Literature update week 29 (2019)

[1] *Zhang L, Wang L, Xie Y et al.* **Triple Targeting Delivery of CRISRP/Cas9 to Reduce the Risk of Cardiovascular Diseases**. Angewandte Chemie (International ed. in English) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31318118

ABSTRACT

High level of low-density lipoprotein cholesterol (LDL-C) is a major risk factor for coronary heart disease. The efficient and permanent down-regulation of LDL-C faces challenges. Herein, we present a triple targeting strategy to generate loss-of-function mutation in the gene of serine protease proprotein convertase subtilisin/kexin type 9 (Pcsk9) which regulates plasma cholesterol levels, by nanocarrier-delivered clustered regularly interspaced short palindromic repeats)/Cas9 (CRISPR/Cas9) system. Nuclear localization signal (NLS)-encoded Cas9 protein and sgRNA targeting to Pcsk9 (sgPcsk9) were complexed with cationic HIV-1- transactivating transcriptor (TAT) peptide-modified gold nanoclusters (GNCs) to form a dual-nucleus targeting complex which was further encapsulated by galactose moiety (Gal, targeting liver cells)-modified lipid layer to form Gal-PEG-lipid/TAT-GNCs/Cas9 protein/sgPcsk9 (Gal-LGCP). Gal-LGCP led to gene editing of Pcsk9 in vitro by ~60%. Furthermore, Gal-LGCP successfully targeted to the liver where PCSK9 is specifically expressed and led to effective mutation in Pcsk9 and ~30% of plasma LDL-C decrease in mice. No off-target mutagenesis was detected in 10 potential sites with high similarity. This approach may have therapeutic potential for the prevention and treatment of cardiovascular disease without side effects.

[2] *Dyrbus K, Gasior M, Desperak P et al.* **The prevalence and management of familial hypercholesterolemia in patients with acute coronary syndrome in the Polish tertiary centre: Results from the TERCET registry with 19,781 individuals**. Atherosclerosis 2019; 288:33-41.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31319356

ABSTRACT

BACKGROUND AND AIMS: The prevalence of familial hypercholesterolemia (FH) is high among patients with stable coronary artery disease (CAD). However, data on FH on admission among patients with acute coronary syndrome (ACS) are still relatively scarce. Therefore, we aimed to assess the prevalence, lipid-lowering therapy and short- and long-term outcomes in patients with FH among ACS patients. METHODS AND RESULTS: The investigation was performed in a cohort of 19,781 consecutive patients from the TERCET Registry. There were 7319 patients admitted with ACS: 3085 due to STEMI, 2256 due to NSTEMI, and 1978 due to UA. The stable CAD group (n=12,462) was considered the reference group. Based on the personal and familial history of premature cardiovascular disease and LDL cholesterol concentration, the Dutch Lipid Clinic Network (DLCN) algorithm was used for FH diagnosis. The overall occurrence of probable/definite FH and possible FH was 1.2% and 13.5% respectively. Among patients with ACS, 1.6% had probable/definite FH and 17.0% possible FH. The highest occurrence of FH was observed in the STEMI subgroup (20.6%). Patients with definite and probable FH had higher 30-day mortality than patients without FH (8.2% and 3.8% vs. 2.0%, respectively; p=0.0052). No significant differences were observed between the FH groups in the 12-, 36- and 60-month follow-up. Propensity-score matching analysis showed that definite/probable FH patients had significantly higher all-cause mortality at 36- and 60-month follow-up in comparison to non-FH subjects (11.4% vs. 4.8% and 19.2% vs. 7.2%, respectively; p</=0.021 for both). CONCLUSIONS: The prevalence of FH according to the DLCN criteria in the Polish very high-risk population is

significantly higher in patients with ACS than in patients with sCAD. FH is a cause of increased all-cause mortality in the long-term follow-up.

[3] *Pastori D, Ettorre E, Carnevale R et al.* **Interaction between serum endotoxemia and proprotein convertase subtilisin/kexin 9 (PCSK9) in patients with atrial fibrillation: A post-hoc analysis from the ATHERO-AF cohort**. Atherosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31303312
ABSTRACT
BACKGROUND AND AIMS: Lipopolysaccharides (LPS) is emerging as a novel risk factor for cardiovascular events (CVEs). Furthermore, in vitro evidence suggested that LPS may elicit proprotein convertase subtilisin/kexin 9 (PCSK9) expression, but their relationship in vivo has not been investigated. METHODS: We conducted a post-hoc analysis of a prospective, single centre cohort study of 907 patients with non-valvular atrial fibrillation (AF). At baseline, PCSK9, LPS and NADPH oxidase (sNox2-dp) were measured. PCSK9 and LPS were correlated with the incidence of CVEs. RESULTS: Median PCSK9 and LPS were 1200 [900-1970] and 49.9 [15.0-108.2] pg/ml, respectively. LPS and PCSK9 were significantly correlated (rS 0.378, p<0.001). Logistic regression analysis showed that LPS was associated with PCSK9 above the median (odds ratio [OR] 1.727 95% confidence interval [CI] 1.147-2.600 p=0.009). Other factors associated with PCSK9 above the median were sNox2-dp (OR 1.759 C.I. 95% 1.167-2.650, p=0.007), use of antiplatelet drugs (OR 0.437 95%CI 0.219-0.871 p=0.017) and high adherence to Mediterranean diet (OR 0.737 95%CI 0.643-0.845 p=0.001). Olive oil (OR 0.376 95%CI 0.185-0.763, p=0.001) and wine (OR 0.460 95%CI 0.289-0.733 p=0.007) were negatively associated with PCSK9. Patients with concomitant high PCSK9 and LPS (LPS >/=88pg/ml and PCSK9 >/=1570pg/ml) had an increased risk of CVEs compared to those with low levels (LPS <24.3pg/ml and PCSK9 <1000pg/ml, Log-Rank test, p=0.022). CONCLUSIONS: This study demonstrated, for the first time in vivo, that circulating levels of PCSK9 and LPS are associated with a mechanism possibly involving NADPH oxidase activation. Patients with concomitant increase of PCSK9 and LPS showed a higher risk of CVEs.

[4] *Carino A, Biagioli M, Marchiano S et al.* **Ursodeoxycholic acid is a GPBAR1 agonist and resets liver/intestinal FXR signaling in a model of diet-induced dysbiosis and NASH**. Biochimica et biophysica acta. Molecular and cell biology of lipids 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31325638
ABSTRACT
Obeticholic acid (OCA), a farnesoid-X-receptor (FXR) ligand, shown effective in reducing steatosis and fibrosis in NASH patients. However, OCA causes major side effects including pruritus, while increases the risk for liver decompensation in cirrhotic patients. Ursodeoxycholic acid (UDCA), is a safe and unexpensive bile acid used in the treatment of liver disorders whose mechanism of action is poorly defined. Here we have compared the effects of OCA and UDCA in a mouse model of NASH. In mice exposed to a diet rich in fat/cholesterol and fructose (HFD-F), treatment with OCA or UDCA effectively prevented body weight gain, insulin resistance, as demonstrated by OGTT, and AST plasma levels. After 12weeks HFD-F mice developed liver microvesicular steatosis, inflammation and mild fibrosis, increased expression of inflammatory (TNFalpha, IL6, F4/80) and fibrosis (alphaSma, Col1alpha1, Tgfbeta) markers, reduced liver

expression of FXR, dysregulated liver FXR signaling and elevated levels of Tauro-alpha and beta-muricholic acid (T-alpha and betaMCA), two FXR antagonists in mice. Both compounds prevented these changes and improved liver histopathology. OCA reduced primary bile acid synthesis worsening the T-CA/T-betaMCA ratio. UDCA effectively transactivated GPBAR1 in vitro. By RNAseq analysis we found that among over 2400 genes modulated by the HFD-F, only 32 and 60 genes were modulated by OCA and UDCA, with only 3 genes (Dbp, Adh7, Osgin1) being modulated by both agents. Both agents partially prevented the intestinal dysbiosis. CONCLUSIONS: UDCA is a GPBAR1 ligand and exerts beneficial effects in a rodent model of NASH by activating non-overlapping pathway with OCA.

[5] *Hai JJ, Wong YK, Wong CK et al.* **Prognostic implications of statin intolerance in stable coronary artery disease patients with different levels of high-sensitive troponin**. BMC cardiovascular disorders 2019; 19:168.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307391
ABSTRACT
BACKGROUND: The prognostic implication of statin in tolerance (SI) in those with stable CAD remains unclear. We hypothesized that SI is of higher prognostic significance in stable CAD patients with elevated high-sensitive cardiac troponin I (hs-cTnI). METHODS: A total of 952 stable CAD patients from the prospective Hong Kong CAD study who had complete clinical data, biomarker measurements and who were prescribed statin therapy were studied. RESULTS: We identified 13 (1.4%) and 125 (13.1%) patients with complete and partial SI, respectively. At baseline, patients with SI were more likely to have diabetes mellitus and a higher hs-cTnI level, but no difference in LDL-C level compared with those without SI. After 51 months of follow-up, patients with SI had a higher mean LDL-C level than those without SI. A total of 148 (15.5%) patients developed major adverse cardiovascular events (MACEs). Both SI (HR 1.52, 95% CI 1.06-2.19, P = 0.02) and elevated hs-cTnI (HR 3.18, 95% CI 2.07-4.89, P < 0.01) were independent predictors of a MACE in patients with stable CAD. When stratified by hs-cTnI level, SI independently predicted MACE-free survival only in those with elevated hs-cTnI (HR 1.51, 95% CI 1.01-2.24, P = 0.04). CONCLUSIONS: SI independently predicted MACE in patients with stable CAD and high hs-cTnI, but not in those with low hs-cTnI. Hs-cTnI may be used to stratify stable CAD patients who have SI for intensive lipid-lowering therapy using non-statin agents.

[6] *Bahall M, Seemungal T, Khan K, Legall G*. **Medical care of acute myocardial infarction patients in a resource limiting country, Trinidad: a cross-sectional retrospective study**. BMC Health Serv Res 2019; 19:501.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31319824
ABSTRACT
BACKGROUND: Cardiovascular disease remains the most common cause of death. However, effective and timely secondary care contributes to improved quality of life, decreased morbidity and mortality. This study analyzed the medical care of patients in a resource limiting country with a first presentation of acute myocardial infarction (AMI). METHODS: A cross-sectional retrospective study was conducted on first time AMI patients admitted between March 1st 2011 and March 31st 2015 to the only tertiary public hospital in a resource limiting country, Trinidad. Relevant data were obtained from all confirmed AMI patients. RESULTS: Data were

obtained from 1106 AMI patients who were predominantly male and of Indo Trinidadian descent. Emergency treatment included aspirin (97.2%), clopidogrel (97.2%), heparin (81.3%) and thrombolysis (70.5% of 505 patients with ST elevation MI), but none of the patients had primary angioplasty. Thrombolysis was higher among younger patients and in men. There were no differences in age, sex, and ethnicity in all other treatments. Of the 360 patients with recorded times, 41.1% arrived at the hospital within 4 h. The proportion of patients receiving thrombolysis (door to needle time) within 30 min was 57.5%. In-patient treatment medication included: aspirin (87.1%), clopidogrel (87.2%), beta blockers (76.5%), ACEI (72.9%), heparin (80.6%), and simvastatin (82.5%). Documentation of risk stratification, use of angiogram and surgical intervention, initiation of cardiac rehabilitation (CR), and information on behavioral changes were rare. Electrocardiogram (ECG) and cardiac enzyme tests were universally performed, while echocardiogram was performed in 57.1% of patients and exercise stress test was performed occasionally. Discharge treatment was limited to medication and referrals for investigations. Few patients were given lifestyle and activity advice and referred for CR. The in-hospital death rate was 6.5%. There was a significantly higher relative risk of in-hospital death for non-use of aspirin, clopidogrel, simvastatin, beta blockers, and heparin, but not ACE inhibitors and nitrates. CONCLUSIONS: Medication usage was high among AMI patients. However, there was very minimal use of non-pharmacological measures. No differences were found in prescribed medication by age, sex, or ethnicity, with the exception of thrombolysis.

[7] *Wan S, Huang C, Zhu X*. **Systematic review with a meta-analysis: clinical effects of statins on the reduction of portal hypertension and variceal haemorrhage in cirrhotic patients**. BMJ open 2019; 9:e030038.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31315875
ABSTRACT
BACKGROUND: Statins may improve outcomes in patients with cirrhosis. We performed a systematic review and meta-analysis to evaluate the effect of statins on patients with cirrhosis and related complications, especially portal hypertension and variceal haemorrhage. METHODS: Studies were searched in the PubMed, Embase and Cochrane library databases up to February 2019. The outcomes of interest were associations between statin use and improvement in portal hypertension (reduction >20% of baseline or <12 mm Hg) and the risk of variceal haemorrhage. The relative risk (RR) with a 95% CI was pooled and calculated using a random effects model. Subgroup analyses were performed based on the characteristics of the studies. RESULTS: Eight studies (seven randomised controlled trials (RCTs) and one observational study) with 3195 patients were included. The pooled RR for reduction in portal hypertension was 1.91 (95% CI, 1.04 to 3.52; I(2)=63%) in six RCTs. On subgroup analysis of studies that used statin for 1 month, the RR was 2.01 (95% CI, 1.31 to 3.10; I(2)=0%); the pooled RR for studies that used statins for 3 months was 3.76 (95% CI, 0.36 to 39.77; I(2)=75%); the pooled RR for studies that used non-selective beta-blockers in the control group was 1.42 (95% CI, 0.82 to 2.45; I(2)=64%); the pooled RR for studies that used a drug that was not reported in the control group was 4.21 (95% CI, 1.52 to 11.70; I(2)=0%); the pooled RR for studies that used simvastatin was 2.20 (95% CI, 0.92 to 5.29; I(2)=69%); RR for study using atorvastatin was 1.82 (95% CI, 1.00 to 3.30). For the risk of a variceal haemorrhage, the RR based on an observational study was 0.47 (95% CI, 0.23 to 0.94); in two RCTs, the pooled RR was 0.88 (95% CI, 0.52 to

1.50; I(2)=0%). Overall, the summed RR was 0.64 (95% CI, 0.42 to 0.99; I(2)=6%). CONCLUSION: Statins may improve hypertension and decrease the risk of variceal haemorrhage according to our assessment. However, further and larger RCTs are needed to confirm this conclusion.

[8] *Wang Y, Nichol MB, Yan BP et al.* **Descriptive analysis of real-world medication use pattern of statins and antiplatelet agents among patients with acute coronary syndrome in Hong Kong and the USA**. BMJ open 2019; 9:e024937.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31315855
ABSTRACT
OBJECTIVES: The objective was to explore the differences in medication use pattern of lipid-lowering drug (LLD) and antiplatelet agents among post-percutaneous coronary intervention patients with acute coronary syndrome aged <65 in Hong Kong (HK) and the USA. DESIGN: Retrospective study. SETTING: This study used deidentified claims data from Clinformatics Data Mart database (OptumInsight, Eden Prairie, Minnesota, USA) and electronic health records from HK Hospital Authority Clinical Data Analysis and Reporting System database. PARTICIPANTS: We used 1 year prescription records of LLDs and antiplatelet agents among 1013 USA patients and 270 HK Chinese patients in 2011-2013. PRIMARY AND SECONDARY OUTCOME MEASURES: Continuity was investigated on the assumption that one defined daily dose represented 1 day treatment. Medication possession ratio method was used to evaluate the adherence. Multivariate-adjusted logistic regressions were constructed to compare the good continuity and adherence levels in the merged database with the cutoffs set at 80%, and Cox proportional hazard models were built using the time to discontinuation as the dependent variable, to assess the persistence level. RESULTS: HK Chinese patients were less adherent (67.41% vs 84.60%, adjusted odds ratio (AOR) for Americans over Chinese=2.23 (95% CI=1.60 to 3.12), p<0.001) to antiplatelet agents compared with American patients but better adherent to statins (90.00% vs 78.18%, AOR=0.37 (0.23 to 0.58), p<0.001). The discontinuation with statins was more common in American patients (13.33% vs 34.25%, adjusted hazard ratio (AHR)=2.95 (2.05 to 4.24), p<0.001). Low-to-moderate potency statins and clopidogrel were favoured by our HK local physicians, while American patients received higher doses of statins and prasugrel. CONCLUSIONS: We seemed to find HK physicians tended to prescribe cheaper and lower doses of statins and antiplatelet agents when compared with the privately insured patients in the USA, though the adherence and persistence levels of HK patients with statins were relatively good.

[9] *Sheikholeslami K, Ali Sher A, Lockman S et al.* **Simvastatin Induces Apoptosis in Medulloblastoma Brain Tumor Cells via Mevalonate Cascade Prenylation Substrates**. Cancers 2019; 11.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31319483
ABSTRACT
Medulloblastoma is a common pediatric brain tumor and one of the main types of solid cancers in children below the age of 10. Recently, cholesterol-lowering "statin" drugs have been highlighted for their possible anti-cancer effects. Clinically, statins are reported to have promising potential for consideration as an adjuvant therapy in different types of cancers. However, the anti-cancer effects of statins in medulloblastoma brain tumor cells are not

currently well-defined. Here, we investigated the cell death mechanisms by which simvastatin mediates its effects on different human medulloblastoma cell lines. Simvastatin is a lipophilic drug that inhibits HMG-CoA reductase and has pleotropic effects. Inhibition of HMG-CoA reductase prevents the formation of essential downstream intermediates in the mevalonate cascade, such as farnesyl pyrophosphate (FPP) and gernaylgerany parophosphate (GGPP). These intermediates are involved in the activation pathway of small Rho GTPase proteins in different cell types. We observed that simvastatin significantly induces dose-dependent apoptosis in three different medulloblastoma brain tumor cell lines (Daoy, D283, and D341 cells). Our investigation shows that simvastatin-induced cell death is regulated via prenylation intermediates of the cholesterol metabolism pathway. Our results indicate that the induction of different caspases (caspase 3, 7, 8, and 9) depends on the nature of the medulloblastoma cell line. Western blot analysis shows that simvastatin leads to changes in the expression of regulator proteins involved in apoptosis, such as Bax, Bcl-2, and Bcl-xl. Taken together, our data suggests the potential application of a novel non-classical adjuvant therapy for medulloblastoma, through the regulation of protein prenylation intermediates that occurs via inhibition of the mevalonate pathway.

[10] *Diaz Rodriguez A, Blasco Valle M, Mantilla Morato T et al.* **Management of atherogenic dyslipidemia in the primary care setting in Spain**. Clinica e investigacion en arteriosclerosis : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31320121
ABSTRACT
AIM: To describe the management of atherogenic dyslipidemia (AD) in routine clinical practice in the Primary Care (PC) setting in Spain. METHODS: Observational, descriptive, cross-sectional study based on a structured questionnaire designed for this study and addressed to PC physicians. The questionnaire content was based on a literature review and was validated by 3 experts in AD. RESULTS: A total of 1029 PC physicians participated in the study. 96.99% indicated that AD is determinant for cardiovascular risk, even if LDL-C levels are appropriate. 88.43% evaluated residual cardiovascular risk in their clinical practice, however, only 27.89% of them evaluated it in secondary prevention. Regarding diagnosis, 82.22% reported that TC, TG, HDL-C and non-HDL-C are essential measures when evaluating AD. Almost all physicians reported that they can request fractionated cholesterol to assess HDL-C and LDL-C, however 3.69% could not. Physicians (95.63%) considered that the first step in AD treatment should be diet, regular exercise, smoking cessation and pharmaceutical treatment, if necessary. 19.1% agreed partially or completely that gemfibrozil is the most suitable fibrate to associate with statins. 74.83% completely agreed that fenofibrate is the most suitable fibrate to combine with statins. CONCLUSIONS: Physicians have access to general Spanish guidelines and recommendations associated with AD management, however, it is necessary to continue rising awareness about the importance of early detection and optimal control of AD to reduce patients' cardiovascular risk.

[11] *Peikert A, Kaier K, Merz J et al.* **Residual inflammatory risk in coronary heart disease: incidence of elevated high-sensitive CRP in a real-world cohort**. Clinical research in cardiology : official journal of the German Cardiac Society 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31325043

ABSTRACT

BACKGROUND: Inflammation drives atherosclerosis and its complications. Anti-inflammatory therapy with interleukin 1 beta (IL-1beta) antibody reduces cardiovascular events in patients with elevated high-sensitive C-reactive protein (hsCRP). This study aims to identify the share of patients with coronary heart disease (CHD) and residual inflammation who may benefit from anti-inflammatory therapy. METHODS: hsCRP and low-density lipoprotein (LDL) levels were determined in 2741 all-comers admitted to the cardiological ward of our tertiary referral hospital between June 2016 and June 2018. Patients without CHD, with acute coronary syndrome, chronic or recurrent systemic infection, use of immunosuppressant or anti-inflammatory agents, chronic inflammatory diseases, chemotherapy, terminal organ failure, traumatic injury and pregnancy were excluded. RESULTS: 856 patients with stable CHD were included. 42.7% of those had elevated hsCRP >/= 2 mg/l. Within the group of patients with LDL-cholesterol < 70 mg/dl, 30.9% shared increased hsCRP indicating residual inflammation. After multivariate adjusted backward selection elevated Lipoprotein (a) (OR 1.61, p = 0.048), elevated proBNP (OR 2.57, p < 0.0001), smoking (OR 1.70, p = 0.022), and obesity (OR 2.28, p = 0.007) were associated with elevated hsCRP. In contrast, the use of ezetimibe was associated with normal hsCRP (OR 0.51, p = 0.014). In the subgroup of patients with on-target LDL-cholesterol < 70 mg/dl, backward selection identified elevated proBNP (OR 3.49, p = 0.007) as independent predictor of elevated hsCRP in patients with LDL-cholesterol < 70 mg/dl. CONCLUSION: One-third of all-comers patients with CHD showed increased levels of hsCRP despite a LDL-cholesterol < 70 mg/dl potentially qualifying for an anti-inflammatory therapy. Elevated proBNP is an independent risk factor for hsCRP elevation.

[12] *Cho KI, Kim BH, Park YH et al.* **Efficacy and Safety of a Fixed-Dose Combination of Candesartan and Rosuvastatin on Blood Pressure and Cholesterol in Patients With Hypertension and Hypercholesterolemia: A Multicenter, Randomized, Double-Blind, Parallel Phase III Clinical Study**. Clinical therapeutics 2019.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307833

ABSTRACT

PURPOSE: The aim of this study was to evaluate the blood pressure-lowering and cholesterol-lowering effects of a fixed-dose combination therapy using candesartan (CND)/rosuvastatin (RSV) compared with CND or RSV monotherapy in patients with hypertension and hypercholesterolemia. METHODS: This study was a 12-week, randomized, double-blind, placebo-controlled, multicenter study. A total of 394 patients were screened. After a 4-week run-in period, 219 of these patients with hypertension and primary hypercholesterolemia were randomized. Patients received 1 of 3 regimens for 8 weeks: (1) CND 32 mg/RSV 20 mg, (2) RSV 20 mg, or (3) CND 32 mg. The primary outcome variables were changes in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) and the percentage changes in LDL-C from baseline to the drug treatment at 8 weeks. The secondary outcome variables were percentage changes of total cholesterol, triglycerides, HDL-C, non-HDL-C, apolipoprotein B, apolipoprotein A-I, high-sensitivity C-reactive protein, and glucose metabolic indices, including percentage changes of the homeostasis model assessment of insulin resistance (HOMA-IR), adiponectin, and hemoglobin A1c. Tolerability of combination therapy was compared with other

monotherapy groups. FINDINGS: The percentage changes of LDL-C were -48.6% (from 157.2 to 80.1 mg/dL) in the RSV group and -49.8% (from 160.2 to 78.9 mg/dL) in the CND/RSV group from baseline to the end of 8 weeks of treatment. Mean SBP and DBP were significantly decreased in the CND/RSV and CND groups after 8 weeks ($P < 0.001$ for all); however, no significant differences were found between the 2 groups. Total cholesterol levels, triglycerides, non-HDL-C, and apolipoprotein B were significantly reduced in the CND/RSV and RSV groups, with no significant differences between the groups compared with the CND group ($P < 0.001$ for all). The percentage changes of HOMA-IR, adiponectin, and hemoglobin A1c had no significant differences between the combination groups and monotherapy groups. However, in a 2-sample t test, HOMA-IR was significantly decreased in the CND/RSV group compared with the RSV group in nondiabetic patients (mean [SD] percentage change of HOMA-IR, -8.7% [37.6%] vs 17.1% [53.1%]; $P = 0.048$). There were no significant differences in metabolic indices between the diabetic groups. Adverse events in the CND/RSV group were similar to those in the monotherapy group. IMPLICATIONS: Once-daily fixed-dose combination therapy with CND/RSV is an effective, tolerable, convenient treatment option for patients with essential hypertension and hypercholesteremia. ClinicalTrials.gov identifier: NCT02770261. (Clin Ther. 2019;XX:XXX-XXX) (c) 2019 Elsevier HS Journals, Inc.

[13] *Santos HO, Kones R, Rumana U et al.* **Lipoprotein(a): Current Evidence for a Physiologic Role and the Effects of Nutraceutical Strategies**. Clinical therapeutics 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307832
ABSTRACT
PURPOSE: Cardiovascular (CV) diseases account for most worldwide mortality, and a higher level of lipoprotein (Lp)-(a) is recognized as a prevalent contributing risk factor. However, there is no consensus regarding nutritional strategies for lowering Lp(a) concentration. Thus, the purposes of this literature review were to: (1) critically examine data concerning the effects of dietetic interventions and nutraceutical agents on Lp(a) level; and (2) review the feasibility and utility of their clinical use. METHODS: A literature search was conducted for studies published between August 2018 and March 2019. The search was performed using the Cochrane, Medline, and Web of Science databases. In order to expand the research, there were no delimitations on the type or year of the studies. A total of 1932 articles were identified using this search procedure. After duplicates were eliminated, 740 abstracts of articles written in English were screened to identify those of highest relevance. In the final tally, a total of 152 full-text articles were included in this review. FINDINGS: Several foods and decreases in saturated fat and ethanol intake, especially red wine intake, may lower Lp(a) concentration, but limits are necessary. Coffee and tea intake may decrease Lp(a) level; further investigation is crucial before they can be considered potent Lp(a)-lowering agents. Among supplementation strategies, only l-carnitine and coenzyme Q10 are promising clinical candidates to lower Lp(a) level. Since both l-carnitine and coenzyme Q10 supplementation are commonly used for CV support, they deserve further exploration regarding clinical applicability. In contrast, despite potential CV benefits, current research fails to justify use of higher intakes of vitamin C, soy isoflavones, garlic, and omega-3 for decreasing Lp(a) concentration. IMPLICATIONS: Definitive long-term clinical trials are needed to confirm the effects of dietetic interventions and nutraceutical

agents on Lp(a) concentration when anticipating improved CV outcomes. (Clin Ther. 2019; 41:XXX-XXX) (c) 2019 Elsevier Inc.

[14] *Gharaibeh NE, Rahhal MN, Rahimi L, Ismail-Beigi F*. **SGLT-2 inhibitors as promising therapeutics for non-alcoholic fatty liver disease: pathophysiology, clinical outcomes, and future directions**. Diabetes, metabolic syndrome and obesity : targets and therapy 2019; 12:1001-1012.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31308716
ABSTRACT
Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as a major expanding national and international health problem. Despite numerous investigations using a variety of therapeutic agents, the positive result on any single medication has not been established enough to gain widespread approval. This is in part related to concerns regarding side effects of agents, but is also related to the complex etiology of NAFLD. An often discussed question has been whether insulin resistance that is frequently present in those with NAFLD is a cause of NAFLD or is merely associated with the condition. Nevertheless, it is clear that a very high proportion of patients with NAFLD are obese, have elements of metabolic syndrome, or have type 2 diabetes (T2DM). Also, much progress has been made toward a better understanding of the pathophysiology of NAFLD. Life-style interventions resulting in weight loss remain the foundation for the prevention and treatment of NAFLD. In addition, agents such as Vitamin E and pioglitazone as well as other glycemia-lowering agents including Glucagon Like Peptide-1 (GLP-1) receptor agonists and Sodium Glucose Contransporter-2 inhibitors (SGLT-2i(s)) exhibit positive effects on the clinical course of NAFLD. This narrative review summarizes the current understanding of the diagnosis, epidemiology, and pathophysiology of NAFLD and specifically focuses on the efficacy of SGLT2i(s) as a potentially promising group of agents for the management of patients with NAFLD.

[15] *Nascimento EBM, Konings M, Schaart G et al.* **In vitro effects of sitosterol and sitostanol on mitochondrial respiration in human brown adipocytes, myotubes and hepatocytes**. European journal of nutrition 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31317217
ABSTRACT
PURPOSE: Lowering of LDL cholesterol levels by plant sterols and stanols is associated with decreased risk of cardiovascular disease in humans. Plant sterols and stanols also lower triacylglycerol (TG). However, it is not fully understood how reduction in TG is achieved and what the full potential of plant sterols and stanols is on whole-body metabolism. We here hypothesize that high levels of plant sterols and stanols stimulate whole-body energy expenditure, which can be attributed to changes in mitochondrial function of brown adipose tissue (BAT), skeletal muscle and liver. METHODS: Phytosterolemic mice were fed chow diets for 32 weeks to examine whole-body weight gain. In vitro, 24-h incubation were performed in adipocytes derived from human BAT, human myotubes or HepG2 human hepatocytes using sitosterol or sitostanol. Following mitochondrial function was assessed using seahorse bioanalyzer. RESULTS: Chow feeding in phytosterolemic mice resulted in diminished increase in body weight compared to control mice. In vitro, sitosterol or sitostanol did not change

mitochondrial function in adipocytes derived from human BAT or in cultured human myotubes. Interestingly, maximal mitochondrial function in HepG2 human hepatocytes was decreased following sitosterol or sitostanol incubation, however, only when mitochondrial function was assessed in low glucose-containing medium. CONCLUSIONS: Beneficial in vivo effects of plant sterols and stanols on lipid and lipoprotein metabolism are well recognized. Our results indicate that alterations in human mitochondrial function are apparently not involved to explain these beneficial effects.

[16] *Khan SU, Michos ED*. **Bempedoic acid and ezetimibe - better together**. European journal of preventive cardiology 2019:2047487319864672.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31311303
ABSTRACT

[17] *Luo Y, Zheng M, Zhang Y et al.* **Familial hypercholesterolemia with early coronary atherosclerotic heart disease: A case report**. Experimental and therapeutic medicine 2019; 18:981-986.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31316595
ABSTRACT
Patients with familial hypercholesterolemia usually present with high levels of serum low-density lipoprotein, xanthomas and early coronary artery disease. A 13 years old female patient was admitted to Children's Hospital of Chongqing Medical University presenting symptoms of heart failure. Laboratory tests showed that her cholesterol and low-density lipid levels were extremely high. Electrocardiogram test revealed that she had sinus tachycardia, QT lengthening and ST-T change. Multiple cardiac function abnormalities were diagnosed by echocardiogram. Multiple coronary artery stenosis was determined by computed tomography angiography. After the combination of lipid lowering, anti-thrombosis, and cardiac remodeling therapies, the patient's symptoms were significantly improved and the patient was discharged.

[18] *Nikiforov NG, Wetzker R, Kubekina MV et al.* **Trained Circulating Monocytes in Atherosclerosis: Ex Vivo Model Approach**. Frontiers in pharmacology 2019; 10:725.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31316385
ABSTRACT
Inflammation is one of the key processes in the pathogenesis of atherosclerosis. Numerous studies are focused on the local inflammatory processes associated with atherosclerotic plaque initiation and progression. However, changes in the activation state of circulating monocytes, the main components of the innate immunity, may precede the local events. In this article, we discuss tolerance, which results in decreased ability of monocytes to be activated by pathogens and other stimuli, and training, the ability of monocyte to potentiate the response to pathological stimuli, and their relation to atherosclerosis. We also present previously unpublished results of the experiments that our group performed with monocytes/macrophages isolated from atherosclerosis patients. Our data allow assuming the existence of relationship between the formation of monocyte training and the degree of atherosclerosis progression. The suppression of trained immunity ex vivo seems to be a perspective model for searching anti-atherogenic drugs.

[19] *Colivicchi F, Vagnarelli F, Caldarola P et al.* **[ANMCO Position paper: New perspectives on the role of n-3 polyunsaturated fatty acids in cardiovascular prevention]**. Giornale italiano di cardiologia (2006) 2019; 20:431-438.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31320765

ABSTRACT
Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most important long-chain polyunsaturated fatty acids of the n-3 series (n-3 PUFA). Recent studies have clarified that EPA and DHA have different tissue distribution and influence target organs in a distinct way. In addition to the main effect of reducing triglycerides (TG), they exert antithrombotic, antiarrhythmic, anti-inflammatory, anti-atherogenic, and hemodynamic effects. The different action of PUFA n-3 depends on the dosage and duration of treatment: the effect on TG requires high doses and a few weeks/months of treatment.Several epidemiological studies have shown a relationship between hypertriglyceridemia and cardiovascular risk, confirmed by post-hoc analysis of statin trials and by recent genetic linkage studies. Moreover in secondary prevention, the evidence of a significant "residual risk", even in the presence of an adequate control of LDL-cholesterol, has led the scientific community to consider further intervention objectives in the context of the individual lipid profile, the most promising of which is certainly hypertriglyceridemia.The recent landmark REDUCE-IT study is the first major lipid intervention study to demonstrate a benefit deriving from an approach not based on the LDL target, focusing on a determinant factor of residual risk such as hypertriglyceridemia and treating it with high doses of n-3 PUFA (4 g/day).Overall, the "lipid residual risk" approach involves two integrated actions: (i) the achievement of the LDL-cholesterol target (<70 mg/dl) by using statins, ezetimibe, PCSK9 inhibitors; (ii) checking TG levels in order to start n-3 PUFA in case of TG values >150 mg/dl, at an initial dosage of 2-3 g/day (up to 4 g/day after 10-12 weeks).

[20] *Raggi P*. **[Coronary artery calcium: pathogenesis and cardiovascular risk]**. Giornale italiano di cardiologia (2006) 2019; 20:401-408.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31320761

ABSTRACT
Atherosclerosis is an almost universal disease of human kind and involves infiltration of lipids, inflammation and calcification in the subintimal space. Coronary artery calcium (CAC) accumulates within the context of subintimal atherosclerosis and is a highly specific marker of pre-clinical disease. The prognostic significance of CAC has been elucidated during the past 20 years of research and it is now considered the best non-invasive marker to enhance prediction of adverse events in the general population as well as several disease states, such as diabetes mellitus, chronic kidney disease and HIV. However, the prognostic significance of CAC is not the same for all carriers of this marker, although it is well established that its absence is associated with an extremely low and long-lasting probability of cardiovascular events even in subjects at high risk. In this review, we discuss the current knowledge of the epidemiology and clinical significance of CAC in patients of different race, sex and age and summarize the current recommendations on its use in clinical practice.

[21] *Masson W, Lobo M, Siniawski D et al.* **Impact of Lipid-Lowering Therapy on Mortality According to the Baseline Non-HDL Cholesterol Level: A Meta-Analysis**. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31313082

ABSTRACT

INTRODUCTION: Previous report showed that more intensive lipid-lowering therapy was associated with less mortality when baseline LDL-C levels were > 100 mg/dL. Non-HDL-C is a better predictor of cardiovascular risk than simpler LDL-C. AIM: The objective of this meta-analysis was to define the impact of lipid-lowering therapy on the reduction of total and cardiovascular mortality by different baseline levels of non-HDL-C. METHODS: We performed a meta-analysis including randomized, controlled clinical trials of lipid-lowering therapy, reporting mortality with a minimum of 6 months of follow-up, searching in PubMed/Medline, EMBASE and Cochrane Clinical Trials databases. The random-effects model and meta-regression were performed. RESULTS: Twenty nine trials of lipid-lowering drugs, including 233,027 patients, were considered eligible for the analyses. According to the baseline non-HDL-C level, the results on cardiovascular mortality were: (1) >/= 190 mg/dL: OR 0.63 (95% CI 0.53-0.76); (2) 160-189 mg/dL: OR 0.82 (95% CI 0.75-0.89); (3) 130-159 mg/dL: OR 0.71 (95% CI 0.52-0.98); (4) < 130 mg/dL: OR 0.95 (95% CI 0.87-1.05). When evaluating mortality from any cause, the results were the following: (1) >/= 190 mg/dL: OR 0.70 (95% CI 0.61-0.82); (2) 160-189 mg/dL: OR 0.91 (95% CI 0.83-0.98); (3) 130-159 mg/dL; OR 0.88 (95% CI 0.77-1.00); (4) < 130 mg/dL: OR 0.98 (95% CI 0.91-1.06). The meta-regression analysis showed a significant association between baseline non-HDL-C and mortality. CONCLUSIONS: In these meta-analyses, lipid-lowering therapy was associated with reduction in the risk of all-cause and cardiovascular mortality when baseline non-HDL-C levels were above than 130 mg/dL.

[22] *Kang MK, Kim CJ, Choo EH et al.* **Anti-inflammatory effect of statin is continuously working throughout use: a prospective three time point (18)F-FDG PET/CT imaging study**. The international journal of cardiovascular imaging 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31312997

ABSTRACT

No data exist whether statins have robust anti-inflammatory effects of atherosclerotic plaques primarily during the early treatment period or continuously throughout use. This prospective three time point (18)F-fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG PET/CT) study of the carotid artery assessed anti-inflammatory effects of statin during the early treatment period (initiation to 3 months) and late treatment period (3 months to 1 year) and their correlation with lipid and inflammatory profile changes during a year of therapy. Nine statin-naive stable angina patients with inflammatory carotid plaques received 20 mg/day atorvastatin after undergoing initial (18)F-FDG PET/CT scanning of carotid arteries and ascending thoracic aorta, and then completed serial (18)F-FDG PET/CT imaging at 3 and 12 months whose data were analyzed. The primary outcome was the inter-scan percent change in target-to-background ratio (DeltaTBR) within the index vessel. At 3 months of atorvastatin treatment, mean serum low-density lipoprotein cholesterol (LDL-C) level decreased by 36.4% to < 70 mg/dL (p = 0.001) and mean serum high-density lipoprotein cholesterol level increased to > 40 mg/dL (p = 0.041), with both maintained with no further reduction up to 1

year (p = 0.516 and 0.715, respectively) while mean serum high sensitivity C-reactive protein level only numerically decreased (p = 0.093). The index vessel DeltaTBR showed continuous plaque inflammation reduction over 1 year, by 4.4% (p = 0.015) from the initiation to 3rd months and 6.2% (p = 0.009) from 3rd months to 1 year, respectively, without correlation with lipid profile changes. The DeltaTBR of the bilateral carotid arteries and ascending aorta also continuously decreased from 3 months to 1 year. Three time point (18)F-FDG PET/CT imaging demonstrates that statin's anti-inflammatory effect continues throughout its use up to 1 year, even though yielding stable below-target plasma LDL-C levels at 3 months.

[23] *Biringer RG*. **The Role of Eicosanoids in Alzheimer's Disease**. International journal of environmental research and public health 2019; 16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31323750
ABSTRACT
Alzheimer's disease (AD) is one of the most common neurodegenerative disorders known. Estimates from the Alzheimer's Association suggest that there are currently 5.8 million Americans living with the disease and that this will rise to 14 million by 2050. Research over the decades has revealed that AD pathology is complex and involves a number of cellular processes. In addition to the well-studied amyloid-beta and tau pathology, oxidative damage to lipids and inflammation are also intimately involved. One aspect all these processes share is eicosanoid signaling. Eicosanoids are derived from polyunsaturated fatty acids by enzymatic or non-enzymatic means and serve as short-lived autocrine or paracrine agents. Some of these eicosanoids serve to exacerbate AD pathology while others serve to remediate AD pathology. A thorough understanding of eicosanoid signaling is paramount for understanding the underlying mechanisms and developing potential treatments for AD. In this review, eicosanoid metabolism is examined in terms of in vivo production, sites of production, receptor signaling, non-AD biological functions, and known participation in AD pathology.

[24] *Kwon YJ, Lee JW, Kang HT*. **Secular Trends in Lipid Profiles in Korean Adults Based on the 2005-2015 KNHANES**. International journal of environmental research and public health 2019; 16.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31319575
ABSTRACT
Dyslipidemia is a primary, critical risk factor for cardiovascular disease. Therefore, evaluating the trends in lipid profiles is crucial for the development of health policies and programs. We studied trends in lipid profiles in Korean adults over an 11-year period according to the use of lipid-lowering medications through age-specific analysis. A total of 73,890 participants were included in the Korean National Health and Nutrition Examination Survey III (2005)-VI (2013-2015). The proportion of participants on lipid-lowering medications has increased. This trend was apparent in age groups of over 40 years in both men and women. Lipid-lowering medications successfully reduced mean total cholesterol (TC), but there was no favorable trend in TC in participants not taking lipid-lowering medication in both men and women. Unlike men, triglyceride and non-high-density lipoprotein cholesterol (HDL) decreased in women without lipid-lowering medications. In age-specific hypercholesterolemia, the prevalence of hypercholesterolemia significantly increased in the age groups of 30-59 and 30-49 years in men

and women without lipid-lowering medications, respectively. Meanwhile, mean HDL-C levels increased over the 11-year period regardless of lipid-lowering drug use in both men and women. These analyses identified an upward trend in TC and HDL-C over the 11-year period.

[25] *Li GH, Cheung CL, Au PC et al.* **Positive effects of low LDL-C and statins on bone mineral density: an integrated epidemiological observation analysis and Mendelian randomization study**. International journal of epidemiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31302685
ABSTRACT
BACKGROUND: Low-density lipoprotein cholesterol (LDL-C) is suggested to play a role in osteoporosis but its association with bone metabolism remains unclear. Effects of LDL-C-lowering drugs on bone are also controversial. We aim to determine whether LDL-C is linked causally to bone mineral density (BMD) and assess the effects of LDL-C-lowering drugs on BMD. METHODS: Association between blood lipid levels and BMD was examined by epidemiological observation analyses in a US representative cohort NHANES III (n = 3638) and the Hong Kong Osteoporosis Study (HKOS; n = 1128). Two-sample Mendelian randomization (MR), employing genetic data from a large-scale genome-wide association study (GWAS) of blood lipids (n = 188 577), total body BMD (TB-BMD) (n = 66 628) and estimated BMD (eBMD) (n= 142 487), was performed to infer causality between LDL-C and BMD. Genetic proxies for LDL-C-lowering drugs were used to examine the drugs' effects on BMD. RESULTS: In the NHANES III cohort, each standard deviation (SD) decrease in LDL-C was associated with a 0.045 SD increase in femoral neck BMD (95% CI: 0.009 - 0.081; P = 0.015). A similar increase in BMD was observed in the HKOS at femoral neck and lumbar spine. In MR analysis, a decrease in genetically predicted LDL-C was associated with an increase in TB-BMD {estimate per SD decrease, 0.038 [95% confidence interval (CI): 0.002 - 0.074]; P = 0.038} and eBMD [0.076 (0.042 - 0.111); P = 1.20x10-5]. Reduction in TB-BMD was causally associated with increased LDL-C [0.035 (0.033 - 0.066); P = 0.034]. Statins' LDL-C-lowering proxies were associated with increased TB-BMD [0.18 (0.044 - 0.316); P = 9.600x10-3] and eBMD [0.143 (0.062 - 0.223); P = 5.165x10-4]. CONCLUSIONS: Negative causal association exists between LDL-C level and BMD. Statins' LDL-C-lowering effect increases BMD, suggesting their protective effect on bone.

[26] *Olivieri C*. **The current state of heart disease: statins, cholesterol, fat and sugar**. International journal of evidence-based healthcare 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31318717
ABSTRACT
After decades of improvement in the outlook for cardiovascular disease (CVD), we are now seeing a plateau. Statins, once believed to be the most important advance in the fight against heart disease, have not mitigated the incidence or prevalence of CVD. AIM: New research into lipid-lowering drugs is not only questioning their usefulness in primary care, but identifying them as harmful, resulting in the development of other diseases. When the original research is critically analyzed, the data do not reveal drugs that significantly reduce the incidence or prevalence for primary prevention of CVD in the United States. METHODS: The current article sheds light on our current beliefs into lipid-lowering to treat potential CVD. Through a discussion of the difference between relative risk reduction and absolute risk reduction, the

author suggests lifestyle modifications have been and always will be the best way to fight against this deadly chronic disease. RESULTS: There is over 60 years-worth of scientific research that has been desperately trying to identify sugar as the culprit and driver of CVD disease; however, the medical system continues to fight against fat and cholesterol. This article makes the reader question what the US government, in association with the Medical Establishment (American Heart Association, American Diabetes Association and the American College of Cardiology) have been eschewing for the last 60-70 years as it has NOT been working. CONCLUSION: The time for a culture-wide paradigm change has come. The author suggests this will only happen if Big Pharma and Big Food industries will change their marketing habits from 'purely taste' to 'best for your health'.

[27] *Wu J, Zhang YP, Qu Y et al.* **Efficacy of uric acid-lowering therapy on hypercholesterolemia and hypertriglyceridemia in gouty patients**. International journal of rheumatic diseases 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31317680
ABSTRACT
AIM: To investigate the effects on hypercholesterolemia and hypertriglyceridemia in gouty patients receiving uric acid-lowering therapy (UALT). METHODS: A retrospective study was performed from January 2015 to December 2017 in gouty patients receiving UALT. A total of 124 gouty patients with hypercholesterolemia or hypertriglyceridemia who were administered UALT were monitored. Of the 124 patients with gout, 52 were treated with febuxostat, 29 were treated with allopurinol, and 43 were treated with benzbromarone. Cholesterol and triglyceride levels were recorded and analyzed following treatment for 8-10 weeks. RESULTS: We compared the efficacy of febuxostat, allopurinol, and benzbromarone. All therapies mildly influenced serum cholesterol and triglyceride levels. Febuxostat significantly decreased cholesterol and triglyceride levels in patients who did not receive lipid-lowering therapy. Allopurinol and benzbromarone modestly decreased triglyceride levels, but cholesterol levels were unaffected. CONCLUSION: Uric acid-lowering therapy benefits hyperlipidemia in gouty patients. Febuxostat effectively improved serum cholesterol and triglyceride levels compared to allopurinol and benzbromarone in patients with gout.

[28] *Yarash T, Sharif I, Masood F et al.* **Complementary medicine use and its cost in Australians with type 2 diabetes: The Fremantle Diabetes Study Phase II**. Internal medicine journal 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31314167
ABSTRACT
BACKGROUND: Few studies have examined complementary medicine (CM) use in diabetes. Australian data are inconsistent, limited in scope and have not considered cost. AIMS: To evaluate the prevalence, associates and costs of CMs in a contemporary Australian urban, community-based cohort of people with type 2 diabetes. METHODS: Baseline CM use was determined as part of a detailed assessment in 1,543 of 1,551 FDS2 participants with type 2 diabetes (mean age 65.7 years, 51.8% males, median diabetes duration 9.0 years) recruited to the Fremantle Diabetes Study Phase II (FDS2) between 2008 and 2011 who self-reported medication use including CMs defined as non-prescription medicinal products. RESULTS: 672 FDS2 type 2 participants (43.6%) used at least one type of CM, 92% of which were nutritional supplements (omega-3 fatty acids/fish oil in 24% of CM users followed by calcium in 11%,

glucosamine in 10%, and others in <10%). Independent associates of CM use included older age, female sex, any mobility problem, and, inversely, Southern European or Indigenous Australian background, lack of English fluency, ex-/current smoking status, taking oral glucose-lowering medications, and higher HbA1c . The total annual estimated cost of CM used by FDS2 participants with type 2 diabetes was A$121,640 or A$79+/-208 per person (range A$0-2,993). Extrapolating these data, the 1 million Australians with type 2 diabetes spend A$79 million/year on CMs. CONCLUSIONS: CM use in type 2 diabetes is both common and costly. Healthcare professionals should consider discussing safe and cost-effective use of CM with their patients with type 2 diabetes.

[29] *Iyengar SS, Bansal M, Sawhney J et al.* **Appropriate use of PCSK9 Inhibitors in India**. The Journal of the Association of Physicians of India 2019; 67:74-85.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31311223
ABSTRACT
The burden of atherosclerotic cardiovascular (CV) disease is alarmingly high and increasing in our country. Dyslipidemia is one of the major modifiable risk factors, and INTERHEART study showed that dyslipidemia had the highest population attributable risk for myocardial infarction. In the management of dyslipidemia, low-density lipoprotein cholesterol (LDL-C) is the primary therapeutic target. In addition to therapeutic lifestyle changes, statins and ezetimibe effectively lower LDL-C and consequently improve CV outcomes. However, there are situations where these drugs fall short of achieving the target or they may not be well tolerated.

[30] *Kalra S*. **Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibition: A Lipocrinologic Review**. The Journal of the Association of Physicians of India 2018; 66:70-72.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31317713
ABSTRACT
This review describes the endocrine impact of proprotein convertase subtilisin kexin 9 (PCSK9) biology and PCSK9 inhibition. It discusses the relationship of the pituitary, thyroid, parathyroid, pancreatic, adrenal and gonadal hormones with lipid health. It also explores the status of PCSK9, and impact of PCSK9 inhibition, in dyslipidemia associated with endocrinopathy. This review should stimulate interest in the lipocrinologic aspects of PCSK9 inhibitors.

[31] *Kalra S, Sahay R*. **Improving Diabetic Retinopathy Outcomes: FIELD Fenofibrate**. The Journal of the Association of Physicians of India 2018; 66:55-57.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31313550
ABSTRACT
This brief communication describes evidence which proves the beneficial effects of fenofibrate on the retinal vasculature in type 2 diabetes, acting via both lipid lowering and non-lipid lowering mechanisms. It discusses data from FIELD and other trials to support the use of fenofibrate as a secondary preventive therapy for diabetic retinopathy. These data contrast with the lack of retinal benefit shown in major cardiovascular outcome trials of other blood pressure lowering and glucose lowering agents such as empagliflozin, liraglutide, perindopril + indapamide, and ramipril.

[32] *Nand N, Brijlal, Mittal A*. **Evaluation of Effect of Statins on Erythropoietin Resistance in Patients of Chronic Kidney Disease on Maintenance Haemodialysis**. The Journal of the Association of Physicians of India 2018; 66:29-32.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31313547
ABSTRACT
Methods: Thirty adult patients of end stage renal disease with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. Patients were divided randomly into two groups of 15 patients each. Group A were given atorvastatin in a dose of 20 mg once daily for a period of 4 months along with erythropoietin 6000 IU S/C and IV iron 100mg twice weekly after each hemodialysis. Group B was given erythropoietin 6000 IU S/C and IV iron 100 mg twice weekly after each hemodialysis without addition of atorvastatin for 4 months. Hematological, renal parameters, inflammatory parameters such as erythrocyte sedimentation rate, highly sensitive C reactive protein, serum ferritin and erythropoietin resistance index were done at baseline and then two monthly intervals for 4 months. Results: At the end of study, in group A hemoglobin and haematocrit significantly increased ($p < 0.001$ for both) while HsCRP, ESR and erythropoietin resistance index decreased significantly ($p=0.001$, 0.001 and <0.001 respectively). In group B, the increase in hemoglobin and haematocrit were not statistically significant ($p > 0.05$) similarly fall in HsCRP and ERI were also not significant statistically ($p > 0.05$). The mean rise in hemoglobin between subsequent months was higher in group A as compared to group B which was statically significant. Conclusion: Statin can be used as an adjuvant to erythropoietin in management of anemia in patients of chronic kidney disease, who show hyporesponsiveness to increased doses of erythropoietin, by its anti-inflammatory properties.

[33] *Okura T, Takahashi K, Sakaue T et al.* **A case of spontaneous coronary artery dissection with early de novo recurrence**. Journal of cardiology cases 2019; 20:1-3.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31320943
ABSTRACT
Spontaneous coronary artery dissection (SCAD) is a relatively rare cause of acute coronary syndrome compared with atherosclerotic plaque rupture and predominantly occurs in young women. SCAD is associated with various conditions, such as emotional stress, pregnancy, hormonal therapy, collagen diseases, fibromuscular dysplasia, or vasospasm. Long-term cardiovascular events are common including the recurrence of SCAD. We report a case of SCAD with de novo recurrence at only 4 days after the first attack. <Learning objectives: Spontaneous coronary artery dissection (SCAD) is a relatively rare cause of acute coronary syndrome (ACS) compared with atherosclerotic plaque rupture, but if young to middle-aged women develop ACS, a high suspicion of SCAD is warranted. Recurrence of SCAD is common with 4- to 10-year follow-up. However, SCAD recurred early as in our case.>.

[34] *Browne RW, Jakimovski D, Ziliotto N et al.* **High-density lipoprotein cholesterol is associated with multiple sclerosis fatigue: A fatigue-metabolism nexus?** Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307953
ABSTRACT

BACKGROUND: Fatigue is a frequent symptom in multiple sclerosis (MS). The role of cholesterol and lipids in MS fatigue has not been investigated. OBJECTIVE: To investigate the associations of cholesterol biomarkers and serum neurofilament light chain (sNfL) with fatigue in relapsing-remitting MS. METHODS: This cross-sectional study included 75 relapsing-remitting MS patients (69% female, mean age +/- SD: 49.6 +/- 11 years and median Expanded Disability Status Scale score: 2.0). Fatigue, disability, and depression were assessed with Fatigue Severity Scale (FSS), Expanded Disability Status Scale, and the Beck Depression Index-Fast Screen, respectively. sNfL was measured using single-molecule array technology. Plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and an apolipoprotein panel data were obtained. Soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1), chemokine (C-C motif) ligand 5 (CCL5 or RANTES), and CCL18 levels were measured to assess inflammation. RESULTS: The mean FSS was 4.27 +/- 1.73, and 57% had severe fatigue status (SFS, FSS >/= 4.0). In regression analyses adjusted for age, sex, disability, and depression, lower FSS and SFS were associated with greater HDL-C (P = .006 for FSS, and P = .016 for SFS) and lower TC to HDL-C ratio (P = .011 for FSS, and P = .009 for SFS). Apolipoprotein A-II was also associated with FSS (P = .022). sNfL, CCL5, CCL18, sICAM-1, and sVCAM-1 levels were not associated with fatigue after adjusting for disability and depression. CONCLUSIONS: TC to HDL-C ratio is associated with MS fatigue. Our results implicate a potential role for the HDL-C pathway in MS fatigue and could provide possible targets for the treatment of MS fatigue.

[35] *Farnier M, Salignon-Vernay C, Yao H et al.* **Prevalence, risk factor burden, and severity of coronary artery disease in patients with heterozygous familial hypercholesterolemia hospitalized for an acute myocardial infarction: Data from the French RICO survey**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31324593
ABSTRACT
BACKGROUND: Individuals with heterozygous familial hypercholesterolemia (FH) are at high risk of early myocardial infarction (MI). However, coronary artery disease (CAD) burden of FH remains not well described, especially for French patients. OBJECTIVE: The objective of this study was to assess the prevalence of FH and severity of CAD from a large database of a French regional registry of acute MI. METHODS: All consecutive patients hospitalized for an acute MI in a multicenter database from 2001 to 2017 were considered. FH was diagnosed using an algorithm adapted from the Dutch Lipid Clinic Network criteria. The prevalence and clinical features of FH and the severity of CAD were assessed. RESULTS: Among the 11,624 patients included in the study, the proportion of "probable/definite", "possible", and "unlikely" FH in patients with MI was 2.1% (n = 249), 20.7% (n = 2405), and 77.2% (n = 8970), respectively. When compared with patients with "unlikely" FH, patients with "probable/definite" FH were 20 years younger (51 vs 71, P < .001), with a lower rate of diabetes (17% vs 25%, P = .007) and a higher prevalence of personal and familial history of CAD. Chronic statin treatment was only used in 48% of FH patients and ezetimibe in 8%. After adjustment for age, sex, and diabetes, patients with FH were characterized by increased extent of CAD (SYNTAX score 11 vs 7, P < .001) and multivessel disease (55% vs 40%, P < .001). CONCLUSIONS: In this large cohort of French individuals, FH was common in patients with MI, associated with markedly early age of MI and severity of CAD burden and limited use of preventive lipid-lowering therapy.

[36] *Takaeko Y, Matsui S, Kajikawa M et al.* **Association of extremely high levels of high-density lipoprotein cholesterol with endothelial dysfunction in men**. Journal of clinical lipidology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31311726
ABSTRACT
BACKGROUND: It is not clear whether a high level of high-density lipoprotein cholesterol (HDL-C) is associated with lower risk of atherosclerosis. It is likely that HDL-C is a double-edged sword for atherosclerosis. OBJECTIVE: The purpose of this study was to evaluate the relationship between HDL-C levels and endothelial function in men. METHODS: This was a cross-sectional study. We evaluated flow-mediated vasodilation (FMD) and serum levels of HDL-C in 5842 men aged 18 to 92 years who were not receiving lipid-lowering therapy. All participants were divided into four groups by HDL-C level: low HDL-C (<40 mg/dL), moderate HDL-C (40-59 mg/dL), high HDL-C (60-79 md/dL), and extremely high HDL-C (>/=80 mg/dL). We were not able to evaluate the amount of alcohol intake because there was limited information on the amount of alcohol drinking in our database. RESULTS: FMD values were significantly smaller in the low group and the extremely high group than in the high group (P = .001 and P = .016, respectively). There was no significant difference in FMD between the low group and the extremely high group. Multiple logistic regression analysis revealed that extremely high HDL-C, but not low HDL-C, was independently associated with the lowest quartile of FMD (odds ratio: 1.39, 95% confidence interval: 1.09-1.77; P = .009). CONCLUSIONS: An extremely high level of HDL-C in men (8.1% of this population) was associated with a significant reduction in FMD.

[37] *Qin L, Xie X, Fang P, Lin J*. **Prophylactic simvastatin treatment modulates the immune response and increases survival of mice following induction of lethal sepsis**. J Int Med Res 2019:300060519858508.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307265
ABSTRACT

[38] *van de Peppel IP, Bertolini A, van Dijk TH et al.* **Efficient reabsorption of transintestinally excreted cholesterol is a strong determinant for cholesterol disposal in mice**. Journal of lipid research 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31324653
ABSTRACT
Transintestinal cholesterol excretion (TICE) is a major route for cholesterol elimination from the body and a potential therapeutic target for hypercholesterolemia. The underlying mechanism, however, is largely unclear and its contribution to cholesterol disposal from the body is obscured by the counteracting process of intestinal cholesterol reabsorption. To determine the quantity of TICE independent from its reabsorption, we studied two models of decreased intestinal cholesterol absorption. Cholesterol absorption was inhibited either by ezetimibe or, indirectly, by genetic inactivation of the intestinal apical sodium-dependent bile acid transporter (ASBT, SLC10A2). Both ezetimibe treatment and Asbt inactivation virtually abrogated fractional cholesterol absorption (from 46% to 4% and 6%, respectively). In either model, fecal neutral sterol excretion and net intestinal cholesterol balance were considerably

higher than in control mice (5- and 7-fold, respectively), suggesting that, under physiological conditions, TICE is largely reabsorbed. In both models, the net intestinal cholesterol balance was increased to a similar extent, but was not further increased when the models were combined, suggesting that the effect on cholesterol reabsorption was already maximal under either condition alone. Based on these findings, we hypothesize that inhibition of cholesterol (re)absorption combined with stimulation of TICE will be most effective in increasing cholesterol disposal.

[39] *Muhammad ZA, Ahmad T, Baloch N*. **Can alternate-day Statin regimen minimize its adverse effects on muscle and tendon? A systematic review**. JPMA. The Journal of the Pakistan Medical Association 2019; 69:1006-1013.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31308572
ABSTRACT
OBJECTIVE: To review evidence-based data with respect to safety and efficacy of alternate-day statin therapy in dyslipidaemia compared to the standard daily dose. METHODS: The literature review was conducted at Aga Khan University Hospital, Karachi from July, 2016 to August, 2017. Electronic database search was carried out to compile available literature using PubMed, Excerpta Medica database and Google Scholar. The most relevant evidence-based research articles published over 10 years were selected. The latest search was dated August 03, 2017. RESULTS: A total of 2,074 articles were initially located. Alternate day statin regimen was reported in 53% of articles. Adverse effects on muscle and tendon were reported in 69% of articles. After scrutiny, 19(0.9%) studies covering alternate-day statin-mediated muscle and tendon disorders and 9(0.4%) studies encompassing the potential pathophysiological mechanisms of statin-associated muscle and tendon injury were selected. Except pravastatin and lovastatin, alternate-day statin therapy was almost as effective in lowering total cholesterol, low-density lipoprotein cholesterol and triglycerides as the daily dosing with low incidence of muscle toxicity and tends in opathy. CONCLUSIONS: Alternate-day statin regimen was found to be very well tolerated and might be an effective and safe remedy in clinical practice.

[40] *Jiang X, Wang F, Wang Y et al.* **Inflammasome-Driven Interleukin-1alpha and Interleukin-1beta Production in Atherosclerotic Plaques Relates to Hyperlipidemia and Plaque Complexity**. JACC. Basic to translational science 2019; 4:304-317.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31312755
ABSTRACT
CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) confirmed interleukin (IL)-1beta as an appealing therapeutic target for human atherosclerosis and related complications. However, there are serious gaps in our understanding of IL-1 production in atherosclerosis. Herein the authors show that complex plaques, or plaques derived from patients with suboptimally controlled hyperlipidemia, or on no or low-intensity statin therapy, demonstrated higher recruitable IL-1beta production. Generation of mature IL-1beta was matched by IL-1alpha release, and both were attenuated by inhibition of NLR family pyrin domain containing 3 or caspase. These findings support the inflammasome as the main pathway for IL-1alpha/beta generation in atherosclerosis and high-intensity lipid-lowering

therapies as primary and additional anti-IL-1-directed therapies as secondary interventions in high-risk patients.

[41] *Block RC, Liu L, Herrington DM et al.* **Predicting Risk for Incident Heart Failure With Omega-3 Fatty Acids: From MESA**. JACC. Heart failure 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31302044
ABSTRACT
OBJECTIVES: The aim of this study was to determine if plasma eicosapentaenoic acid (EPA) abundance (%EPA) is associated with reduced hazard for primary heart failure (HF) events in the MESA (Multi-Ethnic Study of Atherosclerosis) trial. BACKGROUND: Clinical trials suggest that omega-3 polyunsaturated fatty acids (omega3 PUFAs) prevent sudden death in coronary heart disease and HF, but this is controversial. In mice, the authors demonstrated that the omega3 PUFA EPA prevents contractile dysfunction and fibrosis in an HF model, but whether this extends to humans is unclear. METHODS: In the MESA cohort, the authors tested if plasma phospholipid EPA predicts primary HF incidence, including HF with reduced ejection fraction (EF) (EF <45%) and HF with preserved EF (EF >/=45%) using Cox proportional hazards modeling. RESULTS: A total of 6,562 participants 45 to 84 years of age had EPA measured at baseline (1,794 black, 794 Chinese, 1,442 Hispanic, and 2,532 white; 52% women). Over a median follow-up period of 13.0 years, 292 HF events occurred: 128 HF with reduced EF, 110 HF with preserved EF, and 54 with unknown EF status. %EPA in HF-free participants was 0.76% (0.75% to 0.77%) but was lower in participants with HF at 0.69% (0.64% to 0.74%) (p = 0.005). Log %EPA was associated with lower HF incidence (hazard ratio: 0.73 [95% confidence interval: 0.60 to 0.91] per log-unit difference in %EPA; p = 0.001). Adjusting for age, sex, race, body mass index, smoking, diabetes mellitus, blood pressure, lipids and lipid-lowering drugs, albuminuria, and the lead fatty acid for each cluster did not change this relationship. Sensitivity analyses showed no dependence on HF type. CONCLUSIONS: Higher plasma EPA was significantly associated with reduced risk for HF, with both reduced and preserved EF. (Multi-Ethnic Study of Atherosclerosis [MESA]; NCT00005487).

[42] *Bach RG, Cannon CP, Giugliano RP et al.* **Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older: A Secondary Analysis of a Randomized Clinical Trial**. JAMA cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31314050
ABSTRACT
Importance: Limited evidence is available regarding the benefit and hazard of higher-intensity treatment to lower lipid levels among patients 75 years or older. As a result, guideline recommendations differ for this age group compared with younger patients. Objective: To determine the effect on outcomes and risks of combination ezetimibe and simvastatin compared with simvastatin monotherapy to lower lipid levels among patients 75 years or older with stabilized acute coronary syndrome (ACS). Design, Setting, Participants: In this prespecified secondary analysis of the global, multicenter, prospective clinical randomized Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), outcomes and risks were compared by age among patients 50 years or older after a hospitalization for ACS. Data were collected from October 26, 2005, through July 8, 2010, with the database locked October

21, 2014. Data were analyzed May 29, 2015, through March 13, 2018, using Kaplan-Meier curves and Cox proportional hazards models. Interventions: Double-blind randomized assignment to combined simvastatin and ezetimibe or simvastatin and placebo with follow-up for a median of 6 years (interquartile range, 4.3-7.1 years). Main Outcomes and Measures: The primary composite end point consisted of death due to cardiovascular disease, myocardial infarction (MI), stroke, unstable angina requiring hospitalization, and coronary revascularization after 30 days. Individual adverse ischemic and safety end points and lipid variables were also analyzed. Results: Of 18144 patients enrolled (13 728 men [75.7%]; mean [SD] age, 64.1 [9.8] years), 5173 (28.5%) were 65 to 74 years old, and 2798 (15.4%) were 75 years or older at randomization. Treatment with simvastatin-ezetimibe resulted in lower rates of the primary end point than simvastatin-placebo, including 0.9% for patients younger than 65 years (HR, 0.97; 95% CI, 0.90-1.05) and 0.8% for patients 65 to 74 years of age (hazard ratio [HR], 0.96; 95% CI, 0.87-1.06), with the greatest absolute risk reduction of 8.7% for patients 75 years or older (HR, 0.80; 95% CI, 0.70-0.90) (P = .02 for interaction). The rate of adverse events did not increase with simvastatin-ezetimibe vs simvastatin-placebo among younger or older patients. Conclusions and Relevance: In IMPROVE-IT, patients hospitalized for ACS derived benefit from higher-intensity therapy to lower lipid levels with simvastatin-ezetimibe compared with simvastatin monotherapy, with the greatest absolute risk reduction among patients 75 years or older. Addition of ezetimibe to simvastatin was not associated with any significant increase in safety issues among older patients. These results may have implications for guideline recommendations regarding lowering of lipid levels in the elderly. Trial Registration: ClinicalTrials.gov identifier: NCT00202878.

[43] *Gotto AM, Jr.* **Intensive Lipid Lowering in Elderly Patients**. JAMA cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31314042
ABSTRACT

[44] *Konnov MV, Deev AD*. **[Own and Parental Predictors of Hypertriglyceridemia in Children of Persons with Early Ischemic Heart Disease]**. Kardiologiia 2019; 59:11-18.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31322084
ABSTRACT
AIM: to elucidate predictors of high level of basal triglycerides (TG) in blood of children of persons with early (onset: men </=55, women </=60 years) ischemic heart disease (EIHD). MATERIALS AND METHODS: We examined 316 families: patients (probands) (n=295; 77.9 % after MI) with EIHD, their spouses (n=219; 83.1 % women) and native children of probands (n=413; 55.7 % men) aged 5-38 years. In children aged 5-17 and 18-38 years proband's spouse was mother in 88 and 77 % of cases, respectively. Hypertriglyceridemia in children (HTG) was defined in persons aged 5-17 years as >/=90 percentile (Lipid Research Clinics), >/=18 years - >/=1.7 mmol / l or HTG drug treatment. Predictors of HTG were selected by binary logistical regression with adjustment for age, sex and drugs. RESULTS: HTG was found in 31 / 158 children aged 5-17 years. Its independent predictors were systolic arterial pressure (odds ratio [OR] of top [>108] vs. two bottom [</=108 mm Hg] tertiles 3.85, 95 % confidence interval [CI] 1.38-10.7, small er, Cyrillic=0.010), heart rate (HR, OR of top [>78] vs. two bottom [</=78 bpm] tertiles 2.94, 95 % CI 1.20-7.23, small er, Cyrillic=0.019), and high density lipoprotein

cholesterol (HDL-C, OR 0.35, 95 % CI 0.13-0.94; small er, Cyrillic=0.038) of their children; HR (OR of top [>72] vs. two bottom [</=72 bpm] tertiles 3.56, 95 % CI 1.38-9.11, small er, Cyrillic=0.008), low density lipoprotein cholesterol (OR 2.49, 95 % CI 1.12-5.52, p=0.025]), and type 2 diabetes (OR 25.9, 95 % CI 1.01-665.3; p=0.049) of the parent - proband's consort. HTG was found in 35 / 255 children aged 18-38 years and was associated with own age (OR 1.10, 95 % CI 1.02-1.19, small er, Cyrillic=0.012) and male sex (OR 6.21, 95 % CI 2.45-15.8; small er, Cyrillic=0.000). HTG was independently associated with body mass index (OR top [>25.4] vs. two bottom [</=25.4 kg / m2] tertiles 4.94, 95 % CI 2.13-11.4, small er, Cyrillic=0.000); basal glycemia (OR top [5.1] vs. two bottom [</=5.1 mmol / l] tertiles 2.52, 95 % CI 1.17-5.43, small er, Cyrillic=0.019); HDL-C (OR 0.17, CI 0.04-0.81, 0.027); alcohol consumption (OR consuming more than once vs. once a week and less 2.27, 95 % CI 1.02-5.02, p=0.044) of these children; HDL-C (OR 0.19, 95 CI 0.04-0.94; p=0.041) of the proband-parent. CONCLUSIONS: HTG in children aged 5-38 years with parental early IHD was independently associated mainly with own characteristics, forming components of metabolic syndrome. Attention should be paid to the dominance of maternal transmission in children and adolescents (age group 5-17 years).

[45] *Dansinger ML, Williams PT, Superko HR, Schaefer EJ*. **Effects of weight change on apolipoprotein B-containing emerging atherosclerotic cardiovascular disease (ASCVD) risk factors**. Lipids in health and disease 2019; 18:154.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31311555
ABSTRACT
BACKGROUND AND AIMS: Non-high-density (HDL)-cholesterol, low-density lipoprotein (LDL)-particle number, apolipoprotein B, lipoprotein(a) (Lp(a)), and small-dense (sdLDL) and large-buoyant (lbLDL) LDL-subfractions are emerging apo B-containing atherosclerotic cardiovascular disease (ASCVD) risk factors. Current guidelines emphasize lifestyle, including weight loss, for ASCVD risk management. Whether weight change affects these emerging risk factors beyond that predicted by traditional triglyceride and LDL-cholesterol measurements remains to be determined. METHOD: Regression analyses of fasting apo B-containing lipoproteins vs. BMI were examined in a large anonymized clinical laboratory database of 33,165 subjects who did not report use of lipid-lowering medications. Regression slopes (+/-SE) were estimated as: *mmol/L per kg/m(2), (dagger)g/L per kg/m(2), (double dagger)% per kg/m(2), and (section sign)mumol/L per kg/m(2). RESULTS: When adjusted for age, BMI was significantly related to nonHDL-cholesterol (males: 0.0238 +/- 0.0041, P = 7.9 x 10(- 9); females: 0.0330 +/- 0.0037, P < 10(- 16))*, LDL-particles (males: 0.0128 +/- 0.0024, P = 2.1 x 10(- 7); females: 0.0114 +/- 0.0022, P = 3.2 x 10(- 7))(*), apo B (males: 0.0053 +/- 0.0010, P = 7.9 x 10(- 8); females: 0.0073 +/- 0.0009, P = 2.2 x 10(- 16))(dagger), sdLDL (males: 0.0125 +/- 0.0015, P = 2.2 x 10(- 16); females: 0.0128 +/- 0.0012, P < 10(- 16))*, percent LDL carried on small dense particles (%sdLDL, males: 0.296 +/- 0.035, P < 10(- 16); females: 0.221 +/- 0.023, P < 10(- 16))(double dagger), triglycerides (males: 0.0358 +/- 0.0049, P = 2.0 x 10(- 13); females: 0.0304 +/- 0.0029, P < 10(- 16))*, and LDL-cholesterol (males: 0.0128 +/- 0.0034, P = 0.0002; females: 0.0232 +/- 0.0031, P = 1.2 x 10(- 13))* in both males and females. Age-adjusted BMI was significantly related to lbLDL in females (0.0098 +/- 0.0024, P = 3.9 x 10(- 5))* but not males (0.0007 +/- 0.0026, P = 0.78)*. Female showed significantly greater increases in LDL-cholesterol (P = 0.02) and lbLDL (P = 0.008) per BMI than males. BMI had a greater effect on LDL-cholesterol measured directly

than indirect estimate of LDL-cholesterol from the Friedewald equation. When sexes were combined and adjusted for age, sex, triglycerides and LDL-cholesterol, BMI retained residual associations with nonHDL-cholesterol (0.0019 +/- 0.0009, P = 0.03)*, LDL-particles (0.0032 +/- 0.0010, P = 0.001)*, apo B (0.0010 +/- 0.0003, P = 0.0008)(dagger), Lp(a) (- 0.0091 +/- 0.0021, P = 1.2 x 10(- 5))(section sign), sdLDL (0.0001 +/- 0.0000, P = 1.6 x 10(- 11))(*) and %sdLDL (0.151 +/- 0.018, P < 10(- 16)) (double dagger). CONCLUSIONS: Emerging apo B-containing risk factors show associations with weight change beyond those explained by the more traditional triglyceride and LDL-cholesterol measurements.

[46] *van den Berg EH, de Meijer VE, Blokzijl H*. **Author response to Letter to the Editor: "Statins and non-alcoholic fatty liver disease"**. Liver international : official journal of the International Association for the Study of the Liver 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31310401
ABSTRACT
We thank Angelico and colleagues for their interest in our recent article in which we revealed that a substantial proportion of subjects with suspected non-alcoholic fatty liver disease (NAFLD) has increased cardiovascular risk and subjects with dyslipidemias such as high low-density lipoprotein (LDL) cholesterol could benefit from lipid-lowering treatment with statins.

[47] *Hou FJ, Zhou YJ, Ma XT et al.* **Culprit Lesion Characteristics in Young Patients with Hyperhomocysteinemia**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:5306-5311.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31313754
ABSTRACT
BACKGROUND The relationships between culprit coronary plaque characteristics and hyperhomocysteinemia (HHcy) are not fully understood in young patients. In this study we investigated the relationship between culprit atherosclerotic plaque phenotype assessed by optical coherence tomography (OCT) and hyperhomocysteinemia (HHcy) in young patients. MATERIAL AND METHODS We investigated the OCT imaging and HHcy of 123 lesions in 123 young patients (</=45 years of age). According to OCT images, culprit lesions were classified as thin-cap fiber atheroma (TCFA), thrombus, and other. The 123 patients were grouped as: HHcy group (53 cases, HHcy >/=15.5 micromol/l) and control group (70 cases, HHcy <15.5 micromol/l). RESULTS Compared with the control group, the HHcy group had a higher proportion of OCT-TCFA (p=0.03), OCT-vasa vasorum (p=0.013), and OCT-thrombus (p=0.012), and a larger lipid arc (p=0.002). HHcy (P=0.037) and metabolic syndrome (MetS) (P=0.016) remained independent predictors of TCFAs. HHcy (P=0.026) and smoking (P=0.005) remained independent determinants of thrombus. CONCLUSIONS HHcy and MetS are associated with TCFAs, and HHcy and smoking are associated with thrombus in young patients with coronary artery disease.

[48] *Zhang G, Li Q*. **Inflammation Induces Lipid Deposition in Kidneys by Downregulating Renal PCSK9 in Mice with Adriamycin-Induced Nephropathy**. Medical science monitor : international medical journal of experimental and clinical research 2019; 25:5327-5335.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31317882

ABSTRACT

BACKGROUND Previous studies of human and animal models indicate that inflammation alters lipid metabolism. The pro-protein convertase subtilisin kexin type 9 (PCSK9) plays an important role in lipid metabolism. MATERIAL AND METHODS We examined the effect of inflammation on PCSK9 expression and lipid deposition in the kidneys of mice with Adriamycin-induced nephropathy. RESULTS The results indicated an increased expression of inflammatory cytokines and lipid deposition over 12 weeks. During this time, the expression of PCSK9 and its transcriptional activator (hepatocyte nuclear factor 1alpha, HNF1alpha) decreased, and the expression of the low-density lipoprotein receptor (LDLR) and its transcriptional activator (sterol regulatory element binding protein-2, SREBP-2) increased. Exogenous inflammation appeared to further aggravate this process. CONCLUSIONS Our mouse model of nephropathy suggests that a key step in the inflammation-induced deposition of lipids in the kidneys is the downregulation renal PCSK9 expression.

[49] **Erratum: Effects of atorvastatin on chronic subdural hematoma: A systematic review: Erratum**. Medicine (Baltimore) 2017; 96:e7616.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31305691

ABSTRACT

[This corrects the article DOI: 10.1097/MD.0000000000007290.].

[50] *Utama S, Patriawan P, Dewi A*. **Correlation of CD4/CD8 Ratio with Carotid Intima-Media Layer Thickness in HIV/AIDS Patients at Sanglah General Hospital, Bali, Indonesia**. Open access Macedonian journal of medical sciences 2019; 7:1803-1807.

PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31316662

ABSTRACT

BACKGROUND: The discovery of antiretroviral (ARV) drugs in 1996 led to a shift in the causes of mortality and morbidity of patients with HIV/AIDS. Initially, the cause of mortality and morbidity was associated with opportunistic infection HIV/AIDS-related complication, but now are more associated with non-AIDS complication such as cardiovascular disease. Atherosclerosis is a major cause of cardiovascular disease. The atherosclerosis was assessed by measuring carotid intima-media thickness (CIMT) using B mode ultrasound (USG), which is one of the diagnostic tools in indicating the presence of atherosclerotic plaque. AIM: This study aims to evaluate the ratio of CD4 / CD8 towards carotid intima-media thickness. METHODS: Design of study was analytic cross-sectional. This study was conducted in May - July 2017 in HIV patients who taken consecutively came to the VCT polyclinic of Sanglah hospital. Statistical analysis used Spearman correlation test to evaluate the correlation between the CD4/CD8 ratio and carotid intima-media thickness and multiple linear regression to predict carotid intima-media thickness through CD4/CD8 ratio. RESULTS: Total from 50 samples, data characteristic were 33 males (66%) and 17 females (34%), mean of age 30.60 +/- 5.58 years, median of CD4/CD8 ratio 0.275 (0.02-1.39) and median of CIMT 0.75 (0.4-1.5) mm. There is a strong negative correlation (r = -0.85; p = 0.001) CD4/CD8 ratio with CIMT. The calculation of the prediction of carotid intima media thickness can be calculated through the equation Y = 0.727 -0.791 (X1) + 0.012 (X2), where X1 is CD4/CD8 ratio and X2 is the age of the patient. CONCLUSION: there is a significantly

strong negative correlation between the CD4/CD8 ratio and CIMT in HIV patient who comes to VCT polyclinic of Sanglah Hospital. The smaller CD4/CD8 ratio, the value of CIMT will be thicker, and vice versa.

[51] *Hari P, Khandelwal P, Smoyer WE*. **Dyslipidemia and cardiovascular health in childhood nephrotic syndrome**. Pediatric nephrology (Berlin, Germany) 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31302760
ABSTRACT
Children with steroid-resistant nephrotic syndrome (SRNS) are exposed to multiple cardiovascular risk factors predisposing them to accelerated atherosclerosis. This risk is negligible in steroid-sensitive nephrotic syndrome, but a substantial proportion of children with SRNS progress to chronic kidney disease, exacerbating the already existing cardiovascular risk. While dyslipidemia is an established modifiable risk factor for cardiovascular disease in adults with NS, it is uncertain to what extent analogous risks exist for children. There is increasing evidence of accelerated atherosclerosis in children with persistently high lipid levels, especially in refractory NS. Abnormalities of lipid metabolism in NS include hypertriglyceridemia and hypercholesterolemia due to elevated apolipoprotein B-containing lipoproteins, decreased lipoprotein lipase and hepatic lipase activity, increased hepatic PCSK9 levels, and reduced hepatic uptake of high-density lipoprotein. Existing guidelines for the management of dyslipidemia in children may be adapted to target lower lipid levels in children with NS, but they will most likely require both lifestyle modifications and pharmacological therapy. While there is a lack of data from randomized controlled trials in children with NS demonstrating the benefit of lipid-lowering drugs, therapies including statins, bile acid sequestrants, fibrates, ezetimibe, and LDL apheresis have all been suggested and/or utilized. However, concerns with the use of lipid-lowering drugs in children include unclear side effect profiles and unknown long-term impacts on neurological development and puberty. The recent introduction of anti-PCSK9 monoclonal antibodies and other therapies targeted to the molecular mechanisms of lipid transport disrupted in NS holds promise for the future treatment of dyslipidemia in NS.

[52] *Roy R, Ajithan A, Joseph A et al.* **Statin-induced new onset of diabetes in dyslipidemic patients: a retrospective study**. Postgraduate medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31311373
ABSTRACT
Background: Previously conducted studies with statins shows an increased risk of developing new onset of diabetes. This study helps in analyzing the risk of statins to cause new onset of diabetes. Objective: To assess the prevalence, causality, severity, preventability and risk factors of statin-induced new onset of diabetes in dyslipidemic patients. Methods: The study was conducted of a tertiary care hospital. A 6-month retrospective study was carried out in the cardiology department and analyzed between year 2013-2017medical records of dyslipidemic patients treated with statins of age >18 years. Patients with congenital diabetes, previous history of diabetes, patients using antipsychotics and steroids, and patients with incomplete data were excluded. Patients were reported as diabetic according to the American Diabetes Association's classification. Patients who developed statin-induced new onset of diabetes were assessed by the WHO probability scale, Naranjo's causality assessment scale, Hartwig's severity

assessment scale and Modified Schumock and Thornton preventability scale. Results: Out of 270 dyslipidemic patients, 19 patients developed statin induced new onset of diabetes and 69 were classified as pre-diabetic. The major risk factors were: dose, gender, age, geriatric patients, and duration of the therapy. Patients who developed statin induced new onset of diabetes were managed by dose reduction and treatment with anti-diabetic medications. Conclusion The prevalence of statin induced new onset of diabetes is 7.03%. The main risk factors identified in the study were in older patients (>/=60 years), rosuvastatin therapy, high dose and longer duration of statin therapy.

[53] *Fontes-Carvalho R, Marques Silva P, Rodrigues E et al.* **Practical guide for the use of PCSK9 inhibitors in Portugal**. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31324407
ABSTRACT
Reducing low-density lipoprotein cholesterol (LDL-C) levels is one of the most important strategies for reducing the risk of cardiovascular events. However, in clinical practice, a high proportion of patients do not achieve recommended LDL-C levels through lifestyle and lipid-lowering therapy with statins and ezetimibe. PCSK9 inhibitors (PCSK9i) are a new therapeutic option that significantly (50-60%) reduces LDL-C levels, which in clinical trials translates into an additional reduction in risk for cardiovascular events, and has a good safety profile. However, it is a high-cost therapy, and therefore its use in clinical practice should take its cost-effectiveness into account. Priority should be given to use in patients at higher cardiovascular risk and those in whom high LDL-C levels persist despite optimal lipid-lowering therapy. This consensus document aims to summarize the main data on the clinical use of PCSK9i and to make recommendations for Portugal on the profile of patients who may benefit most from this therapy.

[54] *Marques da Silva P, Lima MJ, Neves PM, Espiga de Macedo M*. **Prevalence of cardiovascular risk factors and other comorbidities in patients with hypertension in Portuguese primary health care populations: The PRECISE study**. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307727
ABSTRACT
INTRODUCTION: Cardiovascular (CV) disease is the leading cause of death in Portugal. The prevalence of hypertension, the second most important risk factor accounting for overall disability-adjusted life years (DALYs), is significant. Hypertension rarely occurs in isolation, but is usually associated with other determining risk factors that contribute to greater overall CV risk. The main objective of the PRECISE study, a cross-sectional epidemiological study, was to determine the prevalence of other concomitant modulating CV risk factors in hypertensive patients. METHODS: The prevalence of other CV risk factors and target organ damage was assessed in 2848 hypertensive patients of both sexes followed in primary health care centers. Demographic, anthropometric and clinical data and antihypertensive and lipid-lowering

therapies prescribed were collected. RESULTS: Of the study population (mean age 65.8+/-11.0 years, 60.8% women), 98.0% were treated for hypertension, but only 56.7% had controlled blood pressure. Hypercholesterolemia was the most frequent concomitant CV risk factor (82.1%), followed by sedentary behavior (71.4%). Prevalences of concomitant modulating risk factors were significantly different between the sexes and age groups. Overall, 81.7% of hypertensive patients had three or more concomitant CV risk factors. CONCLUSIONS: The study showed that, in Portugal, hypertensive patients have a high prevalence of other CV risk factors, confirming the need to identify these factors, calculate overall CV risk and continuously monitor the care provided and the results obtained.

[55] *Liu Q, Xie YJ, Qu LH et al.* **Dyslipidemia involvement in the development of polycystic ovary syndrome**. Taiwanese journal of obstetrics & gynecology 2019; 58:447-453.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307731
ABSTRACT
Polycystic ovary syndrome (PCOS) is widely accepted as the most common endocrine abnormality in women of childbearing age and may be accompanied by dyslipidemia, hyperandrogenism, hyperinsulinemia, oxidative stress and infertility. Dyslipidemia is now known to play an important role in the development of PCOS. Lipid abnormalities, including elevated low-density lipoprotein and triglyceride levels and reduced high-density lipoprotein levels, are often found in women with PCOS and play an important role in PCOS; therefore, we summarize the effect of lipid abnormalities on hyperandrogenism, insulin resistance, oxidative stress and infertility in PCOS and review the effects of common lipid-lowering drugs on patients with PCOS. The purpose of this article is to elucidate the mechanisms of lipid metabolism abnormalities in the development of PCOS.

[56] *Corrado E, Mignano A, Coppola G*. **Use of statins in patients with peripheral artery disease**. Trends in cardiovascular medicine 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31307839
ABSTRACT
Atherosclerotic peripheral artery disease (PAD) is a growing health issue that affects more than 200 million individuals worldwide, conferring a high risk of cardiovascular events and death. In spite of its high prevalence, PAD has often been neglected in the past and the heightened cardiovascular risk of patients with PAD has been consistently under-recognized by practitioners. Considering that an integrated approach to reduce cardiovascular events and lower limb complications is necessary in this setting, statins represent the cornerstone of therapy as reported by current American and European guidelines. Literature has extensive data about the importance of lipid-lowering therapy in patients with PAD demonstrating that statins reduce symptoms, cardiovascular events and mortality. Despite data extrapolated from many studies on coronary artery diseases, moderate-dose statin therapy seems to be safe, and the minor risks posed in terms of myopathy-related symptoms are greatly outweighed by benefits. Other lipid-lowering drugs did not show the same results in terms of outcome and they should not be considered as first line therapy in these patients. The role of anti-PCSK9 inhibitors is emerging in the literature but further data are necessary to understand their superiority over statins.

[57] *Fuhrmann S, Koppen A, Seeling A et al.* **Analysis of secondary care data to evaluate the clinical relevance of the drug-drug interaction between amlodipine and simvastatin**. Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen 2019.
PM: http://www.ncbi.nlm.nih.gov/pubmed/?term=31324418

ABSTRACT

BACKGROUND: Pharmacokinetic analyses revealed an increase in the bioavailability of simvastatin when co-administered with amlodipine [Nishio S et al. Hypertensin research 2005; Son H et al. Drug metabolism and pharmacokinetics 2014]. This may induce an increased risk of muscle toxicity for patients who receive this combination. So far, no in vivo data on the clinical relevance of this interaction exist. The objective of the present analysis was to determine the number of patients with concomitant treatment of amlodipine and simvastatin. Subsequently, the data was analyzed for the indication of muscular discomfort. Patients with combined prescription of amlodipine and another hydroxymethylglutaryl-CoA-reductase inhibitor except simvastatin or patients receiving simvastatin without amlodipine served as control groups. METHODS: The present analysis used secondary data from the health insurance company AOK PLUS including information regarding diagnosis and drug prescriptions. RESULTS: In total, 67,081 patients corresponding to 4.93% of the analyzed collective received a combined prescription of amlodipine and simvastatin. The absolute frequency increased continuously over time. Muscular discomfort was detected in a) 6.20% of the patients receiving amlodipine and simvastatin, b) 6.60% of the patients receiving amlodipine and another hydroxymethylglutaryl-CoA- reductase inhibitor and c) 8.04% of the patients with simvastatin only. CONCLUSIONS: The present analysis shows an increasing trend of combined prescriptions of amlodipine and simvastatin. Evidence for simvastatin dose adaptation or therapy switch to another hydroxymethylglutaryl-CoA-reductase inhibitor, however, was not found. Muscular discomfort does not occur more often in patients with amlodipine and simvastatin compared to the two control groups. The results of the present analysis reveal no evidence for a clinically relevant interaction between amlodipine and simvastatin.