Literature update week 01 (2019)

[1] *Nicholls SJ, Nelson AJ*. **Do Cholesteryl Ester Transfer Protein Inhibitors Have a Role in the Treatment of Cardiovascular Disease?** American journal of cardiovascular drugs : drugs, devices, and other interventions 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30610681
ABSTRACT
Cholesteryl ester transfer protein (CETP) plays an important role in lipid metabolism and has presented an attractive target for drug development, primarily resting on the hope that CETP inhibition would reduce cardiovascular events through its ability to increase levels of high-density lipoprotein cholesterol (HDL-C). However, clinical development of CETP inhibitors has proven disappointing, with a spectrum of results spanning from evidence of harm, to futility, to only modest benefit in large-scale cardiovascular outcomes trials. A number of additional insights from genomic studies have suggested potential benefits from these agents in specific clinical settings. We review the current state of CETP inhibitors as an approach to targeting cardiovascular risk.

[2] *Kazi DS, Penko J, Coxson PG et al.* **Cost-Effectiveness of Alirocumab: A Just-in-Time Analysis Based on the ODYSSEY Outcomes Trial**. Annals of internal medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30597485
ABSTRACT
Background: The ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial included participants with a recent acute coronary syndrome. Compared with participants receiving statins alone, those receiving a statin plus alirocumab had lower rates of a composite outcome including myocardial infarction (MI), stroke, and death. Objective: To determine the cost-effectiveness of alirocumab in these circumstances. Design: Decision analysis using the Cardiovascular Disease Policy Model. Data Sources: Data sources representative of the United States combined with data from the ODYSSEY Outcomes trial. Target Population: U.S. adults with a recent first MI and a baseline low-density lipoprotein cholesterol level of 1.81 mmol/L (70 mg/dL) or greater. Time Horizon: Lifetime. Perspective: U.S. health system. Intervention: Alirocumab or ezetimibe added to statin therapy. Outcome Measures: Incremental cost-effectiveness ratio in 2018 U.S. dollars per quality-adjusted life-year (QALY) gained. Results of Base-Case Analysis: Compared with a statin alone, the addition of ezetimibe cost $81 000 (95% uncertainty interval [UI], $51 000 to $215 000) per QALY. Compared with a statin alone, the addition of alirocumab cost $308 000 (UI, $197 000 to $678 000) per QALY. Compared with the combination of statin and ezetimibe, replacing ezetimibe with alirocumab cost $997 000 (UI, $254 000 to dominated) per QALY. Results of Sensitivity Analysis: The price of alirocumab would have to decrease from its original cost of $14 560 to $1974 annually to be cost-effective relative to ezetimibe. Limitation: Effectiveness estimates were based on a single randomized trial with a median follow-up of 2.8 years and should not be extrapolated to patients with stable coronary heart disease. Conclusion: The price of alirocumab would have to be reduced considerably to be cost-effective. Because substantial reductions already have occurred, we believe that timely, independent cost-effectiveness analyses can inform clinical and policy discussions of new drugs as they enter the market. Primary Funding Source: University of California, San Francisco, and Institute for Clinical and Economic Review.

[3] *Fang C, Luo T, Lin L*. **Elevation of serum proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations and its possible atherogenic role in patients with systemic lupus erythematosus**. Annals of translational medicine 2018; 6:452.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30603640
ABSTRACT
Background: Systemic lupus erythematosus (SLE) patients have tendencies of accelerated atherosclerosis (AS) which can only partly be explained by traditional cardiovascular disease (CVD) risk factors. Imbalanced inflammation also plays a vital role. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new therapeutic target for AS for its dual mechanisms in lipids and inflammation. We aimed to assess serum PCSK9 concentrations in SLE patients and its possible role in atherogenesis of SLE. Methods: Ninety SLE patients and 50 healthy controls were included. SLE patients were further divided into SLE-AS and SLE-NonAS subgroups, according to the carotid intima-media thickness (cIMT). Traditional CVD risk factors, inflammatory biomarkers and PCSK9 concentrations were compared between: (I) SLE patients and controls; (II) SLE-AS subgroup and SLE-NonAS subgroup; (III) SLE patients with and without lupus nephritis (LN). Correlational analysis, univariate and multivariate linear regression analysis were applied to analyze the association between PCSK9 levels and disease parameter in SLE patients. Effects on PCSK9 concentrations by monotherapy with hydroxychloroquine (HCQ), which is thought having protective effects against AS in SLE, were investigated by follow-up analysis in 15 SLE patients. Results: We found that SLE patients had significantly elevated serum PCSK9 levels than controls, especially in SLE-As subgroup or those with LN, accompanied with higher ratio of cIMT thickening. Correlational analysis showed PCSK9 concentrations correlated with C-reactive protein (CRP) levels, age and erythrocyte sedimentation rate (ESR). Univariate and multivariate linear regression revealed that only CRP, but not age or ESR was positive predictors of PCSK9. Interestingly, monotherapy with HCQ for three months significantly reduced PCSK9 and CRP levels in inactive SLE patients. Conclusions: Our results suggested that elevated PCSK9 levels in SLE are probably associated with atherogenic inflammation in SLE. HCQ, which is thought having protective effects against AS in SLE, can effectively reduce PCSK9 levels in SLE patients.

[4] *Ferrieres J*. **Hypercholesterolaemia and coronary artery disease: A silent killer with several faces**. Archives of cardiovascular diseases 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30606472
ABSTRACT

[5] *Bogari NM, Aljohani A, Amin AA et al.* **A genetic variant c.553G > T (rs2075291) in the apolipoprotein A5 gene is associated with altered triglycerides levels in coronary artery disease (CAD) patients with lipid lowering drug**. BMC cardiovascular disorders 2019; 19:2.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30606120
ABSTRACT
BACKGROUND: Elevated plasma triglycerides (TGs) are widely used as a major cardiovascular risk predictor and are thought to play an important role in the progression of coronary heart disease (CHD). It has been demonstrated that lipid lowering was associated with lower

mortality in patients with CHD. The present study therefore aimed to investigate the consequences of the genetic variant c.553G > T (rs2075291) in apolipoprotein A5 gene to determination of triglycerides levels in CAD patients receiving, atorvastatin, lipid lowering drug. METHODS: We here report that a recently identified genetic variant, c.553G > T in the APOA5 gene which causes a substitution of a cysteine for a glycine residue at amino acid residue 185(G185C) is also associated with increased TG levels. To investigate theses effects, a case-control study compressing 608 subjects from the same area was performed. RESULTS: TG levels in T allele patients were significantly lower than the control GT allele patient (chi(2) = 2.382E2(a), P-value < 0.001). Overall, patients carrying T allele showed lower levels of TG than patients carrying GG allele. The homozygous patient for the T allele presented normal cholesterol levels of 134 mg/dl, and the levels in GG patients ranged from 25 to 340 mg/dl (P-value < 0.001). In summary, we demonstrated that the presence of c.553G > T variant (rs2075291); in APOA5 gene increases human plasma TG levels. CONCLUSION: Nevertheless, T allele is found to reduce TG levels in CAD patients who are on the cholesterol medication, atorvastatin. Thus, c.553G > T variant can be considered as a significant predicator of hypertriglyceridemia. In addition, it could be used as a hallmark for the diagnosis and prognosis of CAD.

[6] *Moayedi Y, Kozuszko S, Knowles JW et al.* **Safety and Efficacy of PCSK9 Inhibitors After Heart Transplantation**. The Canadian journal of cardiology 2019; 35:104.e101-104.e103.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30595172
ABSTRACT
Dyslipidemia is common in patients undergoing heart transplantation and is associated with the progression of cardiac allograft vasculopathy. Two monoclonal antibodies directed against PCSK9i-evolocumab and alirocumab-are currently available. However, their use, safety and efficacy in the post-transplant setting have not been studied. We present our experience with 6 heart transplant recipients treated with a PCSK9i. A > 70% reduction in LDL-cholesterol was observed after evolocumab therapy. PCSK9 inhibitors are a potentially lipid-lowering therapeutic option for heart transplant patients with suboptimal LDL despite maximal tolerated statin doses.

[7] *Grabie M, Tai CH, Frishman WH*. **Is Anacetrapib Better Than Its CETP Inhibitor Counterparts?** Cardiology in review 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30601160
ABSTRACT
Cholesterol metabolism and transport has been a major focus in cardiovascular disease risk modification over the past several decades. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) have been the most commonly used agents, with the greatest benefit in reducing both the primary and secondary risks of cardiovascular disease. However, heart disease remains the leading cause of death in both men and women in the United States. Further investigation and intervention are required to further reduce the risk for cardiovascular disease and cardiovascular-related deaths. This review will focus on high-density lipoprotein metabolism and transport, looking particularly at cholesteryl ester transfer protein (CETP) inhibitors. While studies of the other CETP inhibitors in its class have not shown a significant improvement in the

prevention of primary or secondary cardiovascular risk, anacetrapib, the fourth and latest of the CETP inhibitors to be investigated, may be more promising.

[8] *Banach M, Penson PE*. **What have we learned about lipids and cardiovascular risk from PCSK9 inhibitor outcomes trials?** Cardiovascular research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30605511
ABSTRACT

[9] *Garcia D, Hellberg K, Chaix A et al.* **Genetic Liver-Specific AMPK Activation Protects against Diet-Induced Obesity and NAFLD**. Cell Rep 2019; 26:192-208.e196.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30605676
ABSTRACT
The AMP-activated protein kinase (AMPK) is a highly conserved master regulator of metabolism, whose activation has been proposed to be therapeutically beneficial for the treatment of several metabolic diseases, including nonalcoholic fatty liver disease (NAFLD). NAFLD, characterized by excessive accumulation of hepatic lipids, is the most common chronic liver disease and a major risk factor for development of nonalcoholic steatohepatitis, type 2 diabetes, and other metabolic conditions. To assess the therapeutic potential of AMPK activation, we have generated a genetically engineered mouse model, termed iAMPK(CA), where AMPK can be inducibly activated in vivo in mice in a spatially and temporally restricted manner. Using this model, we show that liver-specific AMPK activation reprograms lipid metabolism, reduces liver steatosis, decreases expression of inflammation and fibrosis genes, and leads to significant therapeutic benefits in the context of diet-induced obesity. These findings further support AMPK as a target for the prevention and treatment of NAFLD.

[10] *Kaufman TM, Warden BA, Minnier J et al.* **Application of PCSK9 Inhibitors in Practice**. Circulation research 2019; 124:32-37.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30605414
ABSTRACT
PCSK9i (protein convertase subtilisin/kexin type 9 inhibitors) are set to revolutionize the treatment of hypercholesterolemia in the management of atherosclerotic risk, but numerous reports have detailed unprecedented barriers to access for these drugs. To overcome these challenges, our group created a model to facilitate provision of this new therapy for patients who qualify according to Food and Drug Administration criteria. This report details the real-world follow-up experience of PCSK9i use in a large patient cohort structured to ensure rigor in data collection, analysis, and interpretation. The 271 patients approved and actively followed in our PCSK9i clinic between July 2015 and August 2018 represent a 97% approval rate from insurance, with 28% of prescriptions requiring at least one appeal. Over 50% of patients were statin intolerant. On average, there was a median lapse of 15 days between initial visit and insurance approval. PCSK9i therapy was affordable for most patients, with an average monthly out-of-pocket expense of $58.05 (median $0). Only 2.3% of patients were unable to initiate or continue therapy because of cost. Reductions from baseline in LDL (low-density lipoprotein) cholesterol and Lp(a) (lipoprotein [a])were comparable to published reports with median reductions of 60% and 23% at 1 year, respectively. PCSK9i therapy was well-tolerated overall,

though 9% of patients reported adverse events, and 5% of patients discontinued due mostly to musculoskeletal and flu-like symptoms. Our practice model demonstrates that PCSK9i therapy can be accessed easily and affordably for the majority of eligible patients, resulting in dramatic improvement in lipid profile results. Moreover, our registry data suggest that results from the prospective clinical trials of PCSK9i on LDL and Lp(a) reduction and on tolerability are applicable to a real-world cohort.

[11] *Kameda A, Nakamura A, Kondo Y et al.* **Effects of switching to low-dose rosuvastatin (5 mg/day) on glucose metabolism and lipid profiles in Japanese patients with type 2 diabetes and dyslipidemia: a single-arm, prospective, interventional trial**. Diabetology international 2017; 8:383-391.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30603344
ABSTRACT
Aims: We investigated the effects of switching from other statins, such as pravastatin (5 or 10 mg/day), rosuvastatin (2.5 mg/day), or pitavastatin (1 or 2 mg/day), to low-dose rosuvastatin (5 mg/day) on glucose metabolism and lipid profiles in Japanese patients with type 2 diabetes and dyslipidemia. Methods: This was a prospective, two-center, open-label, single-arm, interventional trial. Several clinical parameters were analyzed at baseline and 24 weeks after switching from other statins to rosuvastatin at 5 mg/day. The primary endpoints were changes in hemoglobin (Hb) A1c level and lipid profile. Results: Forty-five patients were enrolled in the trial. The mean HbA1c level increased significantly from 7.1 +/- 0.7 to 7.5 +/- 0.9% (P < 0.001), whereas the mean low-density lipoprotein cholesterol (LDL-C) level decreased significantly from 108.9 +/- 16.5 to 91.6 +/- 24.5 mg/dL (P < 0.001). Multiple linear regression analysis showed that changes in HbA1c levels were significantly and positively correlated with fasting plasma glucose (FPG) levels at baseline. Receiver operating characteristic (ROC) curve analysis examining the relationship between HbA1c and FPG showed that FPG was a significant predictor of changes in HbA1c levels (area under the curve, 0.72). The cutoff FPG value of 168 mg/dL had a sensitivity of 47% and a specificity of 93%. Conclusions: Switching to a low dose of rosuvastatin impaired glucose metabolism in Japanese patients with type 2 diabetes and dyslipidemia. Patients with high FPG levels were particularly prone to an exacerbation of glucose metabolism.

[12] *Ota T*. **Immune regulation of glucose and lipid metabolism**. Diabetology international 2017; 8:257-267.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30603331
ABSTRACT
The immune response and metabolic regulation are highly integrated, and their interface maintains a homeostatic system. Their dysfunction can cause obesity and its comorbidities, including insulin resistance, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD). Endoplasmic reticulum (ER) stress is a central abnormality linking obesity, insulin resistance, and NAFLD. ER stress in response to increased hepatic lipids may decrease the ability of the liver to secrete triglyceride by limiting apolipoprotein B secretion, thereby worsening fatty liver. Overnutrition or obesity activates the innate immune system, with the subsequent recruitment of immune cells that contributes to the development of insulin resistance. A significant advance

in our understanding of obesity-induced inflammation and insulin resistance has been a recognition of the critical role of adipose tissue macrophages. A role for chemokines, small proteins that direct the trafficking of immune cells to sites of inflammation, has also been demonstrated. Chemokines activate the production of inflammatory cytokines through specific chemokine receptors. This review highlights the chemokine systems linking obesity to inflammation and insulin resistance. Treatment options that target immune cells with the aim of halting the development of insulin resistance and type 2 diabetes remain limited. DPP-4 inhibitors or micronutrients may contribute to the immune regulation of glucose and lipid metabolism by regulating macrophage polarization, thereby reducing insulin resistance and preventing the progression of NAFLD. A detailed understanding of the immune regulation of glucose and lipid homeostasis can lead to the development of a novel therapy for insulin resistance, type 2 diabetes, and NAFLD.

[13] *El-Korashi LA, Soliman MH, Attwa EM, Mohamed NA*. **Role of Atorvastatin in Treatment of Chronic Spontaneous Urticaria Patients: A Controlled Clinical Trial**. The Egyptian journal of immunology 2018; 25:133-139.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30600956
ABSTRACT
Chronic spontaneous urticaria (CSU) is a popular disease, affects patients' life. Its etiologic agents are not well known so; treatment of the patients is difficult. CD203c is a marker that is only present on basophils. Statins are drugs used to lower cholesterol. Nowadays, it is well known that they have immunomodulatory effects. This study evaluated the efficacy of a statin, atorvastatin, in combination with antihistamines in treating CSU patients. Forty CSU patients were divided equally into two groups. The first group was treated with antihistamines and atorvastatin, while the second group was treated with antihistamines and placebo. Both groups received the treatment for three months. The effect of treatment on total severity score (TSS), autologous serum skin test (ASST), basophil histamine release (BHR) assay, in vivo basophil CD203c expression (%) and basophil activation test (BAT-CD203c) was assessed. We found statistically significant reduction in TSS, BHR assay, in vivo basophil CD203c expression (%) (P= 0.000 each), diameter of ASST and BAT-CD203c (P= 0.002, 0.017, respectively), in the patients that received the atorvastatin and antihistamines. In conclusion, atorvastatin is effective in treating CSU patients.

[14] *Ye Z, Lu H, Su Q et al.* **Short-term and long-term effects of a loading dose of atorvastatin before percutaneous coronary intervention on major adverse cardiovascular events in patients with acute coronary syndrome: a meta-analysis of 13 randomized controlled trials**. European heart journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30608526
ABSTRACT
Aims: Whether a loading dose of atorvastatin (80 mg) can reduce major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) remains controversial. Therefore, we performed this meta-analysis. Methods and results: Randomized controlled trials (RCT) comparing a loading dose of atorvastatin to a control in patients with ACS who underwent PCI were identified through searches of medical literature databases. Risk ratios

(RRs) and 95% confidence intervals (CIs) were calculated to compare the primary endpoint. Finally, 13 trials enrolling 22 095 patients were included; of the 22 095 patients, 11 214 (50.7%) received loading doses of 80 mg of atorvastatin. Compared with the control, atorvastatin significantly reduced MACE (RR: 0.66, 95% CI 0.54-0.80), myocardial infarction (MI; RR: 0.61, 95% CI 0.46-0.80), revascularization (RR: 0.76, 95% CI 0.69-0.83), and stroke (RR: 0.69, 95% CI 0.49-0.96). There was no difference in death or rehospitalization between the two groups. In the subgroup analysis, atorvastatin still significantly reduced MACE (RR: 0.57, 95% CI 0.39-0.85) and MI (RR: 0.61, 95% CI 0.42-0.89) within 30 days. Furthermore, atorvastatin still remarkably reduced MACE (RR: 0.70, 95% CI 0.55-0.89), MI (RR: 0.58, 95% CI 0.36-0.95), and revascularization (RR: 0.76, 95% CI 0.69-0.84) after more than 30 days. No significant differences were observed in death or stroke within 30 days or after more than 30 days. Conclusion: Our meta-analysis supports the concept that a loading dose of atorvastatin markedly reduces cardiovascular events in patients with ACS.

[15] *Kayser BD, Lhomme M, Prifti E et al.* **Phosphatidylglycerols are induced by gut dysbiosis and inflammation, and favorably modulate adipose tissue remodeling in obesity**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2019:fj201801897R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30608881
ABSTRACT
Lipidomic techniques can improve our understanding of complex lipid interactions that regulate metabolic diseases. Here, a serum phospholipidomics analysis identified associations between phosphatidylglycerols (PGs) and gut microbiota dysbiosis. Compared with the other phospholipids, serum PGs were the most elevated in patients with low microbiota gene richness, which were normalized after a dietary intervention that restored gut microbial diversity. Serum PG levels were positively correlated with metagenomic functional capacities for bacterial LPS synthesis and host markers of low-grade inflammation; transcriptome databases identified PG synthase, the first committed enzyme in PG synthesis, as a potential mediator. Experiments in mice and cultured human-derived macrophages demonstrated that LPS induces PG release. Acute PG treatment in mice altered adipose tissue gene expression toward remodeling and inhibited ex vivo lipolysis in adipose tissue, suggesting that PGs favor lipid storage. Indeed, several PG species were associated with the severity of obesity in mice and humans. Finally, despite enrichment in PGs in bacterial membranes, experiments employing gnotobiotic mice colonized with recombinant PG overproducing Lactococcus lactis showed limited direct contribution of microbial PGs to the host. In summary, PGs are inflammation-responsive lipids indirectly regulated by the gut microbiota via endotoxins and regulate adipose tissue homeostasis in obesity.-Kayser, B. D., Lhomme, M., Prifti, E., Da Cunha, C., Marquet, F., Chain, F., Naas, I., Pelloux, V., Dao, M.-C., Kontush, A., Rizkalla, S. W., Aron-Wisnewsky, J., Bermudez-Humaran, L. G., Oakley, F., Langella, P., Clement, K., Dugail, I. Phosphatidylglycerols are induced by gut dysbiosis and inflammation, and favorably modulate adipose tissue remodeling in obesity.

[16] *Ye L, Cao Z, Lai X et al.* **Niacin fine-tunes energy homeostasis through canonical GPR109A signaling**. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018:fj201801951R.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30596513
ABSTRACT
The incidence of overweight and obesity has become a global public health problem, constituting a major risk factor for numerous comorbidities. Despite tremendous efforts, effective pharmacological agents for the treatment of obesity are still limited. Here, we showed that in contrast to lactate receptor GPR81, niacin receptor GPR109A-deficient mice had progressive weight gain and hepatic fat accumulation. Using high-fat diet-induced mouse model of obesity, we demonstrated that niacin treatment apparently protected against obesity without affecting food intake in wild-type mice but not in GPR109A-deficient mice. Further investigation showed that niacin treatment led to a remarkable inhibition of hepatic de novo lipogenesis. Additionally, we demonstrated that niacin treatment triggered brown adipose tissue and/or white adipose tissue thermogenic activity via activation of GPR109A. Moreover, we observed that mice exposed to niacin exhibited a dramatic decrease in intestinal absorption of sterols and fatty acids. Taken together, our findings demonstrate that acting on GPR109A, niacin shows the potential to maintain energy homeostasis through multipathways, representing a potential approach to the treatment of obesity, diabetes and cardiovascular disease.-Ye, L., Cao, Z., Lai, X., Wang, W., Guo, Z., Yan, L., Wang, Y., Shi, Y., Zhou, N. Niacin fine-tunes energy homeostasis through canonical GPR109A signaling.

[17] *Agrawal D, Manchanda SC, Sawhney JPS et al.* **To study the effect of high dose Atorvastatin 40mg versus 80mg in patients with dyslipidemia**. Indian Heart J 2018; 70 Suppl 3:S8-s12.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30595326
ABSTRACT
OBJECTIVE: Primary objective was to compare the effects of atorvastatin 40mg vs 80mg on LDL-C in Indian patients with atherosclerotic dyslipidemia. Secondary objectives were to compare the effects of atorvastatin 40mg vs 80mg on HDL-C and triglycerides and also comparing of side effects (myopathy, hepatotoxicity and new onset diabetes mellitus) of both doses. METHOD: This Study is A Prospective, randomized, open-label, comparative study. This study was conducted on 240 patients of dyslipidemia (as per ACC/AHA 2013 lipid guidelines) attending the OPD/wards/CCU of department of cardiology, Sir Ganga Ram Hospital. They were randomly divided into 2 groups of 120 each. Group A consisted patients who received Atorvastatin 40mg daily and Group B Atorvastatin 80mg daily. The follow up period was 6 months. RESULTS: At 3 and 6 month follow up, Atorvastatin 40mg leads to mean LDL cholesterol reduction of 47.18+/-20.81 & 50.03+/-18.06 respectively. While Atorvastatin 80mg results in LDL reduction as 50.11+/-15.85 & 52.30+/-13.72. The comparison between two doses revealed a non-significant difference (p=.118 & p=.149 respectively). At 6 months of follow up, few patients reported myalgia (2 in group A and 7 in Group B). The difference between groups was significant (p=.045). Although none of our patient had significant elevation of CPK. CONCLUSION: This study concluded that both doses of atorvastatin (40 & 80mg) are equally efficacious in improving dyslipidemia but higher dose leads to more incidence of myalgia.

[18] *Kumar M, Rehan HS, Puri R et al.* **Randomized controlled trial comparing the efficacy of daily and every other day atorvastatin therapy and its correlation with serum hydroxymethylglutaryl-CoA reductase enzyme levels in naive dyslipidemic patients**. Indian Heart J 2018; 70 Suppl 3:S64-s67.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30595323
ABSTRACT
OBJECTIVE: Data regarding efficacy comparison of daily regimen (DR) versus every other day regimen (EODR) atorvastatin therapy is not validated by estimation of serum hydroxymethylglutaryl-CoA reductase (HMGCR) levels and HMGCR correlation with lipid indices. METHODS: In this randomized controlled trial, we compared the efficacy of DR versus EODR by measuring lipid indices and serum HMGCR levels at baseline and after 12 weeks of 10mg atorvastatin therapy. Primary endpoint was comparison of mean change in serum HMGCR levels and lipid indices of both groups and their correlation with each other. Secondary endpoints were assessed by estimating serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase MM (CK-MM) levels and adverse drug reactions (ADRs). RESULTS: A total of 61 patients were enrolled of which 46 completed the study (24 in DR vs 22 in EODR group). The mean reduction in total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and non-high density lipoprotein-cholesterol (HDL-C) was significantly higher in DR group, whereas mean reduction in triglycerides (TG) and increase in HDL-C was similar in both the groups. Reduction in serum HMGCR levels was comparable in both the groups (31.17% vs 28.19%). Change in serum HMGCR levels correlated more with change in lipid indices of DR group. Also, safety parameters were similar between the two groups. CONCLUSION: Both the regimens achieved therapeutic goals, however DR was found to be superior as it achieved greater reduction in TC and LDL-C. Further, these findings are substantiated by correlation of lipid indices with serum HMGCR levels.

[19] *Ramakumari N, Indumathi B, Katkam SK, Kutala VK*. **Impact of pharmacogenetics on statin-induced myopathy in South-Indian subjects**. Indian Heart J 2018; 70 Suppl 3:S120-s125.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30595243
ABSTRACT
OBJECTIVES: Statins are the most commonly prescribed medications for the treatment of atherosclerotic cardiovascular disease. Statin-associated adverse effects occur in approximately 10% of patients and are associated with polymorphisms in several key genes coding for transporters and metabolizing enzymes that affect statin pharmacokinetics. In the present study, we examine the association between cytochrome P450 3A5*3 (CYP3A5*3) T>C (rs776746), COQ G>C (rs4693075), and SLCO1B1 T>C (rs4149056) genetic variants with the risk of myopathy in South Indian patients on statin therapy. METHODS: A total of 202 patients on atorvastatin or rosuvastatin therapy for 12 years were recruited in the study. Genotyping of drug metabolic CYP3A5*3 gene variant and drug transporter genes COQ G>C (rs4693075) and SLCO1B1 T>C (rs4149056) was analyzed by Sanger's sequencing. RESULTS: In our study subjects, the percentage of patients diagnosed to have statin-induced myopathy was 18%. The majority of the patients were on 10 mg/day dose of either atorvastatin or rosuvastatin. The homozygous nonexpressors genotype CYP3A5*3/3 frequency of the CYP3A5 polymorphism was higher in

patients with myopathy. But we could not find association of CYP3A5, COQ, and SLCO1B1 gene polymorphisms with either rosuvastatin or atorvastatin. CONCLUSION: Our results clearly demonstrate that the frequency of CYP3A5*3 splicing variant is higher in myopathy group than in the tolerant group. We did not find significant association of genetic polymorphisms in CYP3A5, COQ, and SLCO1B1 with atorvastatin- or rosuvastatin-induced myopathy.

[20] *van Crevel R, Koesoemadinata R, Hill PC, Harries AD*. **Clinical management of combined tuberculosis and diabetes**. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 2018; 22:1404-1410.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30606312
ABSTRACT
Optimal management of combined tuberculosis (TB) and diabetes (DM) is important but challenging in terms of achieving good disease outcomes and avoiding toxicity, drug interactions and other challenges. DM management during anti-tuberculosis treatment, aimed at improving TB treatment outcomes and reducing DM-related morbidity and mortality, consists of glycaemic control and measures to reduce the risk of cardiovascular disease. Metformin, the glucose-lowering drug of choice for TB patients, has no meaningful interaction with rifampicin (RMP), and may reduce TB mortality. Insulin is effective for severe hyperglycaemia, but has several disadvantages that limit its use in TB patients. Cardiovascular risk assessment should be considered in TB-DM patients to guide management in terms of counselling and prescription of antihypertensive, lipid-lowering and anti-platelet treatment. With regard to anti-tuberculosis treatment, DM is associated with an increased risk of drug resistance, lower exposure to anti-tuberculosis drugs, treatment failure and recurrent TB. Patients therefore need careful assessment before, during and possibly after anti-tuberculosis treatment. Although no studies have been performed, anti-tuberculosis treatment may also have to be prolonged or intensified in terms of regimen or drug dosage if DM is present. With regard to service delivery, combined treatment should probably be administered, supervised and monitored as much as possible in a TB clinic. Local circumstances and severity of DM will guide the need for referral of patients to specialised DM care, and continuation of DM care after completion of anti-tuberculosis treatment. More data are also needed for the management of TB-DM patients with human immunodeficiency virus co-infection.

[21] *Holm Nielsen S, Tengryd C, Edsfeldt A et al.* **Markers of Basement Membrane Remodeling Are Associated With Higher Mortality in Patients With Known Atherosclerosis**. Journal of the American Heart Association 2018; 7:e009193.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30608207
ABSTRACT
Background Patients with atherosclerosis have a high risk of cardiovascular events and death. Atherosclerosis is characterized by accumulation of lipids, cells and extracellular matrix proteins in the intima. We hypothesized that dysregulated remodeling of the basement membrane proteins may be associated with clinical outcomes in patients with atherosclerosis. Methods and Results Neoepitope fragments of collagen type IV (C4M) and laminin (LG 1M) were assessed by ELISA s in serum from 787 endarterectomy patients. Matrix metalloproteinase s

were measured using proximity extension assay and correlated to C4M and LG 1M levels using Spearman correlations. A total of 473 patients were followed up for 6 years using national registers, medical charts, and telephone interviews. The incidence of cardiovascular events, cardiovascular mortality, and all-cause mortality were associated to levels of C4M and LG 1M using Kaplan-Meier curves and Cox regression analyses. A total of 101 patients had cardiovascular events, 39 died of cardiovascular mortality, and 64 patients died from all-cause mortality. C4M levels were increased in patients with symptomatic carotid atherosclerotic disease before surgery (P=0.048). High C4M and LG 1M levels were associated with increased risk of all-cause mortality (P=0.020 and 0.031, respectively) and predicted all-cause death together with glomerular filtration rate and diabetes mellitus. Conclusions High LG 1M and C4M levels were associated with all-cause mortality, together with glomerular filtration rate and diabetes mellitus. These novel biomarkers need further evaluation but might be tools to identify high-risk patients.

[22] *Nabati M, Janbabai G, Esmailian J, Yazdani J*. **Effect of Rosuvastatin in Preventing Chemotherapy-Induced Cardiotoxicity in Women With Breast Cancer: A Randomized, Single-Blind, Placebo-Controlled Trial**. Journal of cardiovascular pharmacology and therapeutics 2019:1074248418821721.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30599756
ABSTRACT
OBJECTIVE:: Chemotherapy-induced cardiotoxicity is a major and leading cause of death in breast cancer survivors. It can present decades after chemotherapy and can manifest in different ways; some chemotherapeutic agents have a powerful dose-dependent relationship with cardiotoxicity. The aim of this study was to investigate the effect of rosuvastatin on preventing chemotherapy-induced cardiotoxicity in patients with breast cancer. METHODS:: Our study was a randomized, single-blind, placebo-controlled trial that involved 89 women with newly diagnosed breast cancer who were scheduled to receive chemotherapy. Patients were randomly assigned to receive rosuvastatin or a placebo in a 1:1 ratio for 6 months. Echocardiography, using 2-dimensional (2D) Doppler, tissue Doppler, and speckle-tracking methods, was used to determine the absolute changes in the left ventricular systolic ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left atrial (LA) diameter, transmitral Doppler early diastolic velocity (E wave), tissue Doppler early diastolic (e') and peak systolic (s') mitral annular velocities, E/e' ratio, and global longitudinal systolic strain. RESULTS:: The LVEF was significantly reduced in the placebo group at the end of the study when compared with the baseline value. However, there was no significant difference in the LVEF in the intervention group (intergroup P = .012). Furthermore, compared with the intervention group at the end of the study, there was a significant increase in the 4- and 2-chamber LVESV, LA diameter, and E/e' ratio in the placebo group (intergroup P = .019, P = .024, P < .001, and P = .021, respectively) and a significant decrease in the e' and s' velocities in the placebo group (intergroup P < .001 and P < .006, respectively). CONCLUSIONS:: The present study showed that the prophylactic use of rosuvastatin may prevent the development of chemotherapy-induced cardiotoxicity.

[23] *Uche A, Vankina R, Gong J et al.* **Capecitabine-induced hypertriglyceridemia: a rare but clinically relevant treatment-related adverse event**. Journal of gastrointestinal oncology 2018; 9:1213-1219.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30603144
ABSTRACT
Capecitabine-induced hypertriglyceridemia (CIHT) represents an increasingly significant treatment-related adverse event from capecitabine given its potential for both acute complications (acute pancreatitis) and chronic metabolic complications (cardiovascular disease). The incidence of CIHT is relatively rare and the majority of cases thus far reported have been managed with lipid-lowering therapy and/or discontinuation of capecitabine followed by resumption of the drug upon normalization of triglyceride levels. We present among the first U.S. cases of CIHT to be reported in the published literature and highlight management approaches for this rare but clinically relevant adverse event. Further understanding of the mechanisms of CIHT and its long-term adverse effects as well as effective preventive strategies, interventions, and monitoring strategies are prudent given the widespread and often prolonged use of capecitabine-based chemotherapy in gastrointestinal and other cancers.

[24] *Abdullah M, Jowett B, Whittaker PJ, Patterson L*. **The effectiveness of omega-3 supplementation in reducing ADHD associated symptoms in children as measured by the Conners' rating scales: A systematic review of randomized controlled trials**. Journal of psychiatric research 2018; 110:64-73.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30594823
ABSTRACT
Omega-3 supplements are considered to have anti-inflammatory effects which may be beneficial as inflammation has been linked to ADHD. The aim of this review is to examine the effectiveness of omega-3 supplementation at reducing ADHD symptoms in children and adolescents. Medline, Cinahl+, PsycINFO, Cochrane and Embase were searched for trials investigating the effects of omega-3 supplementation in children and adolescents with ADHD. The primary outcome measure was a mean difference in Conners' rating scale (CRS) between the intervention and placebo group. Search terms used include ADHD, omega-3, fish oils, eicosapentaenoic acid, docosahexaenoic acids, alpha-linolenic acid and Conners' rating scale. Randomized controlled trials examining the efficacy of omega-3 supplementation in children and adolescents as measured by CRS were included. Studies using a combination of polyunsaturated fatty acids or any other rating scale were excluded. Seven trials were included in this review, totalling 926 participants. We found no evidence of publication bias or heterogeneity between trials. Overall, there was a slightly greater reduction in CRS score in favour of the experiment group. One study found a greater reduction in score in favour of the placebo group. Neither findings were statistically significant. There is little supportive evidence to validate the claim of omega-3 supplementation to reduce the degree of ADHD symptoms experienced by children and adolescents. Both experiment and control groups saw similar reductions in Conners rating scale score.

[25] *Hou D, Mei Y, Ji Y et al.* **Congenital internal carotid artery hypoplasia: Case report**. Medicine (Baltimore) 2019; 98:e13986.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30608441
ABSTRACT
RATIONALE: Congenital internal carotid artery hypoplasia (CICAH) is rarely reported. This study aimed to discuss the epidemiological characteristics, clinical manifestation, imaging and treatment of CICAH. PATIENT CONCERNS: The case was male who showed barylalia and limited abilities of the left limbs as their main clinical manifestation. This patient was diagnosed CICAH by digital subtraction angiography (DSA) and computed tomography (CT). DIAGNOSIS: CICAH. INTERVENTIONS: The patient underwent anti platelet aggregation, lipid-lowering, improving cerebral circulation. OUTCOMES: The patient was in a stable condition after management of cerebrovascular risk. LESSONS: Given the asymptomatic and congenital nature of carotid agenesis, no treatment is necessary or possible to re-establish the internal carotid artery (ICA). However, with the high risk of aneurysm and cerebrovascular insufficiency, management of cerebrovascular risk is important. Urgent radiological assessment is necessary for patients with suspicious neurological symptoms.

[26] *Urke EB, Sobye S, Ellingvag A et al.* **Familial hypercholesterolemia and young patients' thoughts on own condition and treatment**. Patient education and counseling 2018.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30606641
ABSTRACT
OBJECTIVES: Familial hypercholesterolemia (FH) is a hereditary and usually asymptomatic condition characterized by elevated blood cholesterol and increased risk of premature cardiovascular disease. It is treated with dietary modifications and lipid lowering drugs. The objective was to learn about young FH patients' perceptions and choices regarding treatment. METHODS: Data were collected through in-depth interviews with 24 patients (ages 16-35), and analysed according to Grounded Theory. RESULTS: The findings are presented as theoretical concepts describing the participants' way of handling their condition. The core category was identified as "Thoughts of consequences vs. Postponing thoughts of consequences", which could be described through the following subcategories: 1. Normalising the condition, 2. Belittling of treatment vs. Committed to treatment and 3. Trust in advice vs. Avoid unnecessary interference. The participants' position regarding these categories was described to affect motivation and challenges with treatment. CONCLUSIONS: Participants who postpone the thoughts of consequences, belittle the treatment and avoid unnecessary interference represent a challenge to health care practitioners. PRACTICAL IMPLICATIONS: Practitioners should explore aspects such as thoughts of consequences, view of treatment and the feeling of interference to be able to better understand illness behaviour, adjust their communication and hopefully improve adherence.

[27] *Ontawong A, Duangjai A, Muanprasat C et al.* **Lipid-lowering effects of Coffea arabica pulp aqueous extract in Caco-2 cells and hypercholesterolemic rats**. Phytomedicine : international journal of phytotherapy and phytopharmacology 2019; 52:187-197.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30599898
ABSTRACT

BACKGROUND: Coffea arabica pulp (CP) is the first by-product obtained from coffee berries during coffee processing. The major constituents of CP, including chlorogenic acid, caffeine, and epicatechin exhibit anti-hyperlipidemic effects in in vitro and in vivo models. Whether Coffea arabica pulp aqueous extract (CPE) has a lipid-lowering effect remains unknown. PURPOSE: This study examined the effect of CPE on cholesterol absorption, and identified the mechanisms involved in lowered cholesterol in in vitro and in vivo models. METHODS: Uptake of [(3)H]-cholesterol micelles and the mode of CPE inhibition were determined using human intestinal Caco-2 cells, and subsequently, confirmed using isolated rat jejunal loops. In addition, the 12-week high-fat diet-induced hypercholesterolemic rats (HF) received either CPE (1000 mg/kg BW), a sole and high dose which was selected because it contained approximately 12 mg of CGA that was previously shown to have lipid-lowering effects, or ezetimibe (10 mg/kg BW), a cholesterol inhibitor. The rats were divided into HF, HF ++CPE, and HF ++ezetimibe groups for the next 12 weeks. Normal rats received a normal diet (ND) and CPE (ND + CPE). Body weights and lipid profiles were evaluated. Cholesterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), protein expression and liver X receptor alpha (LXRalpha) mRNA expression were determined. In vitro micellar complex properties were also investigated. RESULTS: CPE inhibited [(3)H]-cholesterol micelle transport in Caco-2 cells and rat jejunal loops in a dose-dependent, non-competitive manner partly by decreasing membrane NPC1L1 expression. Congruently, CPE and its major constituents activated LXRalpha which, in turn, down-regulated NPC1L1. Furthermore, CPE interfered with physicochemical characteristics of cholesterol mixed micelles. These data were consistent with decreased body weight and slowed body weight gain and improved lipid profiles by CPE in hypercholesterolemic rats while no change occurred in these parameters in normal rats. Down-regulated intestinal NPC1L1 expression mediated by increased LXRalpha mRNA were also observed in HF ++CPE and ND + CPE rats. CONCLUSION: CPE has a cholesterol-lowering effect in in vitro and in vivo via inhibition of intestinal cholesterol absorption by down-regulating NPC1L1 mediated LXRalpha activation and interfering with micellar complex formation. Accordingly, CPE could be developed as nutraceutical product to prevent dyslipidemia-induced obesity and insulin resistance.

[28] *Hackam DG, Hegele RA*. **Cholesterol Lowering and Prevention of Stroke**. Stroke 2019:Strokeaha118023167.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30602355
ABSTRACT

[29] *Nazish S, Zafar A, Shahid R et al.* **Relationship Between Glycated Haemoglobin and Carotid Atherosclerotic Disease Among Patients with Acute Ischaemic Stroke**. Sultan Qaboos University medical journal 2018; 18:e311-e317.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30607271
ABSTRACT
Objectives: This study aimed to determine the relationship between glycaemic control and carotid atherosclerotic disease among patients with acute ischaemic stroke (AIS). Methods: This retrospective cross-sectional study took place in the Neurology Department of King Fahad Hospital of University, Khobar, Saudi Arabia, from April to October 2017. Data were collected from the medical records of 244 patients with a diagnosis of AIS confirmed by computed

tomography. Doppler ultrasounds of the carotid artery were performed to determine the presence of increased carotid intima media thickness (CIMT) and plaques. Results: Significantly higher mean glycated haemoglobin (HbA1c) levels were noted in cases with high CIMT values (P = 0.002), but not in cases with carotid plaques (P = 0.360). In addition, there was a significant association between diabetes mellitus (DM) and high CIMT (P = 0.045), but not with carotid plaques (P = 0.075). Finally, while dyslipidaemia and age were independently correlated with high CIMT values (P = 0.034 and <0.001, respectively) and carotid plaques (P <0.001 each), no independent relationships were noted in terms of gender and other risk factors like DM, hypertension and smoking (P >0.050 each). Conclusion: High HbA1c levels were associated with high CIMT values, but not with carotid plaques. Therefore, HbA1c levels may be useful as an indirect marker of the initial stages of carotid artery atherosclerosis.

[30] *Koh JS, Park Y, Ahn JH et al.* **Influence of Amlodipine on Haemostatic Measurements during Clopidogrel Treatment in Patients with Coronary Artery Disease**. Thrombosis and haemostasis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30609441
ABSTRACT
Amlodipine has a potential to reduce clopidogrel bioactivation through the cytochrome P450 3A4 enzyme in vivo, but the clinical impact of this interaction remains controversial. This randomized, open-label, two-period, crossover study was performed to evaluate the influence of amlodipine on the haemostatic profiles of high-risk patients during clopidogrel treatment. We recruited 40 Asian patients (Male/Female: n = 36/4) receiving clopidogrel (75 mg/day), aspirin (100 mg/day) and rosuvastatin for at least 6 months following percutaneous coronary intervention. Patients were randomly assigned to receive either 5 mg daily amlodipine or not for 2 weeks, and then were crossed over to the other treatment for 2 weeks. Haemostatic measurements were conducted with the VerifyNow assay and thromboelastography (TEG). Primary endpoint was P2Y12 Reaction Units (PRU) during on- versus off-amlodipine treatment. The on-amlodipine strategy showed higher level of PRU compared with the off-amlodipine strategy (176.8 +/- 75.4 vs. 150.7 +/- 65.5 PRU; mean: 26.1 PRU; 95% confidence interval [CI]: 4.5-47.7 PRU; p = 0.019). Platelet-fibrin clot strength measured by TEG was lower during on- versus off-amlodipine treatment (7,712 +/- 1,889 vs. 8,559 +/- 2,174 dyne/cm(2); mean: -847 dyne/cm(2); 95% CI: -1,632 to -62 dyne/cm(2); p = 0.035). After amlodipine discontinuation, 27 patients (67.5%) showed a decrease in PRU, which was associated with 'PRU >/= 160 on-amlodipine' in multivariate analysis (odds ratio: 62.014; 95% CI: 2.302-1670.328; p = 0.014). In conclusion, amlodipine increases platelet reactivity and decreases platelet-fibrin clot strength during clopidogrel treatment. In addition, the effect of amlodipine discontinuation on clopidogrel responsiveness is associated with on-amlodipine platelet reactivity.

[31] *Martinelli N, Baroni M, Castagna A et al.* **Apolipoprotein C-III Strongly Correlates with Activated Factor VII-Anti-Thrombin Complex: An Additional Link between Plasma Lipids and Coagulation**. Thrombosis and haemostasis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30602199
ABSTRACT

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Activated factor VII-anti-thrombin (FVIIa-AT) complex is a potential biomarker of pro-thrombotic diathesis reflecting FVIIa-tissue factor (TF) interaction and has been associated with mortality in patients with coronary artery disease (CAD). Previous data indicated plasma lipids as predictors of FVIIa-AT variability, and plasma lipoproteins as potential stimulators of the coagulation cascade. Our aim was to evaluate the relationships between FVIIa-AT plasma concentration and a broad apolipoprotein profile (including ApoA-I, ApoB, ApoC-III and ApoE). Within the framework of the observational Verona Heart Study, we selected 666 subjects (131 CAD-free and 535 CAD, 75.4% males, mean age: 61.1 +/- 10.9 years) not taking anticoagulant drugs and for whom plasma samples were available for both FVIIa-AT assay and a complete lipid profile. Plasma concentration of FVIIa-AT levels significantly and directly correlated with total and high-density lipoprotein cholesterol, triglycerides, ApoA-I, ApoC-III and ApoE levels. ApoC-III showed the strongest correlation (R = 0.235, p = 7.7 x 10(-10)), confirmed in all the sub-group analyses (males/females and CAD/CAD-free). Only ApoC-III remained associated with FVIIa-AT plasma concentration, even after adjustment for sex, age, CAD diagnosis, body mass index, renal function, smoking status, lipid-lowering therapies and FVIIa levels. The APOC3 gene locus-tagging polymorphism rs964184, previously linked with cardiovascular risk and plasma lipids by genome-wide association studies, was associated with both ApoC-III and FVIIa-AT plasma concentration. Our results indicate a strong association between ApoC-III and FVIIa-AT levels, thereby suggesting that an increased ApoC-III concentration may identify subjects with a pro-thrombotic diathesis characterized by an enhanced TF-FVIIa interaction and activity.

[32] *Paciullo F, Momi S, Gresele P*. **PCSK9 in Haemostasis and Thrombosis: Possible Pleiotropic Effects of PCSK9 Inhibitors in Cardiovascular Prevention**. Thrombosis and haemostasis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=30605918

ABSTRACT

Since increased cholesterol levels are crucial in determining the development of atheroma, their reduction represents a mainstay in primary and secondary cardiovascular prevention. The most recent spectacular advancement in cholesterol-lowering therapy is represented by proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors. Although their benefit over currently available treatments has been ascribed primarily to their strong low-density lipoprotein (LDL)-cholesterol reducing action, several clues suggest that PCSK9 inhibitors may also influence platelet function and blood coagulation. PCSK9 knockout mice develop less venous and arterial thrombosis and show reduced in vivo platelet activation upon arterial injury. In patients with acute coronary syndromes (ACSs) treated with P2Y12 inhibitors, a direct association between PCSK9 serum levels and residual platelet reactivity was found. A direct correlation between urinary excretion of 11-dehydro-thromboxane-B2, a marker of in vivo platelet activation, and circulating PCSK9 levels was reported in patients with atrial fibrillation. Moreover, recombinant human PCSK9 added in vitro to human platelets potentiated activation induced by weak agonists. Finally, blood clotting factor VIII (FVIII), which is associated with stroke and ACS risk, is cleared from the circulation by members of the LDL receptor (LDLR) family. Given that PCSK9 degrades LDLR, it is conceivable that PCSK9 inhibitors by enhancing the expression of LDLR may slightly decrease circulating FVIII, in this way contributing to the prevention of cardiovascular events. This review aims to discuss the possible and hypothetical

interactions between PCSK9 and the haemostatic system and to examine the possible pleiotropic effects of PCSK9 inhibitors in cardiovascular prevention.