 in group A and 104 in group B. The incidence of HT was 14.2%, and the median onset time was 2 d (interquartile range, 1-7 d). The percentages of patients with large infarct size and cortex involvement in group B were 80.8 and 79.8%, respectively, which were both significantly higher than those in group A (28.7 and 33.4%, respectively). The incidence rate of atrial fibrillation (AF) in group B was significantly higher than that in group A (39.4% vs. 13.9%, $P < 0.001$). The adjusted multivariate analysis results showed that large infarct size, cortex involvement and AF were independent risk factors of HT, while total cholesterol (TC) was a protective factor of HT (OR = 0.359, 95% CI 0.136-0.944, $P = 0.038$). With every 1 mmol/L reduction in normal TC levels, the risk of HT increased by 64.1%. The mortality and morbidity at 3 months in group B (21.2 and 76.7%, respectively) were both significantly higher than those in group A (8.0 and 42.8%, respectively). The adjusted multivariate analysis results showed that large infarct size (OR = 12.178, 95% CI 5.390-27.516, $P < 0.001$) was an independent risk factor of long-term unfavorable outcomes, whereas low-density lipoprotein cholesterol (LDL-C) was a protective factor (OR = 0.538, 95% CI 0.300-0.964, $P = 0.037$). With every 1 mmol/L reduction in normal LDL-C levels, the risk of an unfavorable outcome increased by 46.2%. Major therapies, including intravenous recombinant human tissue plasminogen activator (rTPA), intensive lipid-lowering statins and anti-platelets, were not significantly related to either HT or long-term, post-ACI poor prognosis. CONCLUSION: For patients with large infarct sizes, especially those with cortex involvement, AF, or lower levels of TC, the risk of HT might increase after ACI. The risk of a long-term unfavorable outcome in these patients might increase with a reduction in LDL-C.

[33] Boffa MB, Koschinsky ML. **Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease.** *Nature reviews. Cardiology* 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30675027>

ABSTRACT

Epidemiological and clinical studies over the past decade have firmly established that elevated plasma concentrations of lipoprotein(a) (Lp(a)) are an important, independent and probably causal risk factor for the development of cardiovascular diseases. Whereas a link between Lp(a) levels and atherosclerotic cardiovascular disease (ASCVD) has been appreciated for decades, the role of Lp(a) in calcific aortic valve disease (CAVD) and aortic stenosis has come into focus only in the past 5 years. ASCVD and CAVD are aetiologically distinct but have several risk factors in common and similar pathological processes at the cellular and molecular levels. Oxidized

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phospholipids, which modify Lp(a) primarily by covalent binding to its unique apolipoprotein(a) (apo(a)) component, might hold the key to Lp(a) pathogenicity and provide a mechanistic link between ASCVD and CAVD. Oxidized phospholipids colocalize with apo(a)-Lp(a) in arterial and aortic valve lesions and directly participate in the pathogenesis of these disorders by promoting endothelial dysfunction, lipid deposition, inflammation and osteogenic differentiation, leading to calcification. The advent of potent Lp(a)-lowering therapies provides the opportunity to address directly the causality of Lp(a) in ASCVD and CAVD and, more importantly, to provide both a novel approach to reduce the residual risk of ASCVD and a long-sought medical treatment for CAVD.

[34] *Earl G. PCSK9 inhibitors: Add-on therapy to reduce stroke risk. Nursing ... critical care 2019; 14:42-48.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30662381>

ABSTRACT

PCSK9 inhibitors.

[35] *Lu Y, Chang R, Yao J et al. Effectiveness of long-term using statins in COPD - a network meta-analysis. Respiratory research 2019; 20:17.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30674312>

ABSTRACT

OBJECTIVES: To evaluate the effectiveness of long-term treatment of statins for chronic obstructive pulmonary disease (COPD), and to answer which one is better. **METHODS:** General meta-analysis was performed to produce pooled estimates of the effect of mortality, inflammatory factors, and lung function index in COPD patients by the search of PubMed, Web of Science, Embase, and China National Knowledge Infrastructure for eligible studies. A network meta-analysis was performed to synthetically compare the effectiveness of using different statins in COPD patients. **RESULTS:** General meta-analysis showed that using statins reduced the risk of all-cause mortality, heart disease-related mortality and COPD acute exacerbation (AECOPD) in COPD patients, the RR (95% CI) were 0.72 (0.63,0.84), 0.72 (0.53,0.98) and 0.84 (0.79,0.89), respectively. And using statins reduced C-reactive protein (CRP) and pulmonary hypertension (PH) in COPD patients, the SMD (95% CI) were - 0.62 (- 0.52,-0.72) and - 0.71 (- 0.85,-0.57), respectively. Network meta-analysis showed that Fluvastatin (97.7%), Atorvastatin (68.0%) and Rosuvastatin (49.3%) had higher cumulative probability than other statins in reducing CRP in COPD patients. Fluvastatin (76.0%) and Atorvastatin (75.4%) had higher cumulative probability than other statins in reducing PH in COPD patients. **CONCLUSIONS:** Using statins can reduce the risk of mortality, the level of CRP and PH in COPD patients. In addition, Fluvastatin and Atorvastatin are more effective in reducing CRP and PH in COPD patients.

[36] *Koch CA, Krabbe S, Hehmke B. Statins, metformin, proprotein-convertase-subtilisin-kexin type-9 (PCSK9) inhibitors and sex hormones: Immunomodulatory properties? Reviews in endocrine & metabolic disorders 2019.*

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30673921>

ABSTRACT

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The immune system is closely intertwined with the endocrine system. Many effects of medications used for various clinical endocrine conditions such as the metabolic syndrome, hypercholesterolemia, diabetes mellitus, hypertension, Graves' disease and others also have an impact on the immune system. Some drugs including statins, metformin, angiotensin converting enzyme and proprotein-convertase-subtilisin-kexin type-9 (PCSK9) inhibitors and sex hormones are known to have immunomodulatory properties. We here review the literature on this topic and provide some clinical examples including the use of statins in Graves' orbitopathy, rheumatoid arthritis, multiple sclerosis, and adult-onset Still's disease. In that context, we introduce a special immunodiagnosics method developed at the Institute of Diabetes "Gerhardt Katsch" in Karlsburg, Germany, to not only measure but also monitor immune disease activity.

[37] Schettler VJ, Muellendorff F, Schettler E et al. **NMR-based lipoprotein analysis for patients with advanced hypercholesterolemia undergoing chronic lipoprotein apheresis or PCSK9-inhibitor therapy (NAPALI)-Study.** Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2019.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30663261>

ABSTRACT

Taking into account the discordance between LDL cholesterol (LDL-C) and LDL particle (LDL-P) number, cardiovascular risk more closely correlates with LDL-P in patients. The aim of our study was to evaluate the number of lipid particles in patients with severe hypercholesterolemia treated with different lipid lowering regimens. Four groups of patients differing with respect to lipid-lowering therapy were recruited from hypercholesterolemic outpatients and lipoprotein apheresis facilities, and were treated either (A) with statins alone, or (B) with statins and PCSK9 inhibitors (PCSK9i), or (C) with statins and lipoprotein apheresis (LA), or (D) with statins, PCSK9i and LA. Cholesterol, Triglycerides, LDL-C, HDL-C, LDL-P number and size, HDL-P number and size were determined using NMR spectroscopy. The lowest LDL-P number was achieved at the end of LA sessions in combination with statins or in combination with statins and a monoclonal PCSK9i (median; 25th and 75th percentile) (C: 244 nmol/l: 237, 244, $p < 0.05$; D: 244 nmol/l: 99, 307, $p < 0.05$). Comparing LDL-P number at the start of LA (C: 978 nmol/l: 728, 1404; D: 954 nmol/l: 677, 1521) to the other patients groups (A, B), the lowest LDL-P number was measured in patients treated with PCSK9i and a statin (B): LDL-P (762 nmol/l: 604, 1043, $p < 0.05$), large LDL-P (472 nmol/l: 296, 574, $p < 0.05$) and small LDL-P (342 nmol/l: 152, 494, $p < 0.05$). VLDL and HDL particle sizes remained approximately the same in all groups. LA in combination with statins or in combination with statins and PCSK9i most reduced LDL-P numbers in hypercholesterolemic patients. This article is protected by copyright. All rights reserved.

[38] Jin H, He Y, Zhao P et al. **Targeting lipid metabolism to overcome EMT-associated drug resistance via integrin beta3/FAK pathway and tumor-associated macrophage repolarization using legumain-activatable delivery.** Theranostics 2019; 9:265-278.

PM: <http://www.ncbi.nlm.nih.gov/pubmed/?term=30662566>

ABSTRACT

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Epithelial-mesenchymal transition (EMT) is closely associated with the development of drug resistance. Lipid metabolism plays an important role in EMT. This work was to study the cholesterol-lowering drug simvastatin for reversing EMT-associated resistance to chemotherapy via lipid metabolism. **METHODS:** The combination of simvastatin and paclitaxel was used to overcome the EMT-associated drug resistance. For dual-action on both cancer cells and tumor-associated macrophages (TAM), the tumor microenvironment-activatable multifunctional liposomes were developed for drug codelivery. The liposomes were modified with a hairpin-structured, activatable cell-penetrating peptide that is specifically responsive to the tumor-associated protease legumain. **RESULTS:** It was revealed simvastatin can disrupt lipid rafts (cholesterol-rich domains) and suppress integrin-beta3 and focal adhesion formation, thus inhibiting FAK signaling pathway and re-sensitizing the drug-resistant cancer cells to paclitaxel. Furthermore, simvastatin was able to re-polarize tumor-associated macrophages (TAM), promoting M2-to-M1 phenotype switch via cholesterol-associated LXR/ABCA1 regulation. The repolarization increased TNF-alpha, but attenuated TGF-beta, which, in turn, remodeled the tumor microenvironment and suppressed EMT. The liposomal formulation achieved enhanced treatment efficacy. **CONCLUSION:** This study provides a promising simvastatin-based nanomedicine strategy targeting cholesterol metabolism to reverse EMT and repolarize TAM to treat drug-resistant cancer. The elucidation of the molecular pathways (cholesterol/lipid raft/integrin beta3/FAK and cholesterol-associated LXR/ABCA1 regulation) for anti-EMT and the new application of simvastatin should be of clinical significance.